FDA Opening Remarks
June 28, 2023

Theresa Kehoe, MD
Director, Division of General Endocrinology

New Drug Application for Palovarotene
Endocrinologic and Metabolic Drugs Advisory Committee

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Theresa Kehoe, MD
Director, Division of General Endocrinology
FDA Introductory Presentation

• Whether it is reasonable to conclude, based on available data, that palovarotene, used chronically, is a safe and effective drug in patients with fibrodysplasia ossificans progressiva (FOP).

• Introductory Comments
  – FOP
  – Palovarotene
  – Review of the Development Program
  – Review of the Issues
  – Discussion and Voting Questions
Fibrodysplasia Ossificans Progressiva

- Rare severely disabling congenital disease, 800 confirmed cases
- Caused by a gain-of-function mutation in the activin A type I receptor ACVR1 (ALK2)
- Mutation is predominantly sporadic but can be inherited
- Renders ALK2 constitutively active to ligands like bone morphogenetic protein (BMP) and drives ectopic chondrogenesis and osteogenesis leading to heterotrophic ossification (HO) in connective tissue, joints, and muscle
Fibrodysplasia Ossificans Progressiva

• HO is the hallmark of FOP
  – Begins to manifest in early childhood
  – Is episodic, with some events starting with soft tissue inflammation (flare-up)
  – The accumulation of extra-skeletal bone is cumulative and irreversible, causing restriction of movement, deformities, severe disability, and early mortality
Fibrodysplasia Ossificans Progressiva

- No approved therapies for FOP
- Conventional therapy is aimed at symptom relief - to treat inflammation and to reduce chronic pain
- Attempts at surgical resection of lesions generally leads to reactivation of disease and new HO formation
- FDA held a Listening Session with patients and caregivers in May 2019
Palovarotene

Mechanism: retinoic acid receptor gamma selective agonist (retinoid) that appears to interfere with ALK2-mediated bone formation indirectly

Proposed Indication: Prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva

Dosing Regimen: oral capsule, 5 mg daily with flare-up dosing of 20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks
Palovarotene Development Program

- Nonclinical models: demonstrated prevention of HO
- The first clinical development program FOP
- Prospective Natural History Study (study 001, NHS)
- **Phase 2 study 201** – evaluated flare-up dosing
  - Placebo-controlled study, 6 weeks of therapy
- **Study 202** – open-label extension, platform for evolving dosing regimen and imaging modalities
- **Study 301** – open-label study using NHS as external control
Phase 3 Study 301

- **Subjects**: 4 years and older, no flare-up in prior 4 weeks
- **Control**: External comparator, NHS
- **Dosing**: Palovarotene 5 mg daily, increased to 20 mg for 4 weeks then 10 mg for 8 weeks at onset of flare-up
- **Imaging**: Whole body CT scan every 6 months
- **Endpoints**:
  - Primary: annualized change in new HO volume
  - Key secondary: proportion of subjects with any new HO
Events During Phase 3

• Evidence of Premature Epiphyseal Closure
  – Known to occur with retinoids, bone safety monitoring plan in place for all palovarotene treatment studies
  – 9 pediatric subjects developed evidence of premature closure
  – Partial clinical hold for under 14 years of age

• Second Interim Analysis of Study 301
  – Futility was declared, dosing stopped
  – Post hoc analyses performed
Description of the Issues

- Study 301 failed the prespecified primary efficacy analysis. The NDA submission relies on post hoc analyses from study 301 to support the effectiveness of palovarotene. Therefore, the following are key efficacy issues during the FDA review:
  - Key issue 1: appropriateness of reliance on post hoc analyses to support effectiveness
  - Key issue 2: use of an external control group (NHS)
Phase 3 Study 301

• Additional post hoc analyses appeared to show evidence of benefit
  – the Bayesian compound model without square root transformation
  – a weighted linear mixed effects (wLME) model
NHS as External Control

• Subjects in the NHS were allowed to transfer out of the study to an interventional study if they met the inclusion/exclusion criteria
  – 8 subjects to study 201, 13 subjects to study 202, 39 subjects to study 301
• Some differences in the groups
  – NHS subjects older with more advanced disease
Description of the Issues

• Key issue 3: an apparent increased incidence of flare-ups
  – Has safety and efficacy considerations
  – Retinoids have been associated with hyperostosis and calcification of ligaments and tendons; musculoskeletal adverse effects including back pain, arthralgia, myalgia; and rare reports of severe myositis
  – Concern that some of these events may trigger or exacerbate flare-up symptoms; flare ups may trigger new HO
Discussion and Voting Questions
Question 1: Discussion

• Discuss the evidence of effectiveness for palovarotene demonstrated in study 301. In your discussion consider the following:
  – The use of post hoc analyses to support a demonstration of efficacy
  – The interpretability of the results using the external control (Natural History Study)
Question 2: Discussion

• Discuss your view of the flare-up events in subjects treated with the proposed palovarotene dosing regimen and the relevance to benefit-risk considerations. Also comment on whether you have concerns about other safety issues included in the meeting materials and slide presentations or discussed today.
Question 3: Voting

• Does the evidence from Study 301 of palovarotene’s treatment effect show the drug is effective in patients with fibrodysplasia ossificans progressiva (FOP)?

  a. Provide the rationale for your vote.
Question 4: Voting

• Do the benefits of palovarotene outweigh its risks for the treatment of patients with FOP?
  
a. If you voted yes, provide the rationale for your vote.
  
b. If you voted no, provide the rationale for your vote, and provide recommendations for additional data that may support a conclusion that the benefits outweigh the risks.
NDA 215559

