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RESEARCH**

APPLICATION NUMBER:

215559Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	Resubmission
Application number(s)	NDA 215559
Priority or standard	Priority
Submit date(s)	2/16/2023
Received date(s)	2/16/2023
PDUFA goal date	8/16/2023
Division/office	Division of General Endocrinology (DGE)
Review completion date	8/14/2023
Established/proper name	Palovarotene
(Proposed) proprietary name	Sohonos
Pharmacologic class	Retinoic acid receptor gamma (RAR γ) selective agonist
Other product name(s)	Retinoid
Applicant	Ipsen Biopharmaceuticals, Inc.
Dosage form(s)/formulation(s)	Capsules 1 mg, 1.5 mg, 2.5 mg, 5 mg, 10 mg
Dosing regimen	Chronic dosing, 5 mg daily; flare-up dosing, 20 mg daily for 4 weeks, followed by 10 mg daily for 8 weeks for a total of 12 weeks (20/10 mg flare-up treatment); doses are weight-adjusted for patients <60 kg
Applicant-proposed indication(s)/population(s)	Prevention of heterotopic ossification (HO) in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva (FOP)
SNOMED CT code for proposed indication disease term(s)¹	82725007 Progressive myositis ossificans (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	Adults and pediatric patients 14 year of age and older: Chronic dosing, 5 mg daily; flare-up dosing, 20 mg daily for 4 weeks, followed by 10 mg daily for 8 weeks for a total of 12 weeks (20/10 mg flare-up treatment); chronic daily and flare-up doses are weight adjusted for pediatric patients <14 years of age
Approved indication(s)/population(s) (if applicable)	Reduction in volume of new heterotopic ossification in adults and pediatric patients (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva (FOP)
SNOMED CT code for approved indication disease term(s)¹	82725007 Progressive myositis ossificans (disorder)

¹ For internal tracking purposes only.

Abbreviations: DGE, Division of General Endocrinology; FOP, fibrodysplasia ossificans progressive; HO, heterotopic ossification; PDUFA, prescription drug user fee act; RAR γ , retinoic acid receptor gamma; SNOMED CT, systematized nomenclature of medicine clinical terms

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Glossary

AE	adverse event
ALK2	activin receptor-like kinase 2
AUC	area under the concentration-time curve
BMC	bone mineral content
BMD	bone mineral density
BMP	bone morphogenetic protein
CAJIS	Cumulative Analogue Joint Involvement Scale
C _{max}	maximum plasma concentration
COPD	chronic obstructive pulmonary disease
CR	Complete Response
CT	computed tomography
DMC	data monitoring committee
DXA	dual x-ray absorptiometry
E-R	exposure-response
P-FAS	principal full analysis set
FDA	Food and Drug Administration
FMQ	FDA Medical Dictionary for Regulatory Activities query
FOP	fibrodysplasia ossificans progressiva
HO	heterotopic ossification
ISS	integrated summary of safety
NDA	new drug application
NHS	natural history study
PI	Prescribing Information
PK	pharmacokinetic
PMR	postmarketing requirement
PPC	premature epiphyseal closure
PROMIS	Patient Reported Outcomes Measurement Information System
PVO	palovarotene
QD	once daily
RAR	retinoic acid receptor
RAR γ	retinoic acid receptor gamma
ROM	range of motion
SAE	serious adverse event
TEAE	treatment-emergent adverse event
WBCT	whole-body computed tomography
wLME	weighted linear mixed effects
WoE	weight of evidence

I. Executive Summary

1. Summary of Regulatory Action

Palovarotene is an orally bioavailable retinoic acid receptor (RAR) gamma (RAR γ) selective agonist (retinoid) proposed for the prevention of heterotopic ossification in adults and children aged 8 years and older for females and 10 years and older for males with fibrodysplasia ossificans progressiva. This new drug application (NDA) received a Complete Response action letter on December 23, 2022. The Applicant's response to the action letter was reviewed by the multidisciplinary review team and an Advisory Committee meeting was held on June 28, 2023. All disciplines recommend approval with a revised indication of treatment to reduce the volume of new heterotopic ossification in adults and children aged 8 years and older for females and 10 years and older for males with fibrodysplasia ossificans progressiva. Palovarotene is the first pharmacologic therapy that is being approved for the treatment of fibrodysplasia ossificans progressiva.

The Applicant submitted one adequate and well-controlled trial and confirmatory evidence providing substantial evidence of effectiveness for the approved indication. The available safety data show that the risks of palovarotene are consistent with the known effects of the drug class and can be mitigated through product labeling which includes a boxed warning for teratogenicity and premature epiphyseal closure. A postmarketing observational registry study will be conducted to obtain further information on the incidence of flare-ups, premature epiphyseal closure, and fractures. The overall benefit-risk is favorable as described in the Benefit-Risk Framework [below](#). For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this Integrated Assessment document and the Product Quality Review.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	Fibrodysplasia ossificans progressiva (FOP) is a rare, severely disabling disease caused by a gain-of-function mutation in the activin A type I receptor ACVR1 (ALK2) which renders ALK2 constitutively active to bone morphogenetic protein ligands, drives ectopic chondrogenesis and osteogenesis, and leads to heterotrophic ossification (HO) in connective tissue, joints, and muscle. Approximately 800 confirmed cases of FOP have been reported globally. Patients with FOP develop extraskeletal bone formation in muscles, tendons and ligaments, known as HO, beginning in early childhood. HO is episodic, with some events starting with soft tissue inflammation (flare-up). The accumulation of extraskeletal bone is cumulative and irreversible, causing restriction of movement, deformities, and severe disability. Complications include chest wall deformity (thoracic insufficiency syndrome), ankyloses of the temporo-mandibular joints resulting in severe tooth decay and malnutrition, and localized skin breakdown. Most patients require mobility assistance by their 20's due to HO around the hips. Survival is shortened (median 56 years), most often by cardio-respiratory failure and pneumonia. There are currently no approved therapies for the treatment of FOP, thus patients face a high unmet medical need to control their disease. Palovarotene is an orally bioavailable retinoic acid receptor (RAR) gamma (RARγ) selective agonist (retinoid) that appears to interfere with ALK2-mediated bone formation indirectly via dampening bone morphogenetic protein signaling. This is thought to lead to blockade of chondrogenic and osteogenic differentiation, reprogramming of progenitor cells into nonskeletal lineage, and prevention of abnormal endochondral bone formation.	FOP is a rare and serious debilitating condition caused by a gain-of-function mutation in the ALK2 receptor that manifests starting in early childhood. Patients with FOP face a high unmet medical need, as no therapies have been shown to treat or slow progression of FOP, specifically the formation of HO and the resulting morbidity associated with chronic HO accumulation. Palovarotene is a retinoic acid receptor (RAR) gamma (RARγ) selective agonist (retinoid) that appears to interfere with ALK2-mediated bone formation and is thus being developed for the treatment of FOP.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	There are currently no approved treatments for patients with FOP. Current conventional therapy is used to provide symptom relief by decreasing inflammation and chronic pain. Attempts at surgical excision of lesions usually leads to reactivation of disease and new HO. Symptomatic treatment with high dose steroids is often used to treat symptom “flares,” however, short term burst steroid therapy has not shown benefit in reducing overall HO burden or slowing disease progression. There are currently no approved therapies for the treatment of FOP.	FOP is a rare disease with no approved therapies, thus only supportive care can be used to decrease pain and inflammation.
Benefit	Two studies were conducted in support of palovarotene in the treatment of FOP: Study 201 which was extended as Study 202 which had multiple parts; and Study 301 which utilized the natural history study as an external control. The proposed dosing regimen includes chronic daily treatment (5 mg), with higher dose treatment (20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks, with extension if needed, referred to as “20/10 mg”) during symptomatic “flare-up” episodes of FOP (all proposed doses are adjusted based on body weight in skeletally immature patients under 18 years of age). This dosing regimen was used in Study 301 and in Part C of Study 202 (202C). The primary endpoint for all studies is new heterotopic ossification as determined by radiologic methods. Earlier studies (Study 201/202A/202B) evaluated the incidence of new HO at the flare-up sites only. However, data from the natural history study revealed that HO frequently occurred outside of flare-ups and the primary endpoint for studies 202C and 301 was changed to annualized change in new HO volume as assessed by whole body CT. This endpoint is clinically meaningful because patients with FOP are known to have progressive accumulation of heterotopic ossification. Based on data from the natural history study, there is a correlation between total body HO volume with increasing Cumulative Analogue Joint Involvement Scale for FOP (CAJIS) score which indicates increasing restrictions on movement and joint range of motion.	Overall, the Agency has concluded that the Applicant demonstrated substantial evidence of the effectiveness of palovarotene to reduce new volume HO in pediatric and adult patients with FOP, but has not provided substantial evidence to support an indication for the prevention of HO in patients with FOP. Further, efficacy of palovarotene treatment in patients with FOP appears to be present only when chronic daily dosing is combined with flare-based dosing, when needed, for flare-up episodes. Substantial evidence of the effectiveness of palovarotene in the treatment of FOP was provided by data from the phase 3 Study 301, using the NHS as an external control, and by supportive efficacy data, primarily from Study 202C, which used the same dosing regimen and protocol design as Study 301, and showed similar trends in reduction in HO volumen in palovarotene-treated patients compared to untreated patients in the NHS. Additional confirmatory evidence of effectiveness was provided by comparisons of HO volumes during ‘pre-pause’ (i.e., active treatment) periods, dose interruption periods, and ‘post-pause’ periods (i.e., after dosing was resumed), which showed similar trends of reductions in HO volume during treatment with palovarotene compared to periods when dosing was stopped. Finally, mechanistic evidence from nonclinical studies in a FOP mouse model provide strong support for the mechanism of action of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Demonstration of the effectiveness of palovarotene comes from Study 301 using the linear mixed effects model where the mean annualized new HO volume was 9.4 cm³/year in subjects receiving palovarotene (study 301) compared with 20.3 cm³/year in untreated subjects from the NHS with a treatment difference of 10.9 cm³/year (95% CI: -21.2, -0.6). Confirmatory evidence of effectiveness comes from post hoc analyses of palovarotene-treated subjects in study 202C compared to untreated subjects from the NHS. Using the matched propensity score analysis, the mean annualized new HO volume was 16.1 cm³/year in subjects receiving palovarotene (study 202C) compared with 28.4 cm³/year in untreated subjects from the NHS with a treatment difference of 12.3 cm³/year. The most concerning weakness of the submitted data include the reliance post hoc analyses and use of an external control group. Post hoc analyses are generally considered hypotheses generating only and not appropriate for providing substantial evidence of effectiveness. However, in this case, the Agency acknowledged that the prespecified primary analysis for Study 301 was inherently biased against palovarotene. Therefore, the review team considered that it was reasonable to look at alternative, more appropriate analyses. The analysis chosen was the primary analysis for the protocol prior to the applicant's amendments. Various post hoc analyses performed by the review team demonstrated a consistency of results across the analyses performed that supported a conclusion of effectiveness. Data from Study 301 and the NHS support the conclusion that chronic daily dosing (i.e., palovarotene 5 mg daily), in addition to flare-based dosing, is needed to achieve benefit. Specifically, these data demonstrate that subjects who reported no flare-ups developed relatively small quantities of new whole body HO, either with or without chronic daily treatment. By comparison, subjects who experienced flare-ups generally developed large quantities of new whole-body HO <i>without</i> chronic daily therapy and derived greater benefit from palovarotene (i.e., reduced volume of new HO, both at and away from flare-up sites). Therefore, both chronic daily and flare-up dosing	palovarotene to inhibit overactivation of the ALK2 receptor and thereby reduce HO volumes. Despite the limitations of these data overall (as discussed above and in additional detail below), the Agency has ultimately concluded that the potential benefits of palovarotene for reducing HO volume in patients with FOP outweigh the known and potential risks associated with this drug, particularly given the progressive and debilitating nature of FOP and the unmet medical need in the FOP patient population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	appear to be important components of the overall palovarotene dosing regimen to support efficacy. However, these findings rely on an unverifiable assumption that no other unmeasured confounding factors mainly related to the use of an external control group could have substantially impacted the study results. When an external control is used, there will be a lack of assurance of comparability between treated and untreated subjects given the lack of randomization. Compared to Study 301, NHS subjects were older and had more severe disease severity at baseline. The review team performed various analyses to assess the impact of baseline imbalances in selected covariates. These analyses suggested that the observed difference in the primary outcome in treated and untreated subjects was unlikely due to any systematic difference in the measured baseline factors that are deemed clinically important. Some NHS subjects were enrolled into Study 301 or other intervention studies after some period of observation in the NHS. The possibility of subject selection bias could not be ruled out. However, sensitivity analyses conducted by the applicant and the review team suggested that it is unlikely that the potential selection bias drove the conclusion of a treatment effect. Treatment with palovarotene showed an effect in decreasing the volume of new heterotopic ossification in patients with FOP. The reduction in HO volume provides a clinically meaningful benefit to patients because of the irreversible, progressive nature of the disease. It is recognized that progressive accumulation of HO over time is associated with worsening mobility. Therefore treatment with palovarotene which leads to small changes in HO volume in short term trials, is expected to slow the progression of the disease with the potential to preserve joint range of motion and movement for longer periods of time.	

Risk and risk management	Safety risks associated with palovarotene include those directly associated with the retinoid drug class of medications, as well as risks seen specifically in patients with FOP. Boxed Warnings and Warnings and Precautions contained in the retinoid class product labels include teratogenicity, psychiatric disorders, pseudotumor cerebri, serious skin reactions, pancreatitis, lipid abnormalities (hypertriglyceridemia), hearing impairment, hepatotoxicity, inflammatory bowel disease, skeletal abnormalities (including decreased bone mineral density, hyperostosis and premature epiphyseal closure), and vision impairment. Regarding the risk of premature epiphyseal closure (PPC) seen with the retinoid class, treatment with palovarotene caused PPC in subjects with open growth plates despite lower, weight-based dosing in younger patients. Potentially, this could result in significant adverse effects on growth, especially in younger age groups. The Applicant proposed an indication that would allow most patients with at least 80% skeletal maturity (bone age 8 years in girls and 10 years in boys) to receive palovarotene for the prevention of HO despite the risk of PPC, given the severity of the disease. Palovarotene is a known teratogen as a member of the retinoid class; however, there are only rare reports of pregnancy in women with FOP, and consensus guidelines urge serious consideration before women with FOP attempt pregnancy given that pregnancy is extremely high risk. As a precaution, clinical studies of palovarotene have included frequent pregnancy testing and contraception requirements, and to date, there are no reports of pregnancy or in utero exposure to palovarotene. The Applicant proposed a Boxed Warning in labeling to mitigate this risk. Regarding effects on bone mineral content, bone density and fractures, results of a biomechanical CT and vertebral fracture analysis suggest that palovarotene treatment may be associated with decreases in vertebral bone strength, BMC and BMD, and a higher risk of new onset morphometric vertebral fractures. These effects are consistent with some data involving other retinoids and are consistent with the BMD findings by DXA in osteochondroma subjects. However, the data do not establish a definitive causal association due to the post	Palovarotene is associated with multiple significant risks related to its mechanism of action as a retinoid derivative (e.g., teratogenicity, premature epiphyseal closure, etc.), as well as specific risks associated with its use in patients with FOP (e.g., potential increase in incidence of “flares”). The Applicant proposed enhanced labeling to communicate the risks of teratogenicity and PPC in a Boxed Warning, Warning and Precaution, and contraindication of pregnancy, along with educational materials for prescribers, pharmacists, patients and their caregivers. To mitigate the risk of PPC associated with palovarotene use in growing children, the Applicant proposed a lower, weight-based dosing regimen for pediatric subjects and to limit treatment to pediatric patients who have achieved at least 80% of their final adult height, which is approximately >8 years of age in girls and >10 years in boys. The potential risk of increase in disease “flares” with flare-based treatment needs to be further investigated in the postmarket setting to better clarify this potential risk. A PMR to assess long term safety of palovarotene in pediatric and adult patients enrolled into an observational safety study will be implemented to further assess the risk of HO flares and other risks associated with palovarotene, including PPC, bone fractures, and any pregnancy data available. This will be a long-term post marketing observational safety study in at least 100 patients with FOP, 50% of whom are pediatric patients and 2/3 of whom are treated with palovarotene, will be required in the form of a PMR.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hoc nature of the analyses, use of nonvalidated measures and differing amounts of follow-up data between the nonrandomized populations of Study 301 and the NHS. There is an unresolved concern that palovarotene could increase the incidence of HO flare-up episodes in patients with FOP. Flare-up episodes were reported by a greater proportion of palovarotene-treated subjects in Study 301 compared to untreated subjects in the NHS and at a higher frequency (0.15 versus 0.07 per month), and within Study 301, new flare-ups were reported at higher rates during cycles of flare-up treatment (0.33 new events per month versus 0.12 per month during chronic dosing). Most of the new flare-ups occurred at sites distant from the initial site. Similarly, data from Studies 201/202 showed higher rates of new flare-ups during flare-up dosing with palovarotene 10/5 mg or 20/10 mg (0.18 to 0.29/month) in comparison to placebo or NHS untreated subjects (0.11 to 0.12/month), or chronic 5 mg dosing (0.10/month). However, flare-ups appear to have been under-reported in the NHS, so the validity of these findings remains unclear. Additional postmarketing data will be necessary to better determine the potential for palovarotene treatment to worsen HO formation and thereby worsen disease severity.	