Overview of Clinical Studies

Stephen Voss M.D.
DGE/OCHEN/OND
Palovarotene/FOP Studies

• Natural History Study (NHS): 3-year observational study
• Study 201: Phase 2 randomized, placebo-controlled
  – Palovarotene treatment of acute flare-ups
• Study 202: Phase 2 open-label extension, no control group
  – Treatment of acute flare-ups
  – Chronic and flare-up treatment, evaluate disease progression
• Study 301: Phase 3 single-arm study
  – Chronic and flare-up treatment, evaluate disease progression
  – External control group: Untreated NHS subjects
Natural History Study (NHS, PVO-1A-001)

- FOP patients age <65 years with R206H mutation, no recent flareup
- Assessments of disease progression (annual)
  - WBCT: whole body heterotopic ossification (HO), by CT
  - CAJIS: Cumulative Analogue Joint Involvement Scale, measures restricted mobility
  - FOP-PFQ: FOP-Physical Function Questionnaire
- Flare-up assessments (12 weeks):
  - Symptoms: pain, swelling, decreased ROM
  - Imaging of flare-up site: CT, radiographs, MRI
NHS Baseline Data: Increasing Age Correlates With HO Accumulation, and With Greater Restriction of Range of Motion (CAJIS Score)

Age vs. Total Body HO Volume

Age vs. CAJIS Total Score

Orphanet J Rare Dis (2019), 14:98
Whole Body HO Volume Correlates With CAJIS Score

CAJIS Total Score

Total Volume of HO (x10^5 mm^3)

r=0.57, p<0.0001

Orphanet J Rare Dis (2019), 14:98
Natural History Study (NHS)

- 114 total enrollment
- Transfers from NHS to palovarotene studies:
  - 8 subjects to phase 2 study 201, to treat a flareup
  - 39 subjects to phase 3 study 301 (without recent flareup)
  - 13 subjects to phase 2 study 202 (without recent flareup)
  - There were no prespecified criteria for transfers, except for enrollment criteria of the interventional study
Study PVO-1A-201

- Phase 2, randomized, double-blind, placebo-controlled, multicenter study
- Treatment of acute FOP flare-up episode, onset within 7 days, at least 2 symptoms
- Treatment groups:
  - Palovarotene 10 mg x 2 weeks, then 5 mg x 4 weeks (n=21)
  - Palovarotene 5 mg x 2 weeks, then 2.5 mg x 4 weeks (n=9)
  - Placebo x 6 weeks (n=10)
- Randomization 3:1 (10/5: Placebo) then 3:3:2 (10/5: 5/2.5: Placebo)
- Treatment for 6 weeks, observation for 6 weeks
- Age ≥15 years initially, then lowered to ≥6 years with weight-based dose adjustments if <90% skeletally immature
Study 201: Endpoints

- **Primary:** proportion of responders, defined as no or minimal new HO (≤3 on 0-6 scale) by AP/lateral radiograph of flare-up site at week 6

- **Secondary:**
  - Subjects with no/minimal new HO at flare-up site, week 12
  - Volume of new HO at flare-up site, week 12 (CT scan)
  - Soft tissue edema (MRI)
  - Pain, swelling
  - Range of motion
Study 201: Subjects

- 40 subjects enrolled, mean age 21 years, range 7-53
- 55% female, 81% White
- Mean number of flare-ups in previous year: 2.3 (placebo), 2.0 (5/2.5 mg), 4.6 (10/5 mg)
- Flare-up sites treated: hip (40%), knee (23%)
- Symptoms: pain (95%), swelling (70%), stiffness (80%)
- Baseline HO present at flare-up site (CT) in 61%
- Edema present at flare-up site (MRI) in 72%
# Study 201: Efficacy Assessments of Flare-up Site

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=10</th>
<th>Palovarotene 5/2.5 mg N=9</th>
<th>Palovarotene 10/5 mg N=21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 6:</strong> new HO (&gt;3/6) by radiograph (primary endpoint)</td>
<td>1/9 (11%)</td>
<td>1/9 (11%)</td>
<td>0/21 (0%)</td>
</tr>
<tr>
<td><strong>Week 12:</strong> new HO, by CT or radiograph</td>
<td>4/10 (40%)</td>
<td>2/9 (22%)</td>
<td>5/21 (24%)</td>
</tr>
<tr>
<td>Volume of new HO at week 12 (CT), cm$^3$</td>
<td>Mean (SD)</td>
<td>16.2 (41.6)</td>
<td>1.2 (3.2)</td>
</tr>
<tr>
<td>Pain, mean change at week 12 (0-10 scale)</td>
<td>-2.2</td>
<td>-1.9</td>
<td>-3.6</td>
</tr>
</tbody>
</table>

Prespecified primary endpoint was not met.
Study 202

• Open-label extension of Study 201; uncontrolled
• All 40 subjects from 201 enrolled, 18 new subjects added in 202 Part B
• **Part A**: additional flare-ups treated, assessments of flare-up sites
  – Palovarotene 10 mg x 2 weeks, then 5 mg x 4 weeks
• **Part B**: dosing increased
  – Flare up dose 20 mg x 4 weeks, then 10 mg x 8 weeks
  – Chronic daily dose 5 mg (>90% skeletally mature subjects only)
• **Part C**: Chronic 5 mg/flare-up 20/10 mg in all subjects
• All doses weight-adjusted for skeletally immature subjects
Whole-body HO by CT Scan (Studies 202B/C, 301 and NHS)

- With chronic/flare up dosing regimen, WBCT became primary imaging modality
- At baseline: HO volume measured in each of 9 body regions
- Post-baseline scans: HO was re-measured in body regions where any new HO was apparent
- Volume data were reported as total for region, changes could be positive or negative
- Data on individual HO lesions (e.g., new vs pre-existing) were not recorded
- Annualized new HO = whole body change from baseline (cm³ or mm³) ÷ time interval (yrs)
Study 202 Part C

• Criteria for initiating flare-up dosing changed between Study 202 Parts B, C
• Only Part C used the same regimen as Study 301:
  – Chronic 5 mg daily between flare-ups
  – At onset of any flare-up symptom, if consistent with previous flare-ups and confirmed by Investigator, begin 20 mg x 4 weeks, then 10 mg x 8 weeks
  – Persistent symptoms: extend 10 mg in 4-week intervals
  – Intercurrent flare-up (at new location, or marked worsening): restart 20/10 mg
  – Protocol amendment: if substantial trauma: restart 20/10 mg
  – All doses weight-adjusted for skeletally immature subjects
• Primary endpoint: Annual rate of new whole-body HO (not powered for comparison to NHS)
Study 202C (and Study 301): Treatment Pause

- Subjects <14 years: clinical hold (Dec 2019) - growth plate closure
- Subjects ≥14 years: treatment paused (Jan 2020) – interim analysis
  - many subjects restarted treatment after pause of 3-24 months
- Three treatment periods:
  - Pre-pause: on treatment (original NDA)
    - In 202C, baseline scan - no flare-up within 1 month (to align with 301, NHS)
  - Interruption period: (mostly) off-treatment
  - Post-pause: on-treatment following restart
Study 202C Population

• 50% female
• Mean age 21 years
• Compared to NHS and Study 301, older and higher baseline WBHO
## Study 202C: New HO, by Treatment Phase

<table>
<thead>
<tr>
<th></th>
<th>Pre-pause Treatment</th>
<th>Interruption</th>
<th>Post-pause Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>23</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Time interval (mean, months)</td>
<td>11.7</td>
<td>19.6</td>
<td>11.8</td>
</tr>
<tr>
<td>Annual new HO volume (cm³/year), mean</td>
<td>19.0</td>
<td>26.8</td>
<td>6.4</td>
</tr>
</tbody>
</table>
### Study 202C: New HO, by Treatment Phase
(Subjects With Data for All 3 Phases)

<table>
<thead>
<tr>
<th></th>
<th>Pre-pause Treatment</th>
<th>Interruption</th>
<th>Post-pause Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Annual new HO volume (cm³/year), mean</td>
<td>23.2</td>
<td>34.0</td>
<td>10.6</td>
</tr>
</tbody>
</table>
Phase 3 Study PVO-1A-301

- Single-arm study, adult and pediatric FOP age ≥4 years, no flare-up within 4 weeks
- Dosing regimen same as Study 202C: chronic (5 mg) + flare-up (20/10 mg, extended as need) regimen, weight-based dose reductions for <90% skeletally mature
- N=107 total; 99 w/ classic R206H mutation
- External control: N=114 subjects in NHS (all w/ R206H mutation), same study sites
- 39 subjects participated in both NHS/301
Phase 3 Primary Efficacy Assessment: Whole body HO volume

• Whole body CT (less head): conducted every 6 months in Study 301, every 12 months in NHS
• Read methodology similar to Study 202C: 9 body regions, changes from baseline HO volume by region
• CT scans from 301/NHS were combined for blinded readings
• Two independent reviewers, consensus and adjudication
• Intra- and inter-reader variability were acceptable
## Study 301/NHS Baseline

<table>
<thead>
<tr>
<th></th>
<th>NHS N=111</th>
<th>Study 301 N=99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range) at enrollment</td>
<td>17.5 (4, 56)</td>
<td>15.1 (4, 61)</td>
</tr>
<tr>
<td>Mean age at diagnosis of FOP</td>
<td>7.5</td>
<td>6.6</td>
</tr>
<tr>
<td>% female</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>% White</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td>% Asian</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>% Hispanic</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>USA</td>
<td>34%</td>
<td>39%</td>
</tr>
<tr>
<td>Europe/UK</td>
<td>41%</td>
<td>39%</td>
</tr>
<tr>
<td>Canada/South America/Japan</td>
<td>24%</td>
<td>22%</td>
</tr>
</tbody>
</table>
### Study 301/NHS Baseline

<table>
<thead>
<tr>
<th>Measure</th>
<th>NHS (N=111)</th>
<th>Study 301 (N=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole-body HO volume, cm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>313 (373.6)</td>
<td>231 (292.5)</td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>195 (0, 1906)</td>
<td>127 (0, 1382)</td>
</tr>
<tr>
<td># of body regions with HO, mean</td>
<td>6.5</td>
<td>6.1</td>
</tr>
<tr>
<td># of flare-ups within 12 months, mean</td>
<td>2.5</td>
<td>1.4</td>
</tr>
<tr>
<td>CAJIS score, mean</td>
<td>11.8</td>
<td>10.0</td>
</tr>
<tr>
<td>FOP-PFQ score, mean</td>
<td>47.0</td>
<td>44.3</td>
</tr>
</tbody>
</table>

- NHS subjects had more advanced disease, possibly related to older age
## Study 301: New HO, by Treatment Phase

<table>
<thead>
<tr>
<th></th>
<th>Pre-pause Treatment</th>
<th>Interruption</th>
<th>Post-pause Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>97</td>
<td>42</td>
<td>17</td>
</tr>
<tr>
<td>Time interval (mean, months)</td>
<td>15.7</td>
<td>25.4</td>
<td>14.4</td>
</tr>
<tr>
<td>Annual new HO volume (cm³/year), mean</td>
<td>9.4</td>
<td>20.1</td>
<td>7.7</td>
</tr>
</tbody>
</table>
# Study 301: New HO, by Treatment Phase
(Subjects With Data for All 3 Phases)

<table>
<thead>
<tr>
<th></th>
<th>Pre-pause Treatment</th>
<th>Interruption</th>
<th>Post-pause Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Annual new HO volume (cm³/year), mean</td>
<td>5.0</td>
<td>29.8</td>
<td>7.7</td>
</tr>
</tbody>
</table>
### Study 301: New HO, by Treatment Phase (Subjects Who Did Not Restart Treatment)