Abbreviations: ACVR1, activin A type I receptor; ALK2, activin receptor-like kinase 2; BMC, bone marrow concentrate; BMD, bone mineral density; CAJIS, cumulative analogue joint involvement scale; CT, computed tomography; DXA, dual x-ray absorptiometry; FDA, Food and Drug Administration; FOP, fibrodysplasia ossificans progressive; FOP-PFQ, FOP physical function questionnaire; HO, heterotrophic ossification; NDA, new drug application; NHS, natural history study; PPC, premature epiphyseal closure; PMR, post marketing requirements; PROMIS, patient reported outcomes measurement information system; R206H, arginine 206 to histidine; RAR, retinoic acid receptor; RARy, retinoic acid receptor gamma; ROM, range of motion

2.2. Conclusions Regarding Benefit-Risk

Fibrodysplasia ossificans progressiva is a rare and severely disabling disease caused by a gain-of-function mutation in the activin A type I receptor ACVR1 (ALK2), which renders ALK2 constitutively active to bone morphogenetic protein ligands, drives ectopic chondrogenesis and osteogenesis, and leads to HO in connective tissue, joints, and muscle.

Palovarotene is an orally bioavailable RAR γ selective agonist (retinoid) that appears to interfere with ALK2-mediated bone formation indirectly by dampening bone morphogenetic protein signaling, leading to blockade of chondrogenic and osteogenic differentiation, reprogramming of progenitor cells into nonskeletal lineage, and prevention of abnormal endochondral bone formation in animal models.

Approximately 800 confirmed cases of FOP have been reported globally. Patients with FOP develop extraskkeletal bone formation in muscles, tendons, and ligaments known as HO beginning in early childhood. HO formation is episodic, with some events starting with soft tissue inflammation (flare-up). The accumulation of extraskkeletal bone is cumulative and irreversible, causing restriction of movement, deformities, and severe disability. Chronic complications may include chest wall deformity (thoracic insufficiency syndrome), ankyloses of the temporo-mandibular joints resulting in severe tooth decay and malnutrition, and localized skin breakdown. Most patients require mobility assistance by their 20's due to HO around the hips, and survival is shortened (median 56 years), usually by cardio-respiratory failure and pneumonia.

Patients with FOP face a high unmet medical need, as there are no approved therapies and no therapies have been shown to treat or slow progression of HO formation and reduce overall disease burden. Current conventional therapy for FOP is aimed at symptom relief by decreasing inflammation and chronic pain. Symptomatic treatment with high dose steroids is often used to treat HO symptom "flares," however, short term burst steroid therapy has no benefit in reducing the overall burden of HO or slowing disease progression. Attempts at surgical excision of lesions usually leads to reactivation of disease and new HO.

Assessment of Effectiveness of Palovarotene in the Treatment of FOP

In support of this application, the Applicant conducted a phase 2, randomized, placebo-controlled, double-blind study in patients with FOP (Study 201), with a phase 2 open-label single arm extension study (Study 202), and a single arm, open-label, externally controlled phase 3 study (Study 301). Studies 201 and 202 Parts A and B evaluated short term treatment of acute flare-ups with assessments of new HO at the flare-up site, while Study 202 Parts B and C evaluated chronic plus flare-up treatment with assessments of new whole-body HO. The external control group for Study 301 was a 36-month NHS, also conducted by the Applicant, in pediatric and adult patients with FOP. The proposed dosing regimen includes chronic daily treatment (5 mg), with higher dose treatment (20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks, with extension if needed, referred to as "20/10 mg" or "flare dosing") during symptomatic "flare-up" episodes (all proposed doses are adjusted based on body weight in skeletally immature patients under 18 years of age). This dosing regimen was used in Study 301 and in Part C of Study 202 (202C).

The primary endpoint for Studies 201/202A/202B was the incidence of new HO at the flare-up site 12 weeks after flare-up initiation. The primary endpoint for Study 202C and Study 301 was annualized change in new whole-body HO volume, and the key secondary endpoint was proportion of subjects with any new HO. Volume of HO is a clinically meaningful endpoint because patients with FOP are known to have progressive, irreversible accumulation of heterotopic ossification as the hallmark of the disease. HO volume was assessed by whole-body CT scans based on prespecified body regions using appropriate adjudication. CT scans from Study 202 B/C were read by the same imaging contractor as in Study 301 and the NHS; however, there were differences in the precise methodology for assessing changes in HO by whole-body computed tomography (WBCT) between the phase 2 and phase 3 studies.

Additional secondary endpoints in Study 301 included the number of body regions with new HO, the proportion of subjects reporting flare-ups, and the rate of flare-ups per subject-month. Exploratory endpoints included change from baseline in ROM assessed by CAJIS for FOP, change from baseline in physical function using age-appropriate forms of the FOP-PFQ (FOP Physical Function Questionnaire), and change from baseline in physical and mental function using age-appropriate forms of the PROMIS Global Health Scale.

Both Studies 201/202 and Study 301 failed to meet the prespecified primary efficacy endpoints. In addition, none of the secondary or exploratory endpoints in Study 301 showed statistically significant differences between palovarotene-treated and untreated/control subjects and thus did not provide supportive evidence of efficacy of this product in the treatment of FOP. Due to failure to achieve the prespecified primary endpoints, the Applicant relied on post hoc analyses from Study 301 to support the effectiveness of palovarotene. The following key efficacy issues were identified during the review.

Appropriateness of Reliance on Post Hoc Analyses To Support Efficacy

Post hoc analyses are generally considered hypothesis generating and are usually not appropriate for providing substantial evidence of effectiveness. However, in this specific setting, the Agency acknowledged that the prespecified primary analysis for Study 301 had an inherent bias against palovarotene. Therefore, the FDA statistical team considered that it was reasonable to look at alternative, more appropriate analyses. Various post hoc analyses performed by the review team suggested that there may be a nominally significant difference between the primary outcomes of Study 301 and NHS subjects when more appropriate analyses are used. The consistency of results from the analyses performed by the FDA review team supports the robustness of this conclusion. However, this finding relies on an unverifiable assumption that no other unmeasured confounding factors could have substantially impacted the study results.

Because Study 201 did not meet its primary endpoint, the Applicant also used post hoc analyses to evaluate the efficacy of palovarotene “flare-up only” dosing (i.e., treatment of flares without chronic daily therapy) with respect to development of new HO at flare-up sites. Pooled data from Studies 201, 202A/B and the NHS showed trends of reduced volume of new HO at flare-up sites in treated compared to untreated FOP patients. However, the data were inconclusive due to differences in study design and patient populations across studies, lack of control and randomization involved in most of the data, and lack of positive dose response across various flare-up treatment regimens. Thus, the evidence to support the efficacy of a “flare-up only” dosing regimen was not considered sufficient to justify approval of flare-based dosing without background chronic daily therapy.

Data from Study 301 and the NHS support the conclusion that chronic daily dosing (i.e., palovarotene 5 mg daily), in addition to flare-based dosing, is needed to achieve benefit. Specifically, these data demonstrate that subjects who reported no flare-ups developed relatively small quantities of new whole-body HO, either with or without chronic daily treatment. By comparison, subjects who experienced flare-ups generally developed large quantities of new whole-body HO without chronic daily therapy and derived greater benefit from palovarotene (i.e., reduced volume of new HO, both at and away from flare-up sites). Therefore, both chronic daily and flare-up dosing appear to be important components of the overall palovarotene dosing regimen to support efficacy.

Use of an External Control Group (NHS) for Evaluation of Efficacy of the Chronic/Flare-Up Regimen

When an external control is used, there will be a lack of assurance of comparability between treated and untreated subjects given the lack of randomization. Compared to Study 301, NHS subjects were older and had more severe disease severity at baseline. The FDA statistical team performed various analyses to assess the impact of baseline imbalances in selected covariates.

FDA's analyses suggested that the observed difference in the primary outcome in treated and untreated subjects was unlikely due to any systematic difference in the measured baseline factors that are deemed clinically important. However, these analyses could not address the impact of unmeasured and unknown confounding.

Nevertheless, findings from within-subject comparisons for subjects who restarted treatment after dose interruption, along with findings from subjects who transferred from the NHS to Study 301, may complement the between-subject comparisons and seem supportive of a drug effect. How much the within-subject comparisons could mitigate the concern for unmeasured and unknown confounding depends on the extent to which the natural progression of the disease would be expected to be relatively stable within the two-year study period. However, it should be acknowledged that the impact of disease progression on the within-subject comparisons could not be fully characterized without a randomized concurrent untreated control.

Furthermore, some NHS subjects were enrolled into Study 301 or other intervention studies after some period of observation in the NHS. The possibility of subject selection bias could not be ruled out. Regardless, sensitivity analyses conducted by the Applicant and FDA suggested that it is unlikely that potential selection bias drove the conclusion of a positive treatment effect.

Uncertain Clinical Implications of Negative New HO Volume Data

Based on the natural history of disease progression in FOP, in which HO accumulates gradually over time, the clinical significance of negative HO volumes (as assessed by whole body CT) remains unclear. Whether negative HO volume represents "noise" on CT imaging due to inflammation occurring at an initial flare-up site, or a natural process of bone consolidation as the transition from cartilaginous tissue to bone occurs, or some other physiologic mechanism, remains unknown. The clinical implication of occurrence of negative HO, if any, may continue to be monitored in the postmarketing setting.

Consistency of Phase 2 and Phase 3 Whole-Body HO Data

As treatment regimens and study endpoints evolved, chronic daily dosing was introduced in Study 202 Part B, but flare-up dosing was not used extensively in this part based on relatively strict protocol criteria to define flare-up events. In contrast, all flare-up symptoms were treated with flare-up dosing in Study 202 Part C and Study 301. Despite use of the same treatment protocol, mean new whole-body HO volume was greater in Study 202C compared to Study 301, and not substantially different from untreated NHS subjects. Although Study 202 was not powered to demonstrate efficacy via comparisons to the NHS, consistency of these data with Study 301 data has been a review issue. With additional information and analyses, FDA reviewers have now concluded that the different outcomes of Studies 301 and 202C do not present a major concern due to differences in the respective study populations, new analyses of 202C versus NHS data and favorable data in 202C subjects who restarted treatment following the extended treatment pause.

Conclusions on Effectiveness

Overall, the Agency has concluded that the Applicant demonstrated substantial evidence of the effectiveness of palovarotene to reduce new HO volume in pediatric and adult patients with FOP but has not provided substantial evidence to support an indication for the prevention of HO in patients with FOP. Reductions in volume of HO is a clinically meaningful endpoint because patients with FOP are known to have progressive accumulation of heterotopic ossification. Based on data from the natural history study, there is a correlation between total body HO volume with increasing CAJIS score which indicates increasing restrictions on movement and joint range of motion.

Substantial evidence of the effectiveness of palovarotene in the treatment of FOP was provided by data from the phase 3 Study 301, using the NHS as an external control. Using the linear mixed effects model, the mean annualized new HO was 9.4 cm³/year in subjects receiving palovarotene (study 301) and 20.3 cm³/year in the NHS with a treatment difference of 10.9 cm³/year (95% CI: -21.2, -0.6). Confirmatory evidence of the efficacy of palovarotene to reduce new HO volume was provided from similar data seen in the phase 2 study, Study 202C, which used the same dosing regimen and protocol design as Study 301. Using the matched propensity score analysis, the mean annualized new HO volume was 16.1 cm³/year in subjects receiving palovarotene (study 202C) compared with 28.4 cm³/year in untreated subjects from the NHS with a treatment difference of 12.3 cm³/year. Additional, but not as robust, supportive evidence was provided by data from Studies 201 and 202A/B, as well as by nonclinical data in a FOP mouse model that supports the mechanism of action of palovarotene to inhibit overactivation of the ALK2 receptor and thereby reduce HO formation. The efficacy of palovarotene treatment in patients with FOP appears to be present only when chronic daily dosing is combined with flare-based dosing, when needed, for flare-up episodes.

Risk Assessment of Palovarotene in the Treatment of FOP

Safety risks associated with palovarotene include those directly associated with the retinoid drug class of medications, as well as risks seen specifically in patients with FOP. Boxed Warnings and Warnings and Precautions contained in the retinoid class product labels include teratogenicity, psychiatric disorders, pseudotumor cerebri, serious skin reactions, pancreatitis, lipid abnormalities (hypertriglyceridemia), hearing impairment, hepatotoxicity, inflammatory bowel

disease, skeletal abnormalities (including decreased bone mineral density, hyperostosis and premature epiphyseal closure), and vision impairment.

Regarding the risk of PPC seen with the retinoid class, treatment with palovarotene caused PPC in subjects with open growth plates despite lower, weight-based dosing in younger patients. Potentially, this could result in significant adverse effects on growth, especially in younger age groups. The Applicant proposed an indication that would allow most patients with at least 80% skeletal maturity (bone age 8 years in girls and 10 years in boys) to receive palovarotene for the prevention of HO despite the risk of PPC, given the severity of the disease.

Palovarotene is a known teratogen as a member of the retinoid class; however, there are only rare reports of pregnancy in women with FOP, and consensus guidelines urge serious consideration before women with FOP attempt pregnancy given that pregnancy is extremely high risk. As a precaution, clinical studies of palovarotene have included frequent pregnancy testing and contraception requirements, and to date, there are no reports of pregnancy or in utero exposure to palovarotene. The Applicant proposed a Boxed Warning in labeling to mitigate this risk.

Regarding effects on bone mineral content, bone density and fractures, results of a biomechanical CT and vertebral fracture analysis suggest that palovarotene treatment may be associated with decreases in vertebral bone strength, BMC and BMD, and a higher risk of new onset morphometric vertebral fractures. These effects are consistent with some data involving other retinoids and are consistent with the BMD findings by DXA in osteochondroma subjects. However, the data do not establish a definitive causal association due to the post hoc nature of the analyses, use of nonvalidated measures and differing amounts of follow-up data between the nonrandomized populations of Study 301 and the NHS.