<table>
<thead>
<tr>
<th></th>
<th>Pre-pause Treatment</th>
<th>Post-pause Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td><strong>Annual new HO volume (cm³/year), mean</strong></td>
<td>2.3</td>
<td>15.6</td>
</tr>
</tbody>
</table>
Statistical Review of Studies 301 and NHS

Alexander Cambon, PhD
Outline

• Study design
• Prespecified analyses and results
• Key efficacy review issues
Study Design

• Study 301: A single-arm study evaluating palovarotene for decreasing HO accumulation as assessed by whole body computed tomography (WBCT)
  – WBCT assessed every 6 months
• Natural history study (NHS) used as an external control
  – WBCT assessed every 12 months
• 39 subjects transitioned from the NHS study to Study 301
• Image readers blinded to the source of the images
Primary and Secondary Endpoints

• Primary Endpoint
  – Annualized change in new HO volume

• Key Secondary Endpoint
  – Proportion of subjects with any new HO.

• Other secondary and exploratory endpoints
  – Change from baseline in number of body regions with new HO
  – Proportion of subjects reporting flare-ups
  – Flare-up rate per subject-month exposure
  – Change from baseline in CAJIS, FOP-PFQ
Prespecified Primary Analysis

- Bayesian Compound Poisson model with two separate components
  - The number of body regions with new HO (change in HO>0)
  - The new HO volume per region where new HO has occurred
- Estimation of mean Annualized change in new HO
  - Mean annual number of event times the mean growth per event
  - Occurrence of a positive new HO as an event
- Treatment effect
  - Ratio of mean annualized new HO between treated and untreated subjects
- Square-root transformation
  - Performed for change in HO since previous scan by region for calculation of mean growth of new HO (HO>0)
## Results From Prespecified Primary Analysis

### Studies 301 and NHS: Ratio of Annualized Change in New HO Volume

<table>
<thead>
<tr>
<th>Study 301</th>
<th>NHS control</th>
<th>Median Ratio (95% CI)</th>
<th>Pr(ratio &lt;1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palovarotene</td>
<td>N=97</td>
<td>N=101</td>
<td>0.95 (0.74, 1.22)</td>
</tr>
</tbody>
</table>

Source: CSR The median ratio is the median of the posterior distribution of the ratio (annualized rate of new HO for subjects in study 301 divided by the annualized rate of New HO for subjects in NHS). Pr(ratio <1) is the probability that the ratio is less than 1, given the data (the posterior probability).
Key Efficacy Review Issues

1. Appropriateness of reliance on post hoc analyses
2. Use of external control (Natural History Study)
ISSUE 1: APPROPRIATENESS OF RELIANCE ON POST HOC ANALYSES
General Considerations on Post Hoc Analyses

• Selection bias towards intended outcome
• Hypotheses generating
• Decisions should be based on appropriate analyses
A Bias of Prespecified Bayesian Analysis

• Square-root transformation performed on each incremental change of HO between CT scan visits
  – Every 6 month in Study 301 and every 12-month in NHS
• Involves comparing sum of the square root of each incremental change to the square root of the sum of each change
An Illustrative Example

Two subjects with identical total change in HO at 1 year could have different estimated annual new HO in the two studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Month 6 Change</th>
<th>Month 12 Change from Month 6</th>
<th>Total Change</th>
<th>Estimated annual new HO#</th>
</tr>
</thead>
<tbody>
<tr>
<td>301</td>
<td>200</td>
<td>200</td>
<td>400</td>
<td>2*√200=28.3</td>
</tr>
<tr>
<td>NHS</td>
<td>Not assessed</td>
<td>400</td>
<td>400</td>
<td>√400=20</td>
</tr>
</tbody>
</table>

Source: FDA reviewer

#Estimated annual new HO is annual number of events times the average amount of new HO per event. Each occurrence of a new HO is counted as an event.

The sum of the square roots of each incremental change is not equal to the square root of the sum of each incremental change.
## Applicant’s Post Hoc Bayesian Analyses Without Square Root Transformation

**Study 301 vs NHS: Ratio of Annualized New HO**

<table>
<thead>
<tr>
<th>Analysis Method</th>
<th>Median Ratio (95% CI)</th>
<th>Pr(ratio &lt;1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No square root transformation</td>
<td>0.64 (0.45, 0.90)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>No square root transformation, added covariates#</td>
<td>0.58 (0.41, 0.82)</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

Source: ISE  
# covariates: baseline HO divided by baseline age, baseline age, sex, baseline CAJIS, time since last flare-up.  
The median ratio is the median of the posterior distribution of the ratio (annualized rate of new HO for subjects in study 301 divided by the annualized rate of New HO for subjects in NHS). Pr(ratio <1) is the probability that the ratio is less than 1, given the data (the posterior probability).
# Applicant’s wLME Analyses on Annualized New HO at Last Scan

<table>
<thead>
<tr>
<th>Study 301</th>
<th>NHS control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palovarotene</td>
<td>N=97</td>
</tr>
<tr>
<td>Annualized HO at baseline, mean (SD)</td>
<td>13.4 (13.1)</td>
</tr>
<tr>
<td>Mean Annualized new HO, (SE)</td>
<td>9.4 (3.1)</td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>0.4 (-30.2, 237)</td>
</tr>
<tr>
<td>LS Mean difference (95% CI)</td>
<td>-10.9 (-21.2, -0.6)</td>
</tr>
<tr>
<td>Nominal p-value, comparison to NHS</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Source: CSR. Abbreviations: HO, Heterotopic Ossification; SD, Standard Deviation; SE, Standard Error; wLME (Weighted Linear Mixed Effects) Analyses; subject level random effect included to account for the correlation among repeated measures on the same subject; No square root transformation; covariates: annualized HO at baseline, calculated by dividing baseline HO by baseline age; Endpoint: annualized new HO(cm³/year), calculated as change from baseline in total HO at last scan divided by actual length of follow-up
Number of Subjects With Whole Body HO Data in Pre-pause Period by Visit

<table>
<thead>
<tr>
<th>Visit</th>
<th>Study 301 Palovarotene</th>
<th>NHS control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>97</td>
<td>101</td>
</tr>
<tr>
<td>Month 6</td>
<td>94</td>
<td>2</td>
</tr>
<tr>
<td>Month 12</td>
<td>93</td>
<td>90</td>
</tr>
<tr>
<td>Month 18</td>
<td>64</td>
<td>11</td>
</tr>
<tr>
<td>Month 24</td>
<td>1</td>
<td>63</td>
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<tr>
<td>Month 30</td>
<td>0</td>
<td>9</td>
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<tr>
<td>Month 36</td>
<td>0</td>
<td>33</td>
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<tr>
<td>Month 42</td>
<td>0</td>
<td>4</td>
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<tr>
<td>Month 48</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data as of the following cutoff dates: In study 301, 12/4/19 for <14 y/o and 1/24/20 for ≥14 y/o; in NHS, 2/28/20
Source: FDA reviewer; Some subjects had some assessments outside the scheduled window
## FDA’s Month 12 Landmark Analyses on Annualized New HO

### Endpoint: annualized new HO (cm\(^3\)/year), calculated as change from baseline in total HO divided by the actual length of follow-up

### Table: Analysis Method/least square mean (SE)

<table>
<thead>
<tr>
<th>Analysis Method/least square mean (SE)</th>
<th>Study 301 (N=97)</th>
<th>NHS (N=101)</th>
<th>Difference (95% CI)</th>
<th>Nominal P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Include only subjects who provided Month 12 HO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covariates 1*</td>
<td>6.7 (2.4)</td>
<td>22.0 (6.4)</td>
<td>-15.3 (-28.5, -2.1)</td>
<td>0.0229</td>
</tr>
<tr>
<td>Covariates 2*</td>
<td>6.2 (2.4)</td>
<td>21.8 (6.1)</td>
<td>-15.5 (-28.8, -2.3)</td>
<td>0.0212</td>
</tr>
<tr>
<td>Covariates 3*</td>
<td>6.6 (2.5)</td>
<td>22.0 (6.2)</td>
<td>-15.4 (-28.8, -2.0)</td>
<td>0.0243</td>
</tr>
<tr>
<td>Include only subjects with HO data up to Month 12</td>
<td>8.1 (2.8)</td>
<td>22.5 (6.3)</td>
<td>-14.3 (-27.8, -0.9)</td>
<td>0.0368</td>
</tr>
<tr>
<td>Covariates 1</td>
<td>7.6 (2.8)</td>
<td>22.3 (6.1)</td>
<td>-14.7 (-28.2, -1.3)</td>
<td>0.0321</td>
</tr>
<tr>
<td>Covariates 2</td>
<td>8.1 (2.9)</td>
<td>22.7 (6.2)</td>
<td>-14.6 (-28.2, -1.0)</td>
<td>0.0354</td>
</tr>
<tr>
<td>Include all subjects using Month 12 data if available $</td>
<td>8.1 (2.8)</td>
<td>20.7 (5.3)</td>
<td>-12.5 (-24.0, -1.1)</td>
<td>0.0317</td>
</tr>
<tr>
<td>Covariates 1</td>
<td>7.5 (2.9)</td>
<td>21.0 (5.2)</td>
<td>-13.5 (-25.3, -1.7)</td>
<td>0.0249</td>
</tr>
<tr>
<td>Covariates 2</td>
<td>7.8 (2.9)</td>
<td>21.7 (5.5)</td>
<td>-13.9 (-26.3, -1.5)</td>
<td>0.0275</td>
</tr>
<tr>
<td>Include all subjects with Month 12 and multiple imputation for missing Month 12; with covariates 3</td>
<td>8.3 (3.0)</td>
<td>22.7 (6.3)</td>
<td>-14.4 (-28.1, -0.7)</td>
<td>0.0395</td>
</tr>
</tbody>
</table>

Source: FDA Reviewer; # Generalized estimation equation; covariates 1: baseline rate of HO: baseline total HO divided by baseline age; covariates 2: baseline rate of HO, sex, baseline age; covariates 3: baseline rate of HO, sex, baseline age, baseline CAJIS, time since last flare-up; $ used last HO changes at month 12 visit window if available; otherwise, used measurements closest to the 12-Month visit window. Conclusion from the multiple imputation-based approach will be overturned when a penalty greater than 45 cm\(^3\)/year is added to the imputed values in treated subjects.
Remarks

• The prespecified analysis has a bias against palovarotene
• More appropriate analyses were conducted post hoc
  – Annualized new HO of treated subjects was lower than that of untreated subjects
ISSUE 2: USE OF EXTERNAL CONTROL
Support Effectiveness Using External Control

• The natural history of the disease is well defined;
• The external control population is very similar to that of the treatment group;
• Concomitant treatments that affect the primary endpoint are not substantially different between the external control and the trial population;
• The results provide compelling evidence of a change in the established progression of disease.
# NHS, Study 301 and Transition Subjects
## Baseline Data