There is an unresolved concern that palovarotene could increase the incidence of HO flare-up episodes in patients with FOP. Flare-up episodes were reported by a greater proportion of palovarotene-treated subjects in Study 301 compared to untreated subjects in the NHS and at a higher frequency (0.15 versus 0.07 per month), and within Study 301, new flare-ups were reported at higher rates during cycles of flare-up treatment (0.33 new events per month versus 0.12 per month during chronic dosing). Most of the new flare-ups occurred at sites distant from the initial site. Similarly, data from Studies 201/202 showed higher rates of new flare-ups during flare-up dosing with palovarotene 10/5 mg or 20/10 mg (0.18 to 0.29/month) in comparison to placebo or NHS untreated subjects (0.11 to 0.12/month), or chronic 5 mg dosing (0.10/month).

However, flare-ups appear to have been under-reported in the NHS, so the validity of these findings remains unclear. Additional postmarketing data will be necessary to better determine the potential for palovarotene treatment to worsen HO formation and thereby worsen disease severity.

A PMR to assess long term safety of palovarotene in pediatric and adult patients enrolled into an observational safety study will be implemented to further assess the risk of HO flares and other risks associated with palovarotene, including PPC, bone fractures, and any pregnancy data available.

Conclusions on Risk

The risks associated with palovarotene use include risks associated with drugs in the retinoid class (e.g., teratogenicity, PPC with the potential for disproportionate growth, fractures, among others) and potential risks specific to patients with FOP (e.g., increase in HO flares with use of

the medication). These risks will be clearly identified in product labeling and further addressed through a PMR for a long-term observational study in children and adults with FOP that will collect data on PPC, fractures, rates of flare episodes, and pregnancy outcomes data. To promote adequate capture of pregnancy outcome data should pregnancy occur during palovarotene use, enhanced pharmacovigilance will also be requested.

Conclusions on Benefit-Risk Assessment

Overall, the Agency has concluded that the Applicant demonstrated substantial evidence of the effectiveness of palovarotene to reduce the volume of new HO in pediatric and adult patients with FOP when chronic daily dosing is combined with flare-based dosing, when needed, for flare-up episodes. The Applicant has not provided substantial evidence for palovarotene's efficacy to prevent HO formation in FOP, the originally proposed indication.

Palovarotene represents the first pharmacologic agent for the treatment of any manifestation of FOP. Treatment with palovarotene showed an effect in decreasing the volume of new HO in patients with FOP. The reduction in HO volume provides a clinically meaningful benefit to patients because of the irreversible, progressive nature of the disease. It is recognized that progressive accumulation of HO is associated with worsening of a patient's movement and mobility. Therefore, treatment with palovarotene which leads to small changes in HO volume in short term trials, is expected to slow the progression of the disease with the potential to preserve joint range of motion and movement for a longer period of time. While there are risks associated with use of palovarotene, these can be managed through product labeling along with further assessment in a postmarketing safety study.

In conclusion, despite the limitations of the efficacy data presented by the Applicant (e.g., efficacy based on post hoc analyses, use of an external control, differences in design across studies, etc.), the Agency has ultimately concluded that the benefits of palovarotene in pediatric and adult patients with FOP outweigh the risks associated with this drug, particularly given the progressive and debilitating nature of FOP and the unmet medical need in the FOP patient population.

II. Interdisciplinary Assessment

3. Introduction

The key review issues relevant to benefit and risk are identified in Section [3.1](#) below and discussed in detail in Sections [6.3](#) and [7.7](#), respectively.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Phase 3: Appropriateness of Reliance on Post Hoc Analyses to Support Efficacy

3.1.1.2. Phase 3: Use of an External Control Group (NHS) for Evaluation of Efficacy of the Chronic/Flare-Up Regimen

3.1.1.3. Uncertain Clinical Implications of Negative New HO Volume Data

3.1.1.4. Consistency of Phase 2 and Phase 3 Whole-Body HO Data

3.1.2. Key Safety Review Issues

3.1.2.1. Increased Rate of Reported Flare-Ups During Palovarotene Treatment; Potential for Retinoid-Induced Myositis

3.1.2.2. Premature Epiphyseal Closure in Growing Children With Potential for Adverse Effects on Growth

3.1.2.3. Embryo-Fetal Toxicity (Retinoid Class Effect)

3.1.2.4. Apparent Adverse Effects of Palovarotene on Vertebral Bone Mineral Density, Bone Mineral Content, and Fractures

3.2. Approach to the Clinical Review

Table 3. Clinical Studies Submitted in Support of Efficacy and/or Safety Determinations¹ for Palovarotene

Study Identifier (NCT#)	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ²	Number of Centers and Countries
PVO-1A-201 NCT 02190747	Subjects at least 6 years of age with clinically diagnosed classic FOP, symptomatic onset of a distinct flare-up in an appendicular area (upper or lower extremity), abdomen or chest within 7 days	Phase 2 Randomized Double-blind Placebo control Multicenter Adaptive dose finding	Treatment of FOP flare-ups: Cohort 1: Randomized 3:1 PVO 10 mg QD for 2 weeks, then 5 mg QD for 4 weeks (n=12); or Placebo for 6 weeks (n=4) Cohort 2: Randomized 3:3:2 PVO 10 mg QD for 2 weeks, then 5 mg for 4 weeks (n=9); PVO 5 mg QD for 2 weeks, then 2.5 mg QD for 4 weeks (n=9); or placebo for 6 weeks (n=6) Total # treated: 40 Placebo (10 subjects) Palovarotene 5/2.5 mg (9 subjects) Palovarotene 10/5 mg (21 subjects) Weight based dosing for skeletally immature subjects	<u>Primary:</u> Percentage of subject responders, defined by no or minimal new HO (3 or less on 0-6 scale) at the flare-up site versus baseline as assessed by plain radiograph at week 6 <u>Secondary</u> Proportion of subjects with new HO at flare-up site at week 12 Volume of new HO at flare-up site at week 12 Soft tissue edema (MRI) Range of motion Pain, swelling:	Planned: 40 Actual: 40	2 centers in US 1 center in France 1 center in UK
PVO-1A-202 Part A NCT 02279095	Subjects from Study PVO-1A-201	Phase 2 open-label extension of Study PVO-1A-201 single arm	Treatment of up to 2 new flare-ups: Treatment of up to 2 new flare-ups:	<u>Primary:</u> Percentage of subject responders as	Planned: 40 Actual: 40	Centers: 4 Countries: 3

Study Identifier (NCT#)	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ²	Number of Centers and Countries
			Palovarotene 10 mg QD for 2 weeks, then 5 mg QD for 4 weeks Weight-based dosing Duration of treatment (each flare-up): 6 weeks	defined by no or minimal new HO at the original flare-up site compared with baseline as assessed by plain radiographs at the follow-up visit. Percentage of subject responders as defined by no or minimal new HO at up to two new, distinct flare-up sites compared with baseline as assessed by low-dose CT scan at Flare- up Week 6. <u>Secondary:</u> Volume of new HO at flare-up site at Week 12 by CT scan See footnotes²		

Study Identifier (NCT#)	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ²	Number of Centers and Countries
PVO-1A-202 Part B	Subjects from Study PVO-1A-201 and up to 20 additional Adult Cohort subjects	Control type: No control (single arm) Randomization: none Open-label	Palovarotene dose: <u>Adult Cohort</u> (chronic/flare-up regimen): 5 mg QD for up to 24 months, with dose escalation for flare-up treatment to 20 mg QD for 4 weeks, then 10 mg QD for 8 weeks (total of 12 weeks or until flareup resolution if treatment extended beyond 12 weeks). <u>Pediatric Cohort</u> (flareup regimen only): same as flare-up dosing in the Adult Cohort except dosing is weight-adjusted. Number treated: 52 (34 from PVO-1A-202 Part A and 18 new) Duration: 12 weeks up to 24 mo	<u>Primary:</u> Proportion of flare-ups with no new HO ("responders") at Week 12. <u>Secondary:</u> Volume of new HO at flare-up sites at Week 12 Volume of new HO by whole-body (less head) CT at Month 12 (Adult Cohort) See footnotes³	Planned: 60 Actual: 54 (2 subjects untreated)	2 centers in US 1 center in France 1 center in UK
PVO-1A-202 Part C	Subjects from Study PVO-1A-202 Part B	Control type: No control (single arm) Randomization: none Open-label	Palovarotene dose: All subjects receive chronic/flare-up regimen (weight-adjusted for skeletally immature subjects). Number treated: 46 (all continuing from PVO-1A-202 Part B) Duration: Up to 36 mo	<u>Primary:</u> Annualized change in new HO volume as assessed by low dose WBCT scan, excluding head. <u>Secondary:</u> See footnotes⁴	Planned: 48 Actual: 46	Centers: 4 Countries: 3

Study Identifier (NCT#)	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ²	Number of Centers and Countries
PVO-1A-301 NCT 03312634	Adult and pediatric subjects ≥4 years of age with FOP	Control type: Historical control Randomization: none Open-label	Chronic/flare-up regimen: 5 mg QD, with dose escalation for flare-up treatment to 20 mg QD for 4 weeks, then 10 mg QD for 8 weeks (total of 12 weeks; may be extended by 4-week intervals until flare-up resolves). Restart for new flare-up or significant trauma Weight-based dosing for skeletally immature subjects according to 3 categories (20 to <40 kg, 40 to <60 kg, and ≥60 kg). Number treated: 107 Duration: Up to 48 months	<u>Primary:</u> Annualized change in new HO volume as assessed by low-dose WBCT, excluding head <u>Secondary:</u> See footnotes ⁵	Planned: 110 Actual: 107	Centers: 16 Countries: 11

Source: Clinical Study Reports and adsl.xpt, and Clinical Reviewer

¹ Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

² Follow-up Component: Proportion of subjects across the seven HO scores (0 to 6) at the original flare-up site as assessed by plain radiographs at the follow-up visit; Flare-up Component: Proportion of subjects across the seven HO scores (0 to 6) at the new, distinct flare-up site as assessed by low-dose CT scan (or plain radiographs for subjects unable to undergo CT scan) at Flare-up Weeks 6 and 12 (Days 42 and 84). Additional secondary endpoints can be found in 202 CSR page 121.

³ Flare-up based treatment: Change from baseline in amount of bone formation (volume) as assessed by low-dose CT scan (or area by plain radiographs for subjects unable to undergo CT scan) at Flare-up Week 12/EOT (Day 84/EOT). Chronic treatment: Change from baseline in whole-body burden of HO as assessed by low-dose WBCT scan, excluding head, at Study Months 12 and 24. Additional secondary endpoints can be found in 202 CSR page 122.

⁴ Percent of subjects with new HO at Months 12, 24, 36, and overall; Change from baseline in ROM as assessed by CAJIS at Months 6, 12, 18, 24, 30, and 36; Change from baseline in physical function using age-appropriate forms of the FOP-PFQ at Months 6, 12, 18, 24, 30, and 36; Change from baseline in physical and mental function for subjects ≥15 years old and mental function for subjects <15 years old using age appropriate forms of the PROMIS Global Health Scale at Months 6, 12, 18, 24, 30, and 36.

⁵ Proportion of subjects with any new HO at Month 12; Number of body regions with new HO at Month 12; Proportion of subjects reporting flare-ups at Month 12; Flare-up rate per subject-month exposure through Month 24.

Abbreviations: CAJIS, cumulative analogue joint involvement scale; CSR, clinical study report; CT, computed tomography; EOT, end of treatment; FOP, fibrodysplasia ossificans progressiva; FOP PFQ, fibrodysplasia ossificans progressiva physical function questionnaire; HO, heterotopic ossification; mo, month(s); MRI, magnetic resonance imaging; n, number of subjects; NCT, national clinical trial; PROMIS, patient reported outcomes measurement information system; PVO, palovarotene; QD, once daily; ROM, range of motion; UK, United Kingdom; US, United States; WBCT, whole-body computed tomography

4. Patient Experience Data

The fibrodysplasia ossificans progressive (FOP) natural history study (NHS, Study PVO-1A-001) and the palovarotene intervention studies included patient-reported outcome measures related to physical function and a clinician-reported index of range of motion. Changes in these measures were found to correlate with more advanced age of FOP patients and with more severe disease but were insufficiently sensitive to show changes over the time scale of the clinical studies, with or without treatment. For this review, these data provided general supportive information but were not central to the regulatory decision.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☒	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☒	Natural history studies	NHS data are discussed in Sections 6.2 , 6.3 , 7.6 and 7.7 of this review.
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☒	Patient-focused drug development meeting summary report	Held at FDA May 2019
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

The original NDA included a series of in vitro and in vivo pharmacodynamic data generated by the Applicant and from published research studies. These nonclinical studies were reviewed in detail and included in the first cycle Integrated Review (December 23, 2022). In this review cycle, no new nonclinical data were submitted. Rather, the NDA resubmission contained a ‘white paper’ that discussed the available nonclinical pharmacology data in the context of supportive mechanistic evidence of benefit.

In Vitro Studies Supporting the Mechanism of Action

In patients with FOP, abnormal bone formation, including ectopic chondrogenesis, osteogenesis, and heterotrophic ossification, are driven by a gain-of-function mutation in the bone morphogenetic protein (BMP) type I receptor activin receptor-like kinase 2 (ALK2) (ACVR1) and overactivation of downstream SMAD signaling proteins. The rationale for evaluating palovarotene for FOP is based on the knowledge that retinoid acid receptor (RAR) activity is an inhibitor of chondrogenesis (Pacifci et al. 1980; Hoffman et al. 2006; Shore and Kaplan 2010; Kaplan et al. 2012). In in vitro studies, palovarotene demonstrated binding and functional selectivity towards retinoic acid receptor gamma (RAR γ), which is expressed in chondrogenic cells and chondrocytes. Pretreatment with palovarotene inhibited BMP-induced chondrogenic differentiation and led to the loss of skeletogenic potential of the chondrogenic progenitor cells (ADTC5) and skeletal stem cells (bone marrow derived mesenchymal stem cells), respectively. Similar findings were recapitulated in a BMP-treated human fibroblast cell line carrying the human relevant gain-of-function R206H mutation of the ALK2 receptor. In these cell lines, palovarotene dampened the BMP/ALK2 downstream signaling pathway by reducing the levels of phosphorylated Smad effector proteins (Smad1, Smad5 and Smad8). The effect of palovarotene on Smad proteins was abrogated in the presence of proteasome inhibitors, suggesting that palovarotene might promote proteasome-mediated degradation of Smad proteins.

In Vivo Nonclinical Data Showing Proof of Concept

Proof of concept in vivo studies with palovarotene were conducted in various injury-induced heterotopic ossification (HO) and FOP mice models, including BMP-2 implant, transgenic mice expressing constitutively active ALK2^{Q207D} mutant and the human relevant ALK2^{R206H} mutation (Shimono et al. 2011; Chakkalakal et al. 2012; Chakkalakal et al. 2016). Across these animal models, treatment with palovarotene led to dose-dependent reductions in the volume of new HO at the site of injury (muscle) compared to vehicle treated animals. These results from the injury-based ALK2^{Q207D} mouse were used to develop a dose-response model that suggested a maximally effective mouse dose of 6 mg/kg (20 mg human equivalent dose by body surface area comparison) may provide greater efficacy in inhibiting HO than the chronic maintenance dose, and these data served as a basis for the selection of the human flare-up initiation dose. Further analysis of the effectiveness of palovarotene at various time points following the induction of

HO showed that the HO inhibitory effect of palovarotene only covered a narrow window of treatment, primarily during pre-treatment prior to Day 1 up to Day 3 postinjury, but effectiveness was lower if treatment initiation was delayed until 7 days postinjury. This observation suggests that palovarotene might block HO by preventing chondrogenic cell differentiation and cartilage formation (pre- and chondrogenic proliferative phase) but not the ossification phase when bone is already present. Palovarotene also improved joint mobility, and reduced mast cell infiltration and fibroproliferative responses at the site of injury. In addition to the injury-based models described above, palovarotene blocked noninjury (spontaneously) induced HO formation in the fore- and hind-limbs of pups when palovarotene was administered orally to nursing transgenic $Prrx1^{R206H}$ mice, which carry the R206H mutation in $Prrx1^+$ skeletal progenitor cells (Chakkalakal et al. 2016).