<table>
<thead>
<tr>
<th></th>
<th>NHS only N=62</th>
<th>Transition subjects</th>
<th>Study 301 data* N=39</th>
<th>Study 301 only N=58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, year</td>
<td>20.5</td>
<td>13.5</td>
<td>15.8</td>
<td>14.6</td>
</tr>
<tr>
<td>Sex, male/female (%)</td>
<td>52/48</td>
<td>62/38</td>
<td></td>
<td>47/53</td>
</tr>
<tr>
<td>WBHO volume, cm³, mean</td>
<td>378.2</td>
<td>207.9</td>
<td>259.2</td>
<td>212.4</td>
</tr>
<tr>
<td>Baseline total HO divided by age, cm³/year</td>
<td>17.5</td>
<td>12.8</td>
<td>14.4</td>
<td>12.7</td>
</tr>
<tr>
<td>Number of body regions with HO, mean</td>
<td>6.8</td>
<td>6.1</td>
<td>6.4</td>
<td>6.2</td>
</tr>
<tr>
<td>time since last flare-up, months</td>
<td>20.8</td>
<td>16.8</td>
<td>17.0</td>
<td>26.8</td>
</tr>
<tr>
<td>CAJIS score, mean</td>
<td>13.1</td>
<td>9.6</td>
<td>10.4</td>
<td>9.4</td>
</tr>
</tbody>
</table>

- NHS subjects tended to be older and have more severe disease at baseline

Source: reviewer’s analysis. *: Transition subjects’ baseline in NHS and baseline in Study 301 were summarized respectively. Abbreviations: CAJIS, Cumulative Analogue Involvement Scale for FOP; WBHO, whole body heterotopic ossification
Methods for Reducing the Effects of Confounding

• Propensity score weighting
• Propensity score matching
• Covariates
  – Baseline age, sex, baseline total HO volume divided by age, CAJIS score, time since last flare up
## FDA’s Landmark Analyses Based on Propensity Score Weighting and Matching

<table>
<thead>
<tr>
<th>Analysis Method</th>
<th>Study 301 (N=97)</th>
<th>NHS (N=101)</th>
<th>Difference (95% CI)</th>
<th>Nominal P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propensity score weighting/ mean(SE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Include all subjects using 12-Month data if available</td>
<td>97</td>
<td>101</td>
<td>-14.0 (-27.0, -0.8)</td>
<td>0.0364</td>
</tr>
<tr>
<td>Covariates 1*</td>
<td>8.9 (3.1)</td>
<td>22.8 (5.9)</td>
<td>-14.2 (-27.2, -1.2)</td>
<td>0.0321</td>
</tr>
<tr>
<td>Covariates 2* (excluded 2 subjects missing covariates)</td>
<td>8.7 (3.0)</td>
<td>22.9 (5.9)</td>
<td>-14.2 (-27.2, -1.2)</td>
<td>0.0321</td>
</tr>
<tr>
<td>Covariates 3* (excluded 4 subjects missing covariates)</td>
<td>9.1 (3.2)</td>
<td>23.0 (6.1)</td>
<td>-13.9 (-27.4, -0.5)</td>
<td>0.0422</td>
</tr>
<tr>
<td>Propensity score Matching #</td>
<td></td>
<td></td>
<td>-16.2 (-25.7, -6.6)</td>
<td>0.0022</td>
</tr>
<tr>
<td>Exact match on sex and age group, nearest neighbor with caliper 0.2 for covariates 3</td>
<td>Matched n=61</td>
<td>Matched n=61</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: FDA reviewer
* covariates 1: baseline rate of HO, sex, baseline age; covariates 2: baseline rate of HO, sex, baseline age, baseline CAJIS; * covariates 3: baseline rate of HO, sex, baseline age, baseline CAJIS, time since last flare up.
# age group: (1) <12 years; (2) 12 to <18 years; (3) >=18 years;
Endpoint: annualized new HO, calculated as change in total HO from baseline divided by actual length of follow-up
# Balance Assessment After Propensity Score Weighting

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study 301 Means (N=97)</th>
<th>NHS Means (N=101)</th>
<th>Standardized Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propensity score, mean (min, max)</td>
<td>0.5 (0.2, 0.67)</td>
<td>0.5 (0.17, 0.67)</td>
<td>0</td>
</tr>
<tr>
<td>Age</td>
<td>16.83</td>
<td>16.60</td>
<td>0.025</td>
</tr>
<tr>
<td>Female (%)</td>
<td>45</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>Baseline rate of HO</td>
<td>15.17</td>
<td>15.11</td>
<td>0.0046</td>
</tr>
<tr>
<td>CAJIS</td>
<td>10.98</td>
<td>10.92</td>
<td>0.0091</td>
</tr>
<tr>
<td>Time since last flare up (month)</td>
<td>21.64</td>
<td>21.09</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Baseline rate of HO is the baseline total HO divided by age.

Baseline covariates well-balanced after weighting
## Applicant’s Analyses on Annualized New HO in Subjects Transitioned to Study 301

<table>
<thead>
<tr>
<th>Analysis Method/Least Square Mean (SE)</th>
<th>Study 301 (N=39)</th>
<th>NHS (N=39)</th>
<th>Difference (95% CI)</th>
<th>Nominal p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>wLME* using the observation associated with the longest follow-up</td>
<td>8.1 (4.0)</td>
<td>16.7 (3.3)</td>
<td>-8.6 (-17.7, 0.5)</td>
<td>0.0634</td>
</tr>
<tr>
<td>wLME using last 12-month change in NHS and first 12-month change in Study 301#</td>
<td>4.9 (4.9)</td>
<td>18.2 (5.2)</td>
<td>-13.2 (-25.7, -0.8)</td>
<td>0.0377</td>
</tr>
</tbody>
</table>

Source: CSR and response to information request; analysis covariate: baseline total HO divided by baseline age; random subject effect. SE: standard error; #For subjects who did not have 12-month observation, the last two measures in NHS or the first two measures in study 301 were used. *wLME, weighted linear mixed effect model
Remarks

• Consistent results from commonly used causal inference methods
• Difference in annualized new HO not driven by systematic difference in selected baseline covariates
• Impact of unknown confounding factors uncertain
Summary

• Appropriateness of reliance on post hoc analyses
  – Post hoc analyses should generally be interpreted with caution
  – Acknowledge limitations of the prespecified analysis