Overall, the information available from published studies and Applicant-provided nonclinical data support the purported mechanism of action: by selective binding to $RAR\gamma$, palovarotene inhibits chondrogenic differentiation by decreasing the overactivated ALK2 signaling pathway through the reduction in phosphorylation of downstream effectors (Smad1/5/8). As such, palovarotene may reduce the volume of new HO in humans, consistent with the robust and consistent nonclinical observations in animal models of FOP.

Nevertheless, the utility of the nonclinical data to provide confirmatory evidence of clinical effectiveness on its own is limited by several factors, including species-specific differences and study design issues ([Table 5](#)). Human FOP is a complex, heterogeneous disease without a well understood pathology, and flare-ups are located in various tissues (muscles, tendons, or ligaments). On the other hand, the injury-based animal models used in this program lack heterogeneity in disease expression, as the animals only had a single injury site at a specified location that was standardized across the treatment groups. Moreover, the disease mechanism between animal and human FOP is different as the BMP-implantation model is created with supraphysiological rhBMP-2 levels. The genetic model bearing the $ALK2^{Q207D}$ mutation is not found naturally in FOP patients. The $ALK2^{R206H}$ and $Prrx1^{R206H}$ mice do carry the most common mutation found in human FOP and do display many of the phenotypic features of FOP patients (hind limb digit malformation, joint fusions, and extensive HO development), but these conditional knock-in models only allow the study of one gene. Furthermore, treatment with palovarotene was initiated at an early age in all transgenic mouse studies (birth to 2-month), corresponding to the period of maximal skeletal growth and maturation, and generally translating to pre-pubertal human childhood but not to sexually and skeletally mature adults. It is also worth noting that the timing for initiation of treatment varies between the nonclinical and clinical studies. In animal models, dosing with palovarotene was initiated prior to or immediately following injury (aligned with the catabolic and chondrogenic phases), whereas flare-up dosing in the clinical trials was targeted after the initiation of the catabolic and chondrogenesis process. Comparisons of nonclinical pharmacology models and study data are shown in [Table 5](#) below.

Table 5. Comparison of Nonclinical FOP Disease Models With Human FOP

Parameters	Mouse Model				Human FOP
	BMP-2 Implant	ALK2 ^{Q207D}	ALK2 ^{R206H}	Prrx1 ^{R206H}	
ACVR1 (R206H) mutation	–	–	Global	Limbs	Global
HO induction	BMP2 implant	Mutation ALK2 ^{Q207D}	Mutation ALK2 ^{R206H}	Mutation ALK2 ^{R206H}	Mutation ALK2 ^{R206H}
	Single site (injury)	Single site (injury)	Single site (injury)	Limited site (spontaneous)	Multiple sites (spontaneous/injury)
HED	0.6 to 19 mg	1 to 15 mg	3 to 19 mg	7 mg	Chronic: 5 mg, Flare-up: 20/10 mg
Age	2 months	16 days	1 months	Birth	Variable
Treatment (post-HO)	Immediately	3 days	Same day	Birth (nursing)	Variable
Treatment duration	12 days	15 days	14 days	30 days	Chronic/flareup regimen
Pharmacologic endpoint	HO vol. (implant site)	HO vol. (muscle)	HO vol. (muscle), mobility, histology	WBCT, mobility, histology	HO volume (WBCT)

Source: Compiled by the pharmacology/toxicology primary reviewer

Abbreviations: ACVR1, activin A type I receptor; ALK2, activin receptor-like kinase 2; BMP-2, bone morphogenetic protein-2; BV/TV, bone volume/total volume; FOP, fibrodysplasia ossificans progressiva; HED, human equivalent dose; HO, heterotrophic ossification; IM, intramuscular; mCT, microcomputed tomography; Prrx1, paired-related homeobox protein 1; SC, subcutaneous; WBCT, whole body computed tomography

5.2. Clinical Pharmacology/Pharmacokinetics

Details regarding the clinical pharmacology characterization of palovarotene can be found in the Integrated Review in DARRTS dated December 23, 2022. No new clinical pharmacology data were submitted in this Application. [Table 6](#) summarized the clinical pharmacology and pharmacokinetic (PK) data related to palovarotene.

Table 6. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Retinoid
Mechanism of action	Binding of palovarotene to RAR γ antagonizes bone morphogenetic protein (BMP) / activin receptor-like kinase 2 (ALK2) downstream signaling by reducing BMP-mothers against decapentaplegic homolog (SMAD) 1/5/8 phosphorylation, potentially by promoting proteasome-mediated SMAD degradation. This leads to blockade of chondrogenesis, osteogenic differentiation, and the reduction in new volume of heterotopic ossification.
Active moieties	Parent drug palovarotene is the active moiety. The pharmacological activity of two metabolites, M3 and M4b, are approximately 1.7% and 4.2% as active as the parent drug based on an in vitro RAR γ transactivation assay.
QT prolongation	At a dose of 2.5 times the maximum recommended dose, palovarotene does not prolong the QT interval to any clinically relevant extent.
	General Information
Bioanalysis	Two validated LC-MS/MS methods were used to determine plasma and seminal fluid concentrations of palovarotene. The established benchtop stability, storage stability and freeze-thaw stability cover the maximum storage periods for corresponding clinical studies.
Healthy subjects versus patients	The PK data of healthy volunteers (N=238), FOP patients (N=123), chronic obstructive pulmonary disease (COPD) patients (N=198) and multiple osteochondromas (MO) patients (N=18) were included in population PK analyses. There was no evidence that disease status has a clinically relevant influence on the PK of palovarotene.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	Drug exposure in FOP patients (Study PVO-1A-301): Parameter (Mean $\pm$ SD) Chronic dose, 5 mg once daily (QD) (N=41) or weight-based equivalent dose (N=29) AUC _{0-t} : 264 $\pm$ 98.4 ng*h/mL C _{max} : 40.6 $\pm$ 16.2 ng/mL CL/F: 17.8 $\pm$ 8.64 L/h Flare-up dose, 10 mg QD (N=26) or weight-based equivalent dose (N=22) AUC _{0-t} : 540 $\pm$ 226 ng*h/mL C _{max} : 78.4 $\pm$ 33.3 ng/mL CL/F: 17.0 $\pm$ 7.80 L/h Flare-up dose, 20 mg QD (N=24) or weight-based equivalent dose (N=29)

Characteristic	Drug Information
	AUC _{0-t} : 1060±449 ng*h/mL C _{max} : 165±72.7 ng/mL CL/F: 16.5±7.43 L/h
Range of effective dose(s) or exposure	Lowest studied flare-up dosing: 5 mg QD for 14 days followed by 2.5 mg QD for 28 days (5/2.5 mg regimen) Highest studied flare-up dosing: 20 mg QD for 28 days followed by 10 mg QD for 56 days (20/10 mg regimen)
Maximally tolerated dose or exposure	Exposure of palovarotene in healthy adults following a single dose of 50 mg in fed state: AUC _{0-inf} = 2370±662 ng*h/mL; C _{max} = 328±92.2 ng/mL
Dose proportionality	From Population PK analyses, palovarotene exhibited linear PK with dose-proportional increases in plasma exposure from 0.02 to 50 mg following QD dosing.
Accumulation	The accumulation ratios of palovarotene 5 mg QD, 10 mg QD and 20 mg QD over 28 days range from 1.04 – 1.16.
Time to achieve steady state	Based on trough palovarotene plasma concentrations, steady state is attained by Day 3 following QD dosing.
Bridge between to-be-marketed and clinical trial/study formulations	The proposed to-be-marketed (TBM) formulation is the same as the formulation used in FOP clinical studies. No bioequivalence (BE) study is needed to bridge the TBM formulation to the phase 3 trial formulation.
	Absorption
Bioavailability	Absolute or relative bioavailability of palovarotene has not been determined.
T _{max}	The median T _{max} in healthy adults under fasting state is 2 hours and a high fat meal delays median T _{max} to 4 hours.
Food effect (fed/fasted) Geometric least square mean and 90% CI	Compared with administration under fasted conditions, a high-fat, high-caloric breakfast increased exposure and delayed absorption of palovarotene: AUC _{0-∞} 139.7% (129.6%, 150.5%) C _{max} 116.5% (101.2%, 134.1%) T _{max} is delayed from 2 hours to 4 hours Plasma palovarotene AUC and C _{max} were comparable when either swallowed whole or the contents sprinkled onto applesauce following a high-fat, high-caloric breakfast.
	Distribution
Volume of distribution	Healthy adults (20 mg single dose): apparent volume of distribution of 237±90 L FOP patients: 131±87 L following chronic dosing 5 mg QD or equivalent (weight-based); 106±53 L following flare-up 10 mg QD or equivalent (weight-based) dosing; 109±61 L following flare-up 20 mg QD or equivalent (weight-based) dosing. Following oral dose 20 mg QD for 5 days, palovarotene was detected in seminal samples at 3 hours post dose on Day 5; the mean semen concentration was 8.84 ng/mL and the mean semen/plasma concentration ratio was 0.0273.
Plasma protein binding	97.9% to 99.6%
Drug as substrate of transporters	In vitro data shows that palovarotene is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3 and OCT1. Substrate interaction assessments with renal transporters OAT1, OAT3, OCT2, MATE1 and MATE2-K transporters were not conducted because only 3.2% of dose was recovered in urine.

Characteristic	Drug Information
	Elimination
Mass balance results	Palovarotene and its four known major metabolites accounted for 40% of the total systemic exposure in plasma [palovarotene (14%), M3 (10%), M4b (7%), M2 (5%), and M4a (4%) based on AUC]. The pharmacological activity of M3 and M4b is approximately 1.7% and 4.2% of the activity of the parent drug based on an in vitro RAR γ transactivation assay. Over 13 days post dose, 97.1% and 3.2% radioactivity were recovered in feces and urine, respectively. Palovarotene and its four known major metabolites accounted for 67.2% of the dose in feces [M4a and M4b (32.2%), M2 (20.2%), M3 (12.4%), palovarotene (2.4%)].
Clearance	The apparent total body clearance (CL/F) across dose levels and across studies estimated by population PK analysis is 19.9 L/h. In FOP patients, the CL/F values across dose levels are 17.8 L/h (chronic dose), 17.0 L/h (low flare-up dose), and 16.5 L/h (high flare-up dose).
Half-life	In healthy subjects receiving 20 mg QD for 14 days, the mean steady-state T _{1/2} was 8.7 hours. In FOP patients, the terminal T _{1/2} values across dose levels are 4.9 h (chronic dose 5 mg QD or equivalent weight-based), 4.4 h (high flare-up dose 20 mg or equivalent weight-based), and 4.3 h (low flare-up dose 10 mg or equivalent weight-based).
Metabolic pathway(s)	Palovarotene is extensively metabolized by CYP3A4, 2C8 and 2C19, but primarily by CYP3A4. Five metabolites, M1 (6,7-dihydroxy), M2 (6-hydroxy), M3 (7-hydroxy), M4a (6-oxo), and M4b (7-oxo) were observed for palovarotene in clinical studies.
Primary excretion pathways (% dose)	97.1% and 3.2% radioactivity were recovered in feces and urine, respectively.
	Intrinsic Factors and Specific Populations
Body weight	Based on population PK analysis, AUC and C _{max} were 8% and 12% higher for a 51 kg subject and 18% and 26% lower for a 98 kg compared to a 70 kg subject, respectively.
Age	According to population PK analysis of PK data from subjects aged 2-85 years, there was no evidence that age has a clinically relevant influence on the PK of palovarotene.
Renal impairment	A PK study was not conducted in subjects with renal impairment because only 3% of radioactivity was recovered in urine and there were no case reports of renal impairment in FOP patients enrolled in clinical studies. Population PK analysis suggests that serum creatinine or renal impairment status are not significant covariates on palovarotene PK.
Hepatic impairment	A postmarketing requirement (PMR) will be issued to conduct a hepatic impairment study and evaluate the effect of moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) on the PK of palovarotene to inform the dosing recommendations in subjects with hepatic impairment. Per the Applicant, hepatic impairment was not reported in the FOP patients enrolled in the natural history study submitted with this application (N ~100). Population PK analyses suggest that there was no significant difference in the PK of palovarotene in subjects with mild (Child-Pugh A, N=66) hepatic impairment compared to subjects with normal hepatic function. The effect of moderate (Child-Pugh B) hepatic impairment on the PK of palovarotene is not conclusive based on the population PK analyses as only a limited number of subjects (N=5) with moderate hepatic impairment. The effect of severe (Child-Pugh C) hepatic impairment on the PK of palovarotene has not been evaluated. Given that 97.1% of radioactivity was recovered in feces in the mass balance study and that palovarotene is extensively metabolized by CYP enzymes, palovarotene exposure may be increased in subjects with moderate or severe hepatic impairment.

Characteristic	Drug Information
	<i>Drug Interaction Liability (Drug as Perpetrator)</i>
Inhibition/induction of metabolism	At clinically relevant plasma concentration, palovarotene did not significantly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Palovarotene did not pose a clinically relevant risk with respect to the inhibition of UGT enzymes. Palovarotene at clinically relevant concentration (0.32μM) did not induce CYP1A2, CYP2C8, CYP2C9 and CYP2C19 but induced CYP3A4 and CYP2B6 mRNA expression by 3.8-5.0 folds and 1.8-2.4 folds in vitro, respectively. In clinical studies, palovarotene 20 mg QD did not induce CYP3A4-mediated metabolism of co-administered midazolam.
Inhibition/induction of transporter systems	Palovarotene is not an inhibitor of P-gp, OAT1, OAT3, OCT2, MATE1, or MATE2-K transporters. In vitro studies showed that palovarotene inhibited BCRP, OATP1B1, OATP1B3, OCT1, and bile salt export pump (BSEP) transporter with IC50 values of 9.69μM, 1.83μM, >3μM, >3μM, and 14.7μM, respectively. At the maximum recommended dose (20 mg QD), palovarotene does not pose a clinically relevant risk with respect to the inhibition of OATP1B1, OATP1B3, OCT1, or BSEP transporters.

Source: Drafted by clinical pharmacology reviewer Peng Zou while employed at the FDA.

Abbreviations: ALK2, activin receptor-like kinase 2; AUC, area under the concentration-time curve; BCRP, breast cancer resistance protein; BE, bioequivalence; BMP, bone morphogenetic protein; BSEP, bile salt export pump; CI, confidence interval; CL/F, oral clearance; C_{max}, maximum observed concentration; COPD, chronic obstructive pulmonary disease; CYP, cytochrome P450; DDI, drug-drug interaction; EPC, established pharmacologic class; FOP, fibrodysplasia ossificans progressiva; LC-MS/MS, liquid chromatography with tandem mass spectrometry; M1, 6,7-dihydroxy metabolite of palovarotene; M2, 6-hydroxy metabolite of palovarotene; M3, 7-hydroxy metabolite of palovarotene; M4a, 6-oxo metabolite of palovarotene; M4b, 7-oxo metabolite of palovarotene; M5, 8-carboxyl β-glucuronide of palovarotene; MATE1, multidrug and toxin extrusion 1; MATE2-K, multidrug and toxin extrusion 2-K; MO, multiple osteochondromas; mRNA, messenger ribonucleic acid; N, number of subjects; OAT1, organic anion transporter 1; OAT3, organic anion transporter 3; OATP1B1, organic anion transporting polypeptide B1; OATP1B3, organic anion transporting polypeptide B3; OCT1, organic cation transporter 1; OCT2, organic cation transporter 1; PBPK, physiological based pharmacokinetics; PK, pharmacokinetics; PMR, post marketing requirement; popPK, population pharmacokinetics; PVO, palovarotene; QD, once daily; RARγ, retinoic acid receptor gamma; SD, standard deviation; SMAD, suppressors of mothers against decapentaplegic homolog; TBM, proposed to-be-marketed; T_{max}, time to maximum observed concentration

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

Regarding details regarding the dose selection for the phase 3 study and exposure-response (E-R) relationship for efficacy, please refer to the Integrated Review in DARRTS dated December 23, 2022. The following key review question regarding dosing of palovarotene has been evaluated under this review:

Is body weight-based dosing necessary for all patients or only for pediatric patients <14 years of age?

In the NDA submission, the Applicant proposed to apply body weight-based dosing for pediatric patients who are less than 14 years old, and to use the fixed dosing for patients who are ≥ 14 years of age (i.e., chronic daily dosing of 5 mg once daily (QD) and flare-up dosing of 20/10 mg). In the advisory committee meeting briefing document, the Applicant updated their position to apply body weight-based dosing for all patients, including adults, adolescents, and children ([Table 7](#)). According to this new proposal, patients who weigh less than 60 kg and are 14 years and older would receive lower doses than the doses investigated in Study 301 ([Table 7](#)). Both proposals allow for a reduction in dosage to lower levels if palovarotene is not well tolerated.

Table 7. Comparison of Applicant Proposed Palovarotene Doses (Flare-Up High/Flare-Up Low/Daily Dosing)

Age Cut-Off	Body Weight Category	Original NDA Proposed Dose (Weight-Based Dosing for <14 Years old)	Updated Proposed Dose (Weight-Based Dosing for All Patients)
<14 Years	10 kg to 19.9 kg	10/5/2.5 mg	10/5/2.5 mg
	20 kg to 39.9 kg	12.5/6/3 mg	12.5/6/3 mg
	40 kg to 59.9 kg	15/7.5/4 mg	15/7.5/4 mg
	≥ 60 kg	20/10/5 mg	20/10/5 mg
≥ 14 Years	20 kg to 39.9 kg	20/10/5 mg	12.5/6/3 mg
	40 kg to 59.9 kg	20/10/5 mg	15/7.5/4 mg
	≥ 60 kg	20/10/5 mg	20/10/5 mg

Source: Compiled by FDA Clinical Pharmacology Primary Reviewer
Abbreviations: FDA, Food and Drug Administration; NDA, new drug application

Applicant's Justification

The Applicant's justification for body weight-based dosing for all patients is that the population PK analysis revealed a significant impact of body weight on the PK of palovarotene. Specifically, it was observed that there is an association between body weight and the exposure of palovarotene, with exposure increasing as weight decreases at the same administered dose. This finding highlights the importance of considering body weight as a significant covariate when determining the appropriate dosing regimen for palovarotene.

FDA Review Conclusion

The review team recommends weight-based dosing only for patients <14 years (see [Table 8](#) and notes below for further details).

Table 8. Efficacy and Safety Assessment of the Original NDA Proposed Dose (Weight-Based Dosing for <14 Years old) and Updated Proposed Dose (Weight-Based Dosing for All Patients) for Patients ≥14 Years of Age With Body Weight Less Than 60 kg

Topic	Original NDA Proposed Dose (Weight-Based Dosing for <14 Years old)	Updated Proposed Dose (Weight-Based Dosing for All Patients)
Difference between the two dosing proposals	Patients ≥14 years 20 kg to 39.9 kg: 20/10/5 mg (flare-up high/flare-up low/ daily dosing) 40 kg to 59.9 kg: 20/10/5 mg	Patients ≥14 years 20 kg to 39.9 kg: 12.5/6/3 mg 40 kg to 59.9 kg: 15/7.5/4 mg
Efficacy	The effectiveness of palovarotene with this dosing regimen has been demonstrated, as it aligns with the regimen used in the phase 3 trial ¹ .	Patients who are ≥14 years with weight <60 kg (~48% patients in Study 301) will receive a lower dose than the dose investigated in Study 301. There is no well-established E-R relationship on change from baseline in heterotopic ossification volume (HO volume)³ to support the efficacy of lower doses.
Safety	PPC risk: No PPC observed in patients aged 14-18 years under this dosing regimen. Dose reduction due to tolerability: our analysis² of the data from Study PVO-1A-301 suggests that patients weighing 40 kg to 60 kg are likely to experience a similar rate of dose reduction, regardless of the body-weight dosing regimen. The incidence of drug-induced flare-up: No exposure-response established	Compared to the dosing regimen tested in Study PVO-1A-301, this new dosing regimen is anticipated to result in lower drug exposures in patients who are 14 years and older with body weight <60 kg, and thus could potentially improve the safety profiles of palovarotene in these patients. However, there is no evidence suggesting that this dosing regimen can effectively reduce the occurrence of AE such as PPC risk, need for dose reduction or the incidence of drug-induced flare-up.

Source: FDA Clinical Pharmacology Primary Reviewer

¹ See [Note 1](#) below for the details of the analyses

² See [Note 2](#) below for the details of the analyses

³ See [Note 3](#) below for the details of the analyses

Abbreviations: AE, adverse event; E-R, exposure response; FDA, Food and Drug Administration; HO, heterotopic ossification; NDA, new drug application; PPC, premature epiphyseal closure; PVO, palovarotene

Note 1

The proposed weight-based dosing only for pediatric subjects who are younger than 14 years is the same dosing regimen used in Study 301 for patients younger than 14 years of age. In this study, patients ≥18 years of age received orally administered 5 mg palovarotene once daily and 20 mg/10 mg dosing at the time of flare-up, whereas a weight-adjusted dose was used for skeletally immature patients under 18 years of age. The study results show that 20 out of 23 pediatric subjects aged 14 to 18 years had bone closure and received the flat adult doses. Three (3) out of 23 pediatric subjects aged 14 to 18 years had partial closure at some checking

point of the treatments but received adult doses during most of the treatment period. Nonetheless, no premature epiphyseal closure (PPC) incidence was observed in these patients. Overall, there were no events of PPC in 38 subjects aged 14 to 18 years in Studies 301 and 202B/C. Overall, although more than 40% of patients had a dose reduction due to tolerability during the high dose flare-up treatment, the impact of dose reduction on efficacy has been reflected in the phase 3 study results.

Note 2

Out of 70 subjects who have the classic R206H mutation and received high flare-up doses in Study 301, a similar dose reduction rate was observed between body weight-based dosing (38%) and flat dosing (45%) in patients with body weight >40 kg. Three subjects who were ≥14 years old and with body weight <40 kg received high flare-up doses (~8% of 70 subjects) and all of them encountered dose reduction at some point of high dose flare-up treatments ([Table 9](#)). However, there was no direct evidence to indicate that drug reduction was due to higher drug exposure, as the E-R relationship for tolerability is unknown. Lastly, the current efficacy data from the phase 3 study included patients with dose reductions.

Table 9. Study 301: Dose Reduction Rate in Subjects Receiving High Flare-Up Doses

Age Cut-Off	BW Category	Studied Flare-Up Dose	Dose Reduction Rate
<14 Years	10 kg to 19.9 kg	10 mg	13% (1/8)
	20 kg to 39.9 kg	12.5 mg	55% (12/22)
	40 kg to 59.9 kg	15 mg	38% (3/8)
≥14 Years	20 kg to 39.9 kg	20 mg	100% (3/3)
	40 kg to 59.9 kg	20 mg	46% (6/13)
	≥60 kg	20 mg	44% (7/16)

Source: FDA Clinical Pharmacology Primary Reviewer

Abbreviations: BW, body weight; FDA, Food and Drug Administration

Note 3

Large variability was observed in the E-R analyses with the efficacy endpoint of HO volume; thus, the review team considered no obvious E-R relationship for palovarotene and new HO volume up to 12 months. In addition, no E-R relationship could be detected for palovarotene exposure and proportion of patients with PPC events for subjects greater than 8/10 years of age (details can be found on in the Integrated Review in DARRTS dated December 23, 2022).

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Phase 3: Study PVO-1A-301

6.2.1.1. Design, Study 301

Study PVO-1A-301 (Study 301) was a phase 3 study with the primary objective of evaluating the efficacy of the chronic/flare-up dosing regimen of palovarotene to decrease new HO development in adult and pediatric patients with FOP. The Applicant chose to use untreated patients from the NHS as an external control arm. The single-arm design of Study 301, with use

of the NHS as an external control group, raises issues of the comparability of these studies/groups, which are discussed in detail in Section [6.3.2](#).

6.2.1.2. Eligibility Criteria, Study 301

Adult and pediatric patients ≥ 4 years of age with a clinical diagnosis of FOP and no flare-up symptoms within the previous 4 weeks were eligible to enroll in Study 301. To facilitate comparisons with the NHS, most of the subjects (i.e., the Principal Analysis population) were required to have the classic R206H mutation and no prior exposure to palovarotene. There were exclusion criteria based on known retinoid safety issues, including pregnancy and increased suicide risk.

6.2.1.3. Statistical Analysis Plan, Study 301

The primary endpoint was the annualized change in new HO volume as measured by whole body computed tomography (WBCT). The prespecified primary analysis for the primary endpoint was based on a Bayesian compound Poisson model. The Bayesian compound model was estimated based on the number of regions with positive new HO and the average growth per region where positive new HO occurred since the previous WBCT scan. Negative new HO values were set to 0 in the analyses. The prespecified analysis included a square root transformation of each change in HO since the previous scan by region. The Applicant chose this statistical model “to more appropriately accommodate the high degree of variability in the volume of new HO assessed by WBCT.” The square root transformation was included in the Bayesian compound Poisson analysis because simulations suggested that if palovarotene reduced the probability of new HO as much or more than it reduced the new HO volume given new HO, introducing a square root transformation could marginally increase power. Additionally, square root transformation would likely decrease the variance of the endpoint by shrinking any extremely large values of new HO volume.

The trial crossed the futility boundary at the second interim analysis and the study was paused for dosing. However, additional post hoc analyses, including the same Bayesian compound model but without square root transformation and a frequentist weighted linear mixed effects (wLME) model, appeared to show evidence of potentially clinically meaningful benefit of palovarotene. Upon review of the additional post hoc analyses, the data monitoring committee (DMC) noted that the impact of the prespecified square root transformation was unexpectedly large and appeared to have moved the statistical conclusion from significant therapeutic benefit to showing futility of the treatment. The DMC concluded that “the dilemma created by these highly disparate results precludes a confident conclusion about futility.” Dosing in Study 301 was thus allowed to resume, and the DMC recommended that “palovarotene be continued in skeletally mature children ≥ 14 years” (due to the risk of PPC in skeletally immature individuals).

In the previous NDA review cycle, the post hoc analyses performed by the Applicant and the additional analyses requested by the FDA review team have been summarized in detail (refer to Integrated Review in DARRTS dated December 23, 2022).

6.2.1.4. Results of Analyses, Study 301

Results from the Applicant’s prespecified analyses and post hoc analyses were extensively discussed in the previous NDA review (December 23, 2022). Some main results were included in this review to facilitate discussion. The appropriateness of these post hoc analyses to support efficacy will be further discussed in the review issue section [below](#). For purposes of this discussion, the “pre-pause” period refers to the period from study start to dosing interruptions (due to partial clinical hold and/or crossing the futility boundary), the “post-pause treatment” period refers to the time after subjects restarted palovarotene treatment, the “interruption” period spans the time between the last scan prior to dosing interruption and the first scan after restart, and the “post off-treatment” period refers to the period from first WBCT scan off treatment secondary to dosing interruption to last subjects last visit for subjects who remained off treatment.

Primary Efficacy Endpoint Results

The primary efficacy analyses represent data collected in the “pre-pause” period during which scans were scheduled at 6-month intervals, while scans were scheduled at 12-month intervals in the NHS. [Table 10](#) summarizes the number of the principal full analysis set (P-FAS) subjects with evaluable computed tomography (CT) data at each visit during this period.

Table 10. Studies 301 and NHS: Number of Subjects With Whole Body HO Data in Pre-Pause Period by Visit (P-FAS)

Visit	Study 301 Palovarotene	NHS Control
Screening	97	101
Month 6	94	2
Month 12	93	90
Month 18	64	11
Month 24	1	63
Month 30	0	9
Month 36	0	33
Month 42	0	4
Month 48	0	0

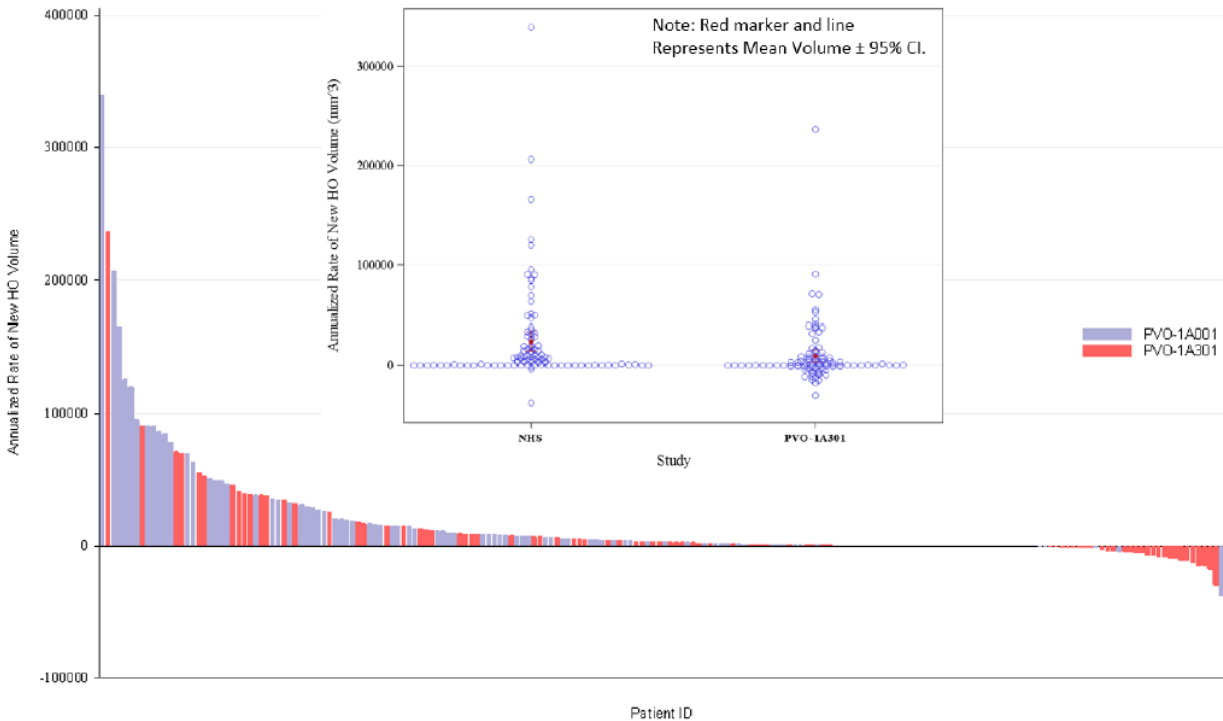
Source: FDA statistical reviewer; some subjects had some assessments outside the scheduled window

Data as of the following cutoff dates: in Study 301, December 4, 2019, for <14 y/o and January 24, 2020, for ≥14 y/o; in NHS, February 28, 2020

Abbreviations: FDA, Food and Drug Administration; HO, heterotopic ossification; NHS, natural history study; P-FAS, principal full analysis set; y/o, year(s) old

[Figure 1](#) shows the distribution of individual subject annualized new HO volume in the “Pre-pause” period of these studies, illustrating the variability of the data. On the left side of the plot, representing subjects with large HO increases, there is a preponderance of untreated subjects (in gray); 4 NHS subjects developed new HO at rates >100 cm³/year, versus one palovarotene recipient in Study 301 (in red). On the right side, numerous subjects, mostly in Study 301, had net negative new HO.

Figure 1. Study 301 and NHS: Individual Subject Annualized New HO Volume Distribution for Palovarotene-Treated and Untreated Subjects (P-FAS)



Source: Study 301 Appendix 16.1.13.5 final IA3, Figure S14.1.1
Abbreviations: CI, confidence interval; HO, heterotopic ossification; NHS, natural history study; P-FAS, principal full analysis set; PVO, palovarotene

Using the Applicant’s pre-specified Bayesian analysis, the primary endpoint of annualized new HO failed to demonstrate efficacy of palovarotene with adequate posterior probability (Table 11). The posterior probability of a reduction in annualized new HO was 0.65. The 95 percent credible interval of the between study ratio of annualized new HO was (0.74, 1.22) (Table 11).

Table 11. Studies 301 and NHS: Ratio of Annualized New HO Volume

Study 301 Palovarotene	NHS Control	Median Ratio (95% CI)	Pr(Ratio <1)
N=97	N=101	0.95 (0.74, 1.22)	0.65

Source: CSR
Prespecified primary analysis method; change in HO values since previous scan were square root-transformed by body region and negative new HO volumes were set to 0. 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).
Abbreviations: CI, confidence interval; CSR, clinical study report; HO, heterotopic ossification; N, number of subjects; NHS, natural history study

Applicant’s Post Hoc Bayesian Analyses

The Applicant’s post hoc Bayesian analyses based on the same model but without square root transformation supported the efficacy of palovarotene with a high posterior probability of reduction (>0.99) in annualized new HO in Study 301 subjects compared with NHS subjects (Table 12). The Applicant’s analyses with additional covariates yielded similar results. The FDA review team was able to replicate these results.

Table 12. Studies 301 and NHS: Ratio of Annualized New HO Volume – Post Hoc Bayesian Analyses

Analysis Method	Median Ratio (95% CI)	Pr(Ratio <1)
No square root transformation	0.64 (0.45, 0.90)	>0.99
No square root transformation, added covariates ^a	0.58 (0.41, 0.82)	>0.999

Source: ISE

^a Covariates: baseline HO divided by baseline age, baseline age, sex, baseline CAJIS, time since last flare-up.

Negative new HO set to zero.

The median ratio is the median of the posterior distribution of the ratio (annualized rate of new HO for subjects in study PVO-1A-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).

Abbreviations: CAJIS, cumulative analogue joint involvement scale; CI, confidence interval; HO, heterotopic ossification; ISE, integrated summary of effectiveness; NHS, natural history study; PVO, palovarotene

The Applicant also conducted a Bayesian analysis with square root transformation but adjusted for the visit schedule (that is, Study 301 visit schedule collapsed into a single Month 12 WBCT to match the timing of the first NHS postbaseline WBCT). The results were also in favor of palovarotene, with a posterior probability of reduction of HO greater than 0.9.

These post hoc analyses suggested that the use of a square root transformation in conjunction with the differential assessment schedule likely contributed to the failure of the prespecified primary analysis.

Applicant's Post Hoc Weighted Linear Mixed Effect Model Analysis

The Applicant's post hoc wLME analysis with baseline annualized HO (calculated as baseline total HO volume divided by baseline age) as the only covariate achieved nominal significance (Table 13). In this analysis, the annualized new HO for each subject was calculated using the change in total HO volume from baseline associated with the longest follow-up divided by the length of follow-up. The length of follow-up varied substantially among subjects and between studies. For example, annualized new HO was based on the Month 18 observation for 66% of subjects in Study 301 and the Month 36 observation for 32% of subjects in the NHS. The wLME model accounted for the various follow-up lengths using a weighted approach. We note that the estimated treatment effect based on various lengths of follow-up could be difficult to interpret without the assumption of a constant rate of change in HO.

Table 13. Studies 301 and NHS: Applicant's wLME Analyses on Annualized New HO at Last Scan

Statistics	Study 301 Palovarotene (N=97)	NHS Control (N=101)
Annualized HO at baseline, mean (SD)	13.4 (13.1)	15.7 (14.0)
Mean annualized new HO, (SE)	9.4 (3.1)	23.7 (4.9)
Median (min, max)	0.4 (-30.2, 237)	6.1 (-37.9, 339)
Mean difference from NHS	-14.3	-
LS mean difference (95% CI)	-10.9 (-21.2, -0.6)	-
Nominal p-value, comparison to NHS	0.039	-

Source: CSR

wLME analyses: subject level random effect included to account for the correlation among repeated measures on the same subject for those who transitioned from NHS to Study 301; No square root transformation, negative new HO included Covariates: annualized HO at baseline calculated by dividing baseline HO by baseline age; response variable- annualized change in HO at last visit.

Abbreviations: CI, confidence interval; CSR, clinical study report; HO, heterotopic ossification; LS, least square; max, maximum; min, minimum; N, number of subjects; NHS, natural history study; SD, standard deviation; SE, standard error; wLME, weighted linear mixed effects

Given that the distribution of annualized new HO is skewed, the Applicant performed sensitivity analyses to investigate the influence of large values on the analyses conclusions. These analyses indicate that the conclusions are not driven by the few extremely large values seen in subjects in the NHS ([Table 41](#) and [Table 42](#) in Appendix).

Subgroup Summary by Sex, Age, Race and Ethnicity

Subgroup summaries indicate a smaller effect size among females and among subjects older than 18 years ([Table 14](#)). This finding may be explained by the smaller annualized growth of new HO in the control group (NHS) subjects in these subgroups. However, it is not possible to rule out that the drug's effect is less in older subjects for whom the disease stage is often more advanced. An explanation for the smaller effect in females is uncertain. Findings from these subgroup analyses should be interpreted with caution because with a smaller number of subjects in each subgroup, the influence of a few large values and imbalances in confounders in the absence of randomization could be greater on the mean difference, compared with analyses based on the overall population.

Table 14. Subgroup Summary on Annualized New HO (cm³/Year) Based on the Pre-Pause Last Scan

Subgroup	Study 301 (N=97)		NHS (N=101)		Difference Mean (SD)
	n	Mean (SD)	n	Mean (SD)	
Sex					
Male	51	8.4 (22.7)	56	31.3 (55.3)	-22.9
Female	46	10.6 (37.3)	45	14.3 (37.7)	-3.7
Age					
≥18	22	8.6 (19.4)	40	10.7 (22.2)	-2.1
<18	75	9.7 (33.)	61	32.3 (58.8)	-22.5
Race					
White	68	10.7 (33.8)	74	24.9 (51.3)	-14.2
Asian	9	5.9 (25.3)	8	1.6 (17.7)	4.3
Black or African American	1	1.6	0	NA	NA
All others including multiple and unknown	19	7.0 (18.9)	19	28.5 (46.6)	-21.5
Ethnicity					
Hispanic or Latino	19	7.1 (18.2)	23	26.2 (40.6)	-19.1
Not Hispanic or Latino	67	9.4 (34.2)	62	24.0 (54.9)	-14.6
Not reported	11	13.8 (22.3)	16	19.0 (33.9)	-5.2

Source: FDA reviewer

Abbreviations: FDA, Food and Drug Administration; HO, heterotopic ossification; N, number of subjects; n, number of subjects in specific subgroup; NA, not applicable; SD, standard deviation

Secondary Efficacy Endpoint Results

The key secondary efficacy endpoint was the proportion of subjects with any new HO at month 12. There was no difference in the proportion of subjects with any new HO (64% in treated subjects, 62% in untreated subjects) at month 12. There was also no difference in the mean (SD) number of body regions with new HO at month 12 [1.3 (1.4) in treated subjects, 1.5 (1.6) in untreated subjects].

Exploratory endpoints included change from baseline in range of motion assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) at month 24, change from baseline in physical function assessed by FOP-FPQ at month 24, and change from baseline in physical and mental function in subjects 15 years and older as assessed by the Patient Reported Outcomes

Measurement Information System (PROMIS) Global Health Scale at month 24. The results do not reveal any significant difference between treated and untreated subjects.

WBCT Data Following Treatment Pause – Study 301

The table [below](#) summarizes WBCT data in Study 301, including available data following the treatment pause. The rate of new HO tended to increase from the pre-pause to dosing interruption period (mean 9.4 to 20.1 cm³/year). In a subgroup of 17 subjects who subsequently restarted treatment, new HO volume was relatively low (7.7 cm³/year), similar to an analogous subgroup in Study 202C. In another subgroup of 16 subjects who did not restart treatment and had available off-treatment data, mean new HO volume in this phase was 15.6 cm³/year, representing an increase from a mean of 2.3 cm³/year in these 16 subjects during the pre-pause Treatment period.

Table 15. Study 301: Annualized New HO Volume by Treatment Phase

Treatment Phase	Pre-Pause Treatment	Interruption	Post-Pause Treatment
N	97	42	17
Time interval (mean months) ^a	15.7	25.4	14.4
Annual new HO volume (cm ³ /year), mean	9.4	20.1	7.7

Source: Table 2 in Response to CRL, February 16, 2023 resubmission M 1.11.4

^a Duration between first and last WBCT scan during the study/phase

Annualized new HO data represents change in volume between first and last WBCT scan in the phase, divided by time interval
Abbreviations: CRL, complete response letter; HO, heterotopic ossification; N, number of subjects; WBCT, whole-body computed tomography

[Table 16](#) and [Figure 2](#) below summarizes WBCT data in Study 301 over the pre-pause treatment period, the dosing interruption period, and the post-pause treatment period for subjects who contributed WBCT data in all three periods. As with [Table 15](#) above, the rate of new HO tended to increase from the pre-pause treatment period to the dosing interruption period, and then decrease during the post-pause treatment period. The FDA review team additionally examined the distribution of the within-subject changes in annualized new HO through the three phases and confirmed that more subjects had increases in annualized new HO in the interruption phase compared to the pre-pause phase, and more subjects had decreases in annualized new HO in the post-pause (restart) phase compared to the interruption phase. It was determined that the observed pattern on the mean annualized new HO was not driven by a few extreme values.

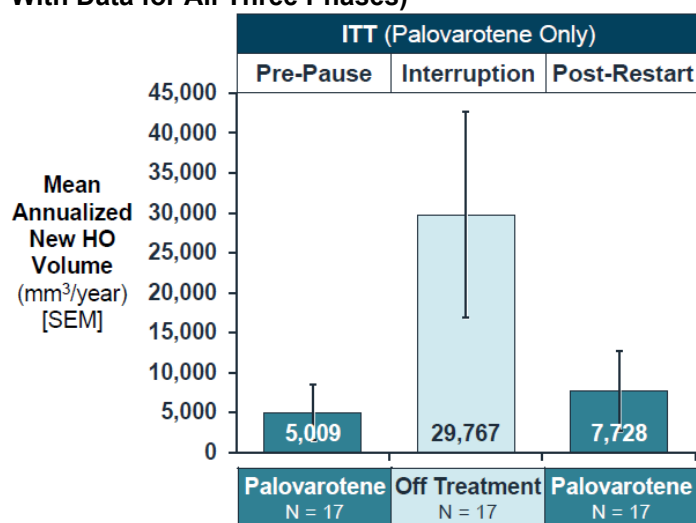
Table 16. Study 301: Annualized New HO Volume by Treatment Phase (Including Only Subjects With Data for All Three Phases)

Treatment Phase	Study 301		
	Pre-Pause Treatment	Interruption	Post-Pause Treatment
N	17	17	17
Annual new HO volume (cm ³ /year), mean	5.0	29.8	7.7

Source: FDA reviewer

Annualized new HO data represents change in volume between first and last WBCT scan in the phase, divided by time interval
Abbreviations: FDA, Food and Drug Administration; HO, heterotopic ossification; N, number of subjects; WBCT, whole-body computed tomography

Figure 2. Study 301: Annualized New HO Volume by Treatment Phase (Including Only Subjects With Data for All Three Phases)



Source: Applicant's AC presentation

Abbreviations: AC, advisory committee; HO, heterotopic ossification; ITT, intent-to-treat; N, number of subjects; SEM, standard error of the mean

6.2.2. Phase 2: Studies PVO-1A-201 and PVO-1A-202A/B/C

6.2.2.1. Design, Studies 201/202

Study 201 was a randomized, double-blind, placebo-controlled study of 40 FOP patients who were experiencing an acute flare-up episode. Subjects were assigned to receive one of two palovarotene regimens, or placebo, for 6 weeks followed by 6 weeks of observation; development of HO at the flare-up site was assessed through week 12. In the open-label extension Study 202, Parts A and B evaluated the treatment of additional flare-up episodes, including the use of new dosing regimens, with similar assessments of HO at the flare-up site at week 12. HO data obtained from a subset of flare-up events reported by untreated patients with FOP in the NHS were used for some comparisons. Please refer to the Integrated Review in DARRTS dated December 23, 2022, for details of dosing regimens and assessments. Similar data, obtained from a subset of flare-up events reported by untreated patients with FOP in the NHS, were used for some comparisons.

Study 202 Parts B and C introduced the palovarotene chronic/flare-up regimen, administered to skeletally mature patients in Part B and then to all patients in Part C, with primary efficacy assessments of whole-body HO by WBCT imaging. The criteria for initiating flare-up dosing changed when subjects transitioned from Study 202 Part B to Part C. Because Study 202C and the separate phase 3 Study 301 began around the same time (2017) and followed an essentially identical protocol for palovarotene treatment, Study 202C is considered relevant confirmatory evidence to the assessment of palovarotene efficacy and is discussed in this subsection. In comparison, flare-up dosing was used more sparingly in Study 202B due to protocol differences with respect to defining flare episodes; the Applicant submitted data to support the view that some subjects were undertreated in Study 202B due to the stricter flare-defining criteria, purportedly impacting efficacy. Upon review by FDA, the validity of this rationale is unclear.

Overall, data from Study 202B are difficult to interpret and are not presented here. Additional details regarding Study 202B were included in the prior NDA review (see Integrated Review in DARRTS dated December 23, 2022).

Study 202C

All subjects in Study 202 Part C transitioned from 202 Part B. Most of the subjects in 202B had initially enrolled in Study 201 at the onset of an acute flare-up and then participated in Study 202 Part A, while an additional group of patients with FOP was newly enrolled and began palovarotene treatment in 202B.

In Study 202C, all subjects (pediatric and adult) received the same regimen as subjects in Study 301:

- Chronic palovarotene 5 mg daily dose
- Flare-up dosing: 20 mg for 4 weeks followed by 10 mg for 8 weeks, extended if needed for persistent symptoms
- Any number of symptoms (≥ 1) was sufficient to begin flare-up dosing
- Intercurrent flare-ups at a different site, or marked worsening at an original site could restart the flare-up dosing cycle
- Reduced doses for skeletally immature subjects
- Protocol amendments (for both Studies 202C and 301) in 2019 added a provision that flare-up dosing could also be triggered by a traumatic event considered likely to result in a flare-up

As in Study 301, all treatment in Study 202C was paused from December 2019 until January 2020, and later restarted in some subjects aged ≥ 14 years.

HO was assessed solely by whole body CT in Study 202C; flare-up site-specific imaging was not conducted. For skeletally mature subjects, who began chronic treatment in 202B, Parts B and C were continuous, with WBCT performed annually starting at Part B baseline. For skeletally immature subjects, WBCT scans were obtained at the initiation of chronic dosing in Part C and then annually. During and after the treatment pause, additional scans were conducted on subjects who restarted palovarotene, through the study conclusion in September 2022.