• Use of external control to support efficacy
  – Most convincing when populations similar and results compelling
  – Conclusion on treatment effect relied on absence of unknown confounding and potential bias (e.g., differential loss to follow-up)
NDA 215559

Overview of Safety

Stephen Voss M.D., DGE/OCHEN/OGD
Known Safety Issues for Retinoid Class

- Teratogenicity
- Premature epiphyseal closure, reduced bone growth
- Reduced bone mineral density, osteoporosis
- Hyperostosis, calcification of ligaments and tendons
- Arthralgia, back pain, myalgia, rarely severe myositis

- Neuropsychiatric: depression, suicidality, seizures, pseudotumor cerebri
- Mucocutaneous: dry skin, pruritis, alopecia
- Lipid abnormalities: hypertriglyceridemia
- Acute pancreatitis, hepatotoxicity, inflammatory bowel disease
- Hearing impairment
- Decreased night vision
Flare-ups: Potential Safety/Efficacy Issue

- Chronic dosing of palovarotene was anticipated to block the initiation of some flare-ups
  - Flare-up incidence and rate were efficacy endpoints in Study 301
- Potential concern for retinoid induced myositis
- Subjects were instructed to report all new flare-ups in all studies
## Study 201: New Flare-ups Reported Within 12 Weeks of Index Flare-up

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Palovarotene 5/2.5 mg</th>
<th>Palovarotene 10/5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td># treated (index) flare-ups</td>
<td>10</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td># index flare-ups followed by a new event (&quot;condition aggravated&quot;) within 12 weeks</td>
<td>3 (30%)</td>
<td>2 (22%)</td>
<td>13 (62%)</td>
</tr>
<tr>
<td># flare-ups in previous year, mean</td>
<td>2.3</td>
<td>2.0</td>
<td>4.6</td>
</tr>
</tbody>
</table>

- Subjects receiving the highest dose regimen (10/5 mg) had a higher incidence of new flare-ups, but also reported more flare-ups prior to enrollment.
# Studies 201/202A/B, NHS

New Flare-ups Reported Within 12 Weeks of an Index Flare-up

<table>
<thead>
<tr>
<th></th>
<th>Untreated NHS</th>
<th>Placebo</th>
<th>Palo 5/2.5 mg</th>
<th>Palo 10/5 mg</th>
<th>Palo 20/10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td># treated/imaged (index) flare-ups</td>
<td>53</td>
<td>10</td>
<td>9</td>
<td>52</td>
<td>66</td>
</tr>
<tr>
<td># index flare-ups followed by a new event within 12 weeks</td>
<td>12 (23%)</td>
<td>3 (30%)</td>
<td>2 (22%)</td>
<td>19 (37%)</td>
<td>24 (36%)</td>
</tr>
</tbody>
</table>
# Increase in Reported Flare-ups - Study 301 vs. NHS

## All subjects

<table>
<thead>
<tr>
<th></th>
<th>Untreated NHS</th>
<th>Palo Study 301</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with at least one flare-up through month 12</td>
<td>62/111 (56%)</td>
<td>66/99 (67%)</td>
</tr>
<tr>
<td>Flare up rate per subject-month (95% CI)</td>
<td>0.07</td>
<td>0.15</td>
</tr>
</tbody>
</table>

## Subjects who participated in both studies (n=39)

<table>
<thead>
<tr>
<th></th>
<th>Untreated NHS</th>
<th>Palo Study 301</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with at least one flare-up through month 12</td>
<td>23/39 (59%)</td>
<td>26/39 (67%)</td>
</tr>
<tr>
<td>Flare up rate per subject-month (95% CI)</td>
<td>0.08</td>
<td>0.15</td>
</tr>
</tbody>
</table>
Flare-ups Were Likely Under-Reported in NHS

- NHS subjects had less frequent interactions with study staff, possibly less motivated to report symptoms compared to Study 301
- Marked worsening of flare-up symptoms was captured as a new event in Study 301, but not in NHS
- Reported rate of 0.07 flare-ups/month in NHS is lower than reported in a published survey of untreated FOP patients = 0.16 flare-ups/month
- 39 subjects who crossed over from NHS to Study 301:
  - During last 12 months of NHS, prospective recording of flare ups = 0.6 per month
  - Same 12-month time period, retrospective recall of flare ups = 1.1 per month
Study 301: Flare-ups Reported During Flare-up Dosing

• Many subjects receiving flare-up (20/10 mg) dosing for an index flare-up reported new (intercurrent) flare-ups – new location (58%), or worsening at original location (42%)
• New flare-up restarted the 12-week treatment sequence (20 mg)
• Mean number of flare-ups per flare-up cycle was 2.2
• Rate of new flare-ups:
  – During chronic (5 mg) dosing: 0.12 per month
  – During flare up (20/10 mg) dosing: 0.33 per month
Safety Issue: Flare-up Rate

Possible explanations for increased flare-ups reported during flare-up dosing:

– Clustering of multiple FOP flare-ups at different sites
  • Rebound symptoms from withdrawal of high dose corticosteroids
– Retinoid-induced inflammatory reaction / myositis
– Retinoid adverse effects misinterpreted as flare-up symptoms
Clinical Significance of Reported Flare-up Rate is Unclear

• Subjects who reported ≥1 flare-up developed more new HO than subjects who reported no flare-ups
  – NHS: mean 38.1 vs. 6.2 cm³
  – Study 301: mean 11.7 vs. 3.2 cm³

• Flare-up rate and rate of new HO: moderate positive correlation
• Flare-up dosing and rate of new HO: weaker correlation
Safety issue: Teratogenicity

- Retinoids are associated with fetal malformations and adverse pregnancy outcomes (boxed warnings)
- In patients with FOP, pregnancy is rare and is high-risk for mother and fetus, as indicated in current guidelines
- Proposed risk mitigation
  - enhanced labeling
  - education
Safety issue: Premature Physeal Closure (PPC)