6.2.2.2. Eligibility Criteria, Studies 201/202

The majority of phase 2 subjects enrolled initially in Study 201 for treatment of an acute flare-up and then continued into Study 202. The initial Study 201 cohort consisted of subjects with clinically diagnosed classic FOP, at least 15 years of age and $\geq 90\%$ skeletal maturity, with symptomatic onset within 7 days of a distinct flare-up and at least two out of 6 specified symptoms (pain, swelling, decreased range of motion (ROM), stiffness, redness, warmth), consistent with their previous flare-ups. Following the initial cohort, enrollment in Study 201 was expanded to children age ≥ 6 years.

An additional group of subjects, whose initial enrollment was in Study 202 Part B, was restricted to subjects who were $\geq 90\%$ skeletally mature, with at least two flare-ups within the past 2 years, but no flare-up symptoms within the past 4 weeks; a confirmed R206H mutation; and a CAJIS

score of 6 to 16. Most of the subjects in this group transferred from the NHS to 202B; any NHS subject meeting these enrollment criteria was eligible for the transfer.

6.2.2.3. Statistical Analysis Plan, Studies 201/202

Flare-Up Site Outcomes (Studies 201, 202 A/B, NHS)

Please see prior Integrated Review in DARRTS dated December 23, 2022, for a discussion of assessments and endpoints related to the treatment of acute flare-ups through Week 12.

Chronic/Flare-Up Dosing Outcomes (Study 202C)

WBCT readings for 202B/C were conducted at the same central imaging facility used for Studies 301 and the NHS, using the same process involving HO measurement in each of nine body regions as described above.

The primary efficacy endpoint for Study 202 at the initiation of Part C (protocol amendment 4) was annualized new HO volume as assessed by low-dose WBCT scan. WBCT readings for 202B/C were conducted at the same central imaging facility used for Studies 301 and the NHS, using the same process involving HO measurement in each of nine body regions as described above. Although Studies 202 and 301 used the same the primary endpoint and imaging methods, Study 202 was an extension study that was not powered to demonstrate efficacy via comparisons to the NHS.

Analyses specific to 202 Part C were conducted on subjects who underwent at least two WBCT scans during Part C, when the first scan was not obtained within 1 month of a flare-up. This provision was intended to align with the enrollment criteria for Study 301 and the NHS and minimize any residual HO accrual that might have resulted from a pre-baseline flare-up.

In the February 16, 2023 NDA resubmission, analyses of data from the “Pre-Pause” treatment period were conducted by the Applicant on the subset of 202C subjects with at least two WBCT scans that were obtained prior to the treatment pause (which occurred from December 2019 to January 2020). Other analysis subgroups included subjects with data from the “Interruption” phase (mostly, but not entirely off-treatment for an interval of variable duration in 2020 to 2022); and subjects who subsequently restarted palovarotene in 2020 to 2021 (referred to as the “Post-Pause” treatment population).

6.2.2.4. Results of Analyses, Studies 201/202

Flare-Up Site Outcomes (Studies 201, 202A/B, NHS)

As described in the previous Integrated Review (dated December 23, 2022), these studies were unable to demonstrate that palovarotene treatment of acute flare-up episodes reduced the incidence of new HO at the flare-up sites, which was the primary endpoint in Study 201. There were trends of reduced volume of new HO at these sites (a secondary endpoint) associated with treatment, but this finding was not definitive due to differences in study designs and treatment regimens, and there was no clear benefit with respect to clinical endpoints such as pain and swelling.

Chronic/Flare-Up Dosing Outcomes (Study 202C)

A total of 46 subjects enrolled in 202C and received treatment for a mean of 20 months in the Pre-pause period, including 36 subjects who required flare-up dosing in this phase. Among 202C subjects, there were 30 who underwent at least two WBCT scans in Part C, wherein the baseline scan was not within 1 month of a flare-up. Among these 30 subjects, there were 23 subjects with ≥ 2 scans prior to dose interruption (Pre-pause population); 19 subjects with ≥ 2 scans during the Interruption period; and 15 subjects with ≥ 2 scans following restart (Post-Pause Treatment population). As in Study 301, no information is available regarding the criteria used for selection of subjects to restart treatment.

Study 202C subjects were 50% female, similar to Study 301 and the NHS. The mean age of the subjects in 202C was 21.1 years, which is older than the mean age of subjects in the NHS (17.5 years) or Study 301 (15.1 years). Whole body HO volume at baseline was also greater in 202C compared to the other studies, likely due to the age differential.

There were no interim analyses planned for Study 202, and the original NDA included only limited descriptive summaries of the Pre-pause 202B/C whole body HO data, which appeared to be inconsistent with findings from Study 301. This raised concerns about consistency of the efficacy data, which were communicated to the Applicant in the Complete Response letter, with requests from FDA for additional analyses of 202 versus NHS data.

The FDA review team requested that the Applicant conduct analyses comparing outcomes of Study 202C subjects with NHS subjects with similar baseline characteristics using propensity score based matching methods. The difference between the annualized new HO of treated subjects in Study 202C and those matched untreated NHS subjects was about 12.3 cm³/year favoring palovarotene, which was consistent with the treatment effect estimated by comparing Study 301 and NHS subjects. The difference did not achieve nominal statistical significance, likely due to the small sample size of matched subjects.

The Applicant also conducted weighted analyses to estimate the average treatment effect among all subjects. It should be noted that the targeted treatment effect based on the Applicant's weighted analysis is different from that of the matched analysis, which estimated the average treatment effect among the treated 21 subjects, a more relevant estimand in this context given the much smaller number of treated subjects. Nevertheless, the two analyses produced estimates of treatment effects in the same direction.

Table 17. Study 202C vs. NHS: Matched and Weighted Analysis of Annualized New HO Volume (cm³/Year)

Analysis Method	Study 202C (N=21)	NHS (N=93*)	Mean Difference	Nominal p-value
Matched analysis				
Matched subjects	19	19		
Mean (SD)	16.1 (55.3)	28.4 (40.3)	-12.3 (15.7)	0.44
Median	0.7	10.4		
Weighted analysis				
N	N=21	N=93		
Mean (SD)	13.7 (53.0)	21.6 (38.2)	-7.9 (12.2)	0.49

Source: Applicant's matched analyses report

Nearest neighbor 1:1 matching with caliper 0.2 for propensity score based on covariates baseline age, month since last flare-up, baseline CAJIS, and baseline total HO divided by age. *: Subjects who transition to Study 202C from NHS was excluded from the NHS population.

Abbreviations: CAJIS, cumulative analogue joint involvement scale; HO, heterotopic ossification; N, number of subjects; NHS, natural history study; SD, standard deviation; vs, versus

Study 202C data from subjects who stopped and re-started palovarotene treatment following the extended treatment pause are informative. The table [below](#) shows summary statistics for the primary endpoint, annualized volume of new HO, in 202C subjects with available data (≥ 2 WBCT scans) during each of the study phases. The rate of new HO in the pre-pause palovarotene treatment phase was 19.0 cm³/year. During the interruption period, this increased to 26.8 cm³/year. Among 15 subjects who restarted palovarotene following the pause in treatment, the rate of new HO in this phase was lower (6.4 cm³/year).

Table 18. Study 202C: Annualized New HO Volume by Treatment Phase

Study Phase	Pre-Pause Treatment	Interruption	Post-Pause Treatment
N	23	19	15
Time interval (mean, months)*	11.7	19.6	11.8
Annual new HO volume (cm ³ /year), mean	19.0	26.8	6.4

Source: Table 2 in Response to CRL, February 16, 2023 resubmission M 1.11.4; Per IR response submitted May 4, 2023, the Pre-Pause Treatment group also includes two subjects (b) (6) whose Part C baseline WBCT was conducted 1 day prior to the first dose under Part C protocol

*Interval between first and last WBCT scan during the study/phase

Annualized new HO data represents change in volume between first and last WBCT scan within the phase, divided by time interval
Abbreviations: CRL, complete response letter; HO, heterotopic ossification; IR, integrated review; N, number of subjects; WBCT, whole-body computed tomography

[Table 19](#) below summarizes WBCT data in Study 202C for the nine subjects who contributed WBCT data in all three phases. As in the overall group (i.e., the table [above](#)), the rate of new HO tended to increase from the pre-pause treatment phase to dosing interruption phase, and then decrease during the post-pause treatment phase.

Table 19. Study 202C: Annualized New HO Volume by Treatment Phase (Including Only Subjects With Data for All Three Phases)

Study Phase	Pre-Pause Treatment	Interruption	Post-Pause Treatment
N	9	9	9
Annual new HO volume (cm ³ /year), mean	23.2	34.0	10.6

Source: FDA reviewer

Annualized new HO data represents change in volume between first and last WBCT scan within the phase, divided by time interval

Abbreviations: FDA, Food and Drug Administration; HO, heterotopic ossification; N, number of subjects; WBCT, whole-body computed tomography

6.3. Key Efficacy Review Issues

6.3.1. Phase 3: Appropriateness of Reliance on Post Hoc Analyses to Support Efficacy

Issue

Appropriateness of reliance on post hoc analyses comparing Study 301 with the NHS to support efficacy.

Background

The prespecified primary analysis for the primary endpoint failed to demonstrate efficacy of palovarotene. The Applicant purported that the failure of the prespecified Bayesian analysis was due to the use of a square root transformation and the difference in WBCT assessment schedules between Study 301 and the NHS. Additional post hoc analyses, including the same Bayesian compound model but without square root transformation and a frequentist weighted linear mixed model, appeared to show evidence of clinical benefit of palovarotene.

Therefore, the submission relies on post hoc analyses to support the efficacy of palovarotene.

Assessment

Post hoc analyses are generally considered hypotheses generating, as they could inflate the chance of a false positive finding and raise concerns of potential bias caused by selection of analyses toward the intended favorable outcome. However, in this specific context, FDA acknowledges that the prespecified primary analysis may not have been the appropriate method for analyzing the primary endpoint for the reasons outlined in detail in the previous NDA review (refer to Integrated Review dated December 23, 2022 in DARRTS). In fact, the prespecified primary analysis had an inherent bias against palovarotene. Acknowledging the limitations of the prespecified analysis, FDA finds it reasonable to consider alternative, more appropriate analyses to assess the evidence of efficacy. Our assessments focus on the robustness and consistency of the conclusions from various post hoc analyses that we considered valid for the primary endpoint under reasonable assumptions.

FDA's Assessment of Post Hoc Bayesian Analysis Without Square Root Transformation

The Applicant's post hoc Bayesian analysis without square root transformation resulted in a high posterior probability in support of efficacy. Adjusting for additional covariates yielded similar results. The Applicant also conducted a post hoc Bayesian analysis with the square root transformation but adjusted for the visit schedule (that is, Study 301 visit schedule collapsed into a single Month 12 WBCT to match the timing of the first NHS postbaseline WBCT). The results were also in favor of palovarotene, with a posterior probability of reduction of HO greater than 0.9. These post hoc analyses indicate that the use of square root transformation in conjunction with the differential assessment schedule contributed to the failure of the prespecified primary analysis.

We note that inference from the Bayesian model could be affected by different specification of prior distributions of the multiple parameters in the model and the results could differ if

influential priors are specified. Additionally, the model targeted only positive changes in HO and set negative changes to zero.

FDA's analyses focused on frequentist methods that directly analyze the annualized new HO for each subject with minimal assumptions.

FDA's Assessment of the Applicant's Post Hoc wLME Analyses

As noted previously, the Applicant's post hoc wLME analysis ([Table 13](#)), based on the CT scan associated with the longest follow-up and without square root transformation, achieved nominal statistical significance. However, results from the Applicant's wLME could be difficult to interpret as the annualized new HO for each subject was based on various length of follow-up.

To assess whether the conclusion is sensitive to the assumption of a constant rate of change, we compared the changes in HO volume between Study 301 and NHS subjects during a 12-month observation period as a landmark analysis given that the majority of the subjects provided 12-month data, which does not rely on assumptions of a constant rate of change. We performed the landmark analyses using different methods for subjects who did not have 12-month data to investigate the consistency of findings. For all these analyses, a robust sandwich variance estimator was used to account for heteroscedasticity in variance.

Results from these landmark analyses with different ways of handling subjects without 12-month data and including different covariates were consistently in favor of palovarotene ([Table 16](#)). Our analyses did not transform negative new HO values to zero.

Table 20. FDA's Landmark Analyses Without Square Root Transformation

Analysis Method ^a /Least Square Mean (SE)	Study 301 (N=97)	NHS (N=101)	Difference (95% CI)	Nominal p-Value
Include only subjects who provided Month 12 HO	93	90		
Covariates 1 ^b	6.7 (2.4)	22.0 (6.4)	-15.3 (-28.5, -2.1)	0.0229
Covariates 2 ^b	6.2 (2.4)	21.8 (6.1)	-15.5 (-28.8, -2.3)	0.0212
Covariates 3 ^b	6.6 (2.5)	22.0 (6.2)	-15.4 (-28.8, -2.0)	0.0243
Include only subjects with HO data up to Month 12	97	92		
Covariates 1	8.1 (2.8)	22.5 (6.3)	-14.3 (-27.8, -0.9)	0.0368
Covariates 2	7.6 (2.8)	22.3 (6.1)	-14.7 (-28.2, -1.3)	0.0321
Covariates 3	8.1 (2.9)	22.7 (6.2)	-14.6 (-28.2, -1.0)	0.0354
Include all subjects using Month 12 data if available ^c	97	101		
Covariates 1	8.1 (2.8)	20.7 (5.3)	-12.5 (-24.0, -1.1)	0.0317
Covariates 2	7.5 (2.9)	21.0 (5.2)	-13.5 (-25.3, -1.7)	0.0249
Covariates 3	7.8 (2.9)	21.7 (5.5)	-13.9 (-26.3, -1.5)	0.0275
Include all subjects with Month 12 and multiple imputation for missing Month 12; with covariates 3	8.3 (3.0)	22.7 (6.3)	-14.4 (-28.1, -0.7)	0.0395

Source: FDA reviewer

^a Generalized estimating equation, no square root transformation, negative new HO included; Endpoint: annualized new HO calculated by dividing change in HO by the follow-up duration

^b 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

^c 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 cm³/year is added to the imputed values in treated subjects.

Abbreviations: CAJIS, cumulative analogue joint involvement scale; CI, confidence interval; FDA, Food and Drug Administration; HO, heterotopic ossification; N, number of subjects; NHS, natural history study; SE, standard error

The FDA review team also conducted analyses based on a random slope model, with change in HO volume from baseline as the response and time from baseline as a continuous variable, adjusting for relevant baseline covariates. Results from these analyses are similar to results of the landmark analyses with generally smaller nominal p-values. We note that the random slope model also assumes a constant rate of change, similar to the Applicant's wLME method, but it is more efficient as it utilizes all available observations rather than just the last observation.

To evaluate whether inference of the treatment effect was affected by the skewness of the distribution or a few extreme large values, the FDA review team performed ordinal logistic regression analyses on annualized new HO. The ordinal logistic regression models the odds of having an annualized new HO larger than an observed value, adjusting for selected covariates and only considering the rank of the outcome, but not the magnitude. This logistic regression model can be viewed as an extension of a nonparametric Wilcoxon rank sum test with covariates adjustment. The results were in favor of palovarotene with high nominal significance, indicating that the conclusion from the Applicant's wLME and FDA's landmark analyses were not likely driven by outliers or skewness of the distribution of the outcome.

Conclusion

The prespecified Bayesian compound Poisson model incorporating square root transformation is not valid and appears to have a bias against palovarotene due to the more frequent assessment in Study 301. FDA finds it reasonable to use valid and more appropriate post hoc analyses to assess evidence of efficacy in this specific setting. Post hoc analyses without the square root transformation conducted by either the Applicant or FDA support that the annualized new HO of Study 301 subjects was lower than that of NHS subjects. These analyses used regression adjustments to account for baseline differences between subjects in the two studies. Analyses methods based on matching and weighting to account for the use of an external control will be described below.

6.3.2. Phase 3: Use of an External Control Group (NHS) for Evaluation of Efficacy of the Chronic/Flare-Up Regimen

Issue

The use of an external control group (NHS subjects) as a comparator.

Background

The Applicant initiated the NHS study in 2014 and enrolled 117 subjects, a relatively large proportion of the known global population of approximately 800 FOP patients. During the subsequent planning of Study 301, despite the FDA recommendation for a randomized, placebo-controlled trial, the Applicant considered that the NHS study population and assessments were suitable to serve as an external control group to compare to Study 301, as the two studies would be conducted at the same centers, with generally consistent standards of care and associated background treatment. In addition, the relative objectivity and blinded assessment of the primary outcome measure—change in HO volume—would minimize the potential for bias. Based on

these considerations and the small number of FOP patients available for recruitment, Study 301 was designed as an open-label, single arm study with the NHS as an external control.

Assessment

Despite the limitations associated with using an external control rather than a randomized concurrent control, FDA recognizes that support for effectiveness can emerge using an externally controlled trial when the following are met (December 2019):

- 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, and
- the results provide compelling evidence of a change in the established progression of disease.

The concomitant treatments in this population are not expected to affect the outcome of interest. The NHS study was performed to characterize the disease process and outcomes. The focus of our assessment was to determine whether the differences between the study populations in the NHS and Study 301 impacted the conclusion regarding efficacy, whether the results are compelling enough to overcome the general concerns of potential confounding factors when using an external control, and if there were impacts on the primary outcome measure from potential selection bias due to differential loss to follow-up between the NHS and Study 301.

FDA's Assessment of Comparability of Study Populations and Potential Selection Bias

The enrollment criteria for the NHS and Study 301 were generally similar. Because the NHS was restricted to subjects with the classic R206H mutation, which represents approximately 97 percent of FOP patients, the P-FAS population of Study 301 excluded a small number of participants with other mutations.

Recruitment of subjects into the NHS and Study 301 was sequential, as NHS enrollment was complete before Study 301 was initiated. All NHS study sites also participated in Study 301, and any NHS subject who met enrollment criteria (e.g., without retinoid-safety-related exclusions) was eligible for this transition. A total of 39 subjects transferred from the NHS into Study 301 and contributed efficacy data to both studies. In addition, eight subjects discontinued the NHS to enroll in Study 201 at the onset of a flare-up, 13 subjects discontinued the NHS to enroll in Study 202B, and 6 subjects discontinued the NHS to enroll in other interventional studies, including for other investigational products for FOP. Given that transfers out of the NHS were voluntary and driven in part by clinical factors that are largely unknown, unmeasured confounding is likely to have occurred. Further, selection bias due to differential loss to follow-up may be of concern if transferring from the NHS to interventional studies was related to disease progression or other outcome-related factors, whereas loss from Study 301 may not be similarly related to such factors, resulting in potential differential capture of outcome between the two studies.

[Table 21](#) presents baseline data for three cohorts within the P-FAS: the 39 transition subjects who contributed efficacy data to both the NHS and Study 301; 62 NHS subjects who did not enroll in Study 301; and 58 subjects in Study 301 who had not participated in the NHS. Transition subjects' data at both NHS baseline and Study 301 baseline (at an average of 2.3 years later) are presented.

As shown, NHS subjects who remained in the NHS were older (mean age of 20.5 years) than subjects who transitioned to Study 301 (mean age of 13.5 years) and other Study 301 subjects (mean age of 14.6 years). Consistent with older age, the NHS-only subjects tended to have more advanced disease, with generally higher whole-body HO volumes, greater number of body regions with HO, and higher scores on CAJIS, indicating more severely impaired range of motion and physical function. Transition subjects reported a higher number of flare-ups prior to NHS enrollment (mean 5.8 within 12 months) than the other groups; however, this observation was primarily driven by two subjects with high numbers of reported flare episodes.

Table 21. NHS, Study 301, and Transition Subjects: Baseline Data (Principal FAS)

Statistics	NHS Only (N=62)	Transition Subjects		Study 301 Only (N=58)
		NHS Data (N=39)	Study 301 Data ^a (N=39)	
Mean age, year	20.5	13.5	15.8	14.6
Sex, male/female (%)	52/48	62/38	62/38	47/53
Race, White/Asian/Other (%)	77/6/17	67/10/23	67/10/23	72/9/19
WBHO volume, cm ³ , mean	378.2	207.9	259.2	212.4
Number of body regions with HO, mean	6.8	6.1	6.4	6.2
Number of flare-ups within 12 months of enrollment, mean	2.4	5.8	1.1	1.7
CAJIS score, mean	13.1	9.6	10.4	9.4

Source: reviewer's analysis.

^a Transition subjects' baseline in NHS and baseline in Study 301 were summarized respectively.

Abbreviations: CAJIS, cumulative analogue involvement scale; FAS, full analysis set; HO, heterotopic ossification; N, number of subjects; NHS, natural history study; WBHO, whole body heterotopic ossification

Assessment of Impact of Subject Difference at Baseline

To assess the impact of subject differences between Study 301 and the NHS, the Applicant conducted sensitivity analyses by adjusting for additional baseline covariates, including the propensity score quartile, and performing matching and weighting based on propensity score among subjects who did not enroll in both the NHS and Study 301 (i.e., nontransition subjects, [Table 22](#)). Results from these analyses did not change the conclusion of the wLME analysis ([Table 13](#)).

Table 22. Propensity Score Matching and Weighting Analysis - Non-Transition Subjects

Analysis Method/Mean	Study 301 (N=58)	NHS (N=61)	Difference	Nominal p-value
Propensity score matching ^a (39 matched)	5.6	24.1	-18.5	<0.05
Unstabilized propensity score weighting	9.5	28.9	-19.4	<0.05
Stabilized propensity weighting	9.5	28.9	-19.4	<0.05

Source: Applicant's matched analysis report.

^a Nearest neighbor, caliper=0.2, covariates (specified by Agency): baseline rate of HO volume, baseline age, sex, months since last flare-up, and baseline CAJIS.

Abbreviations: CAJIS, cumulative analogue involvement scale; HO, heterotopic ossification; N, number of subjects; NHS, natural history study

The FDA review team performed landmark analyses on the P-FAS population using propensity score weighting, matching, and targeted maximum likelihood estimation methods that are used for causal inference for nonrandomized studies. Results from these analyses are also consistent with the wLME analysis ([Table 23](#)). Baseline characteristics achieved reasonable balance after weighting or matching ([Table 24](#) and [Table 25](#)). The FDA review team also examined the impact of different matching algorithms, as well as the impact of including additional available baseline

covariates in the propensity score model such as weight, height, BMI, and baseline total HO (instead of the age standardized total HO), and the results were similar. However, validity of conclusions on treatment effects from these analyses relies on the unverifiable assumption that there are no unknown or unmeasured confounding factors that could impact the difference between Study 301 and NHS subjects. The majority of the subjects in these analyses completed the 12-month follow-up and thus loss to follow-up was less of a concern.

The propensity score-based weighting and matching analyses assume that crossover of the NHS subjects to Study 301 was not due to factors related to disease progression. The within-subject correlation was accounted for in the analysis after matching. To examine the impact of crossover subjects on analyses outcome, FDA review team additionally performed propensity score weighting and matching analyses after excluding subjects who transitioned to Study 301 from the Study 301 analysis population. These analyses produced treatment effects of similar magnitude to that from the wLME and those presented in [Table 23](#) below for the overall population.

Table 23. FDA's Landmark Analyses Without Square Root Transformation Based on Methods for Causal Inference

Analysis Method	Study 301 (N=97)	NHS (N=101)	Difference (95% CI)	Nominal p-Value
Propensity score weighting/mean (SE)				
Include all subjects using 12-Month data if available	97	101		
Covariates 1 ^a	8.9 (3.1)	22.8 (5.9)	-14.0 (-27.0, -0.8)	0.0364
Covariates 2 ^a	8.7 (3.0)	22.9 (5.9)	-14.2 (-27.2, -1.2)	0.0321
Covariates 3 ^a (excluded 4 subjects missing covariates)	9.1 (3.2)	23.0 (6.1)	-13.9 (-27.4, -0.5)	0.0422
Propensity score matching ^b				
Exact match on sex and age group	Matched	Matched	-16.2 (-25.7, -6.6)	0.0022
Nearest neighbor with caliper 0.2 for covariates 3	n=61	n=61		
Targeted maximum likelihood estimation				
Covariates 1	n=97	n=101	-14.3 (-27.3, -1.3)	0.0309
Covariates 3 (excluded 4 subjects missing covariates)	n=97	n=97	-15.2 (-30.7, 0.03) ^c	0.0551
Covariates 3; including all 12-month changes	n=97	n=101	-11.6 (-21.8, -1.2)	0.0281

Source: FDA reviewer; Endpoint: annualized new HO calculated by dividing change in HO by the follow-up duration

^a 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.

^b Age group: (1) <12 years; (2) 12 to <18 years; (3) ≥18 years

^c bootstrap 95% CI: (-31.2, -0.5)

Abbreviations: CAJIS, cumulative analogue involvement scale; CI, confidence interval; FDA, Food and Drug Administration; HO, heterotopic ossification; N, number of subjects; n, number of subjects with given characteristic; NHS, natural history study; SE, standard error

Table 24. Study 301 vs. NHS: Summary of Balance After Weighting

Variable	Study 301 Means (N=97)	NHS Means (N=101)	Standardized Mean Difference
Propensity score, mean (min, max)	0.5 (0.2, 0.67)	0.5 (0.17, 0.67)	0
Age	16.83	16.60	0.025
Female (%)	0.45	0.45	0
Baseline rate of HO	15.17	15.11	0.0046
CAJIS	10.98	10.92	0.0091
Time since last flare-up (month)	21.64	21.09	0.017

Source: FDA reviewer

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

Abbreviations: CAJIS, cumulative analogue joint involvement scale; FDA, Food and Drug Administration; HO, heterotopic ossification; max, maximum; min, minimum; N, number of subjects; NHS, natural history study; vs, versus

Table 25. Study 301 vs. NHS: Summary of Balance After Nearest Neighbor 1:1 Matching

Variable	Study 301 Means (N=61)	NHS Means (N=61)	Standardized Mean Difference
Propensity score	0.51	0.51	0.04
Age	15.70	15.15	0.062
Female (%)	0.39	0.39	0
Baseline rate of HO	13.70	13.11	0.045
CAJIS	10.49	10.18	0.052
Time since last flare-up (month)	21.18	18.40	0.21

Source: FDA reviewer

Exact match on sex and age group (<12;12 to <18; ≥18) and caliper=0.2 for nearest neighbor propensity score matching; Baseline rate of HO is the baseline total HO divided by age.

Abbreviations: CAJIS, cumulative analogue joint involvement; FDA, Food and Drug Administration; HO, heterotopic ossification; N, number of subjects; NHS, natural history study; vs, versus

Assessment of Analyses Based on Subjects Transitioned From NHS to Study 301

The Applicant performed analyses limited to subjects who transitioned from the NHS to Study 301 (i.e., baseline control). One of the Applicant's analyses compared the observations associated with the longest follow-up within each study. The other analysis compared the last 12-month change of HO in the NHS with the first 12-month change in Study 301. Results from the two analyses favored palovarotene ([Table 26](#)).

Table 26. Applicant's Analyses on Annualized New HO (cm³) in Subjects Transitioned to Study 301

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

Source: CSR and response to information request; Endpoint: annualized new HO calculated by dividing change in HO by the follow-up duration

Analysis covariate: baseline rate of HO; random subject effect.

[#]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

Abbreviations: CI, confidence interval; CSR, clinical study report; HO, heterotopic ossification; N, number of subjects; NHS, natural history study; SE, standard error; wLME, weighted linear mixed effect model

These within-subject comparisons complemented a between-subject comparison by using each subject's own observations in the NHS as the control, which may potentially have reduced unmeasured confounding.

Interpretation of results from this analysis should consider to what extent the disease would be expected to progress on average, over time, without treatment (similarly to what was observed in the NHS) after these subjects transitioned to Study 301. However, the impact of disease progression when enrolled into Study 301 could not be fully assessed without a concurrent control.

Nevertheless, the observed average within-subject increase in the rate of HO after the dosing interruption and the subsequent decrease in rate of HO after restarting palovarotene treatment as observed in Study 202C and Study 301 subjects is also supportive of the conclusions from the wLME analysis.

Sensitivity Analysis to Address Potential Selection Bias

Propensity score weighting or matching considering baseline characteristics does not address the concern that loss to follow-up when transferring from the NHS to interventional studies may have been related to disease progression (or other outcome-related factors), whereas loss from Study 301 was minimal or was not similarly related to such factors. The implicit characteristics of NHS subjects who drove self-selection into interventional studies may have been unknown or uncaptured at study baseline. Even if captured, the confounding control methods are inadequate to address potential differential loss to follow-up (i.e., selection bias).

In response to FDA's inquiry, the Applicant conducted analyses comparing new HO during the NHS between subjects who transitioned into interventional studies (Studies 201, 202, or 301) and subjects who remained in NHS. The results indicated slower disease progression in NHS subjects who transferred to interventional studies, compared with subjects who remained in the NHS. Although the difference was not statistically significant, the magnitude of intrinsic difference between transition and nontransition NHS subjects might explain the observed drug effect to some extent, supporting the theoretical concern of presence of selection bias and the potential impact on efficacy assessment. To address this specific concern, the Applicant conducted sensitivity analyses considering palovarotene treatment a time-varying exposure and HO volume by WBCT scan a time-dependent confounder. The sensitivity analysis results were consistent with the wLME analysis in terms of the direction of association between palovarotene treatment and annualized new HO. Of note, specification of such a causal inference model required several strong and untestable statistical assumptions.

To further address the concern for potential selection bias due to the transfer of some NHS subjects to Study 301, the FDA review team additionally conducted analyses excluding subjects who transferred from the NHS to Study 301. The transfer subjects were excluded from the Study 301 analysis population but included in the NHS analysis population. The analyses results based on regression adjustments or propensity score weighting were similar to those for the overall population; however, the same concern of informative censoring in the NHS cohort remains in this subset of the analysis population.

Conclusion

When an external control is used, there will be a lack of assurance of comparability between treated and untreated subjects given the lack of randomization. There were some differences in baseline characteristics between subjects in the NHS and Study 301, such as subjects in the NHS were relatively older and had worse disease severity. To address the potential impact of measured confounding factors, various analyses using methods that are commonly used for

causal inference were performed and these analyses provided consistent results. It appears that the difference in annualized new HO between treated and untreated subjects was not driven by any systemic differences in baseline covariates that are expected to be clinically important, although the impact of unknown confounding factors remains uncertain.

To assess the impact of potential selection bias due to subjects' self-selection to interventional studies, the Applicant and the FDA review team conducted several sensitivity analyses. Although these analyses have limitations, and no single analysis categorically addresses the concern of selection bias, the results were consistent in the direction of association, suggesting an effect of palovarotene in reducing the volume of new HO.

In addition, results from within-subject comparisons, including findings from subjects who restarted treatment after dose interruption, may complement the between-subject comparisons and seem supportive of a drug effect. However, the magnitude of treatment effect could not be accurately quantified without a concurrent randomized control.

6.3.3. Uncertain Clinical Implications of Negative New HO Volume Data

Issue

Negative new HO volume data: clinical significance, and implications for primary phase 3 efficacy analysis.

Background

FOP is characterized by accumulation of HO, which is considered to be irreversible. It was anticipated that the extent of negative HO data would be limited. However, results of these intervention studies showed substantial declines in HO volume in some instances, raising questions about the clinical significance of such changes.

Assessment

In Studies 301 and the NHS, postbaseline WBCT scans were compared to the previous scan. If any new HO was qualitatively present in a certain body region, all HO in that region was remeasured. In many cases