- Literature reports: PPC and growth failure in children with prolonged systemic retinoids
- Palovarotene FOP studies included bone safety monitoring (age <18 years):
  - Hand/wrist x-rays at screening to identify open growth plates, determine bone age
  - Subjects with open growth plates continued monitoring every 6 months:
    - AP knee and PA hand/wrist x-rays
    - Standing height (stadiometry) and knee height (knee caliper)
    - Femur and tibia lengths (CT scans)
Safety issue: Premature Physeal Closure (PPC)

- PPC incidence in studies 301, 202B/C
  - Age <8/10 years: 14/25 subjects (56%)
  - Age ≥8/10 to <14 years: 13/39 subjects (33%)
  - Age ≥14 to <18 years: 0/38 subjects

- All PPC cases except one became first apparent on scheduled x-rays of the knee, mostly at around 12 months

- Advances in bone age (hand/wrist x-rays) were similar to slightly greater than advances in chronologic age in palovarotene treated subjects, with or without PPC

- No consistent trends of higher palovarotene exposure in subjects with PPC
## Mean Height Z-score

<table>
<thead>
<tr>
<th></th>
<th>Natural History Study (NHS)</th>
<th>Study 301 (palovarotene)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group</strong></td>
<td>&lt;8/10</td>
<td>≥8/10 to &lt;14</td>
</tr>
<tr>
<td><strong>Baseline Z-score, mean</strong></td>
<td>0.44</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Month 12, mean change from baseline</strong></td>
<td>-0.18</td>
<td>-0.30</td>
</tr>
</tbody>
</table>

- Height Z-score: moderate declines during NHS and Study 301
- Trends of smaller height gains in children with developing PPC
- Knee height, femur/tibia length (CT): similar trends
Other PPC Related Issues

• Potential for leg length discrepancy
  – Changes in right (femur + tibia) vs. left (femur + tibia) lengths
  – No evidence of developing discrepancy in subjects with/without PPC

• Potential for joint angulation deformities
  – Lateral distal femoral angle measured on AP knee radiographs
  – Measurements mostly in normal range (79-85 degrees), no adverse trends in subjects with/without PPC

• Duration of follow-up was limited, cannot rule out longer term effects
Pediatric Age Groups Based on PPC Risk

• Partial clinical hold (Dec 2019): age <14 years
  – <90% of adult height
  – <90% of skeletal maturity, defined as bone age 12 years (girls), 14 years (boys)
    • Below these cutoffs, study participants received reduced doses based on weight
    – No PPC reports in age ≥14

• 80% of adult height
  – Approximate age 8 years (girls), 10 years (boys)
  – Used to define target proposed population for treatment, based on risk/benefit
Backup Slides
Number of Flare-ups Was Not a Strong Predictor of New Whole Body HO

Study 301

NHS
Flare-up Rate vs Annualized New HO

**Figure 10.1.1**

*Study 301 through Month 12: Flare-up Rate vs. Annualized New HO Volume*

\[ y = c(0.1021) + c(1.264e-06) \cdot x, \quad r^2 = 0.119 \]

*Study 202 B/C through Month 12: Flare-up Rate vs. Annualized New HO Volume*

\[ y = c(0.1064) + c(4.161e-07) \cdot x, \quad r^2 = 0.0771 \]

*Study 001 through Month 12: Flare-up Rate vs. Annualized New HO Volume*

\[ y = c(0.0756) + c(3.486e-07) \cdot x, \quad r^2 = 0.0374 \]
## Setting Regional Negative New HO as Zero (by Region)

<table>
<thead>
<tr>
<th>Analysis Method/least square mean (SE)</th>
<th>Study 301 (N=97)</th>
<th>Study 001 NHS (N=101)</th>
<th>Difference (95% CI)</th>
<th>Nominal P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Include only subjects who provided Month 12 HO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covariates 1*</td>
<td>11.1 (2.2)</td>
<td>23.6 (6.3)</td>
<td>-12.5 (-25.3, 0.4)</td>
<td>0.0569</td>
</tr>
<tr>
<td>Covariates 2*</td>
<td>10.4 (2.3)</td>
<td>23.3 (6.0)</td>
<td>-12.9 (-25.7, -0.1)</td>
<td>0.0476</td>
</tr>
<tr>
<td>Covariates 3*</td>
<td>10.7 (2.3)</td>
<td>23.7 (6.1)</td>
<td>-13.0 (-26.0, 0.1)</td>
<td>0.0517</td>
</tr>
<tr>
<td>Include all subjects using 12-Month data if available $</td>
<td>N=97</td>
<td>N=101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covariates 1</td>
<td>12.6 (2.7)</td>
<td>22.3 (5.1)</td>
<td>-9.8 (-20.8, 1.3)</td>
<td>0.0841</td>
</tr>
<tr>
<td>Covariates 2</td>
<td>11.7 (2.7)</td>
<td>22.8 (5.0)</td>
<td>-11.1 (-22.6, 0.3)</td>
<td>0.0560</td>
</tr>
<tr>
<td>Covariates 3</td>
<td>12.0 (2.8)</td>
<td>23.8 (5.3)</td>
<td>-11.8 (-23.8, 0.2)</td>
<td>0.0539</td>
</tr>
</tbody>
</table>

Source: FDA reviewer
*covariates 1: baseline rate of HO; covariates 2: baseline rate of HO, sex, baseline age, baseline CAJIS; covariates 3: baseline rate of HO, sex, baseline age, baseline CAJIS, time since last flare up.

$Generalized estimating equation, no square root transformation, negative new HO set to 0 by region;

Endpoint: annualized new HO, calculated as change in total HO from baseline divided by actual length of follow-up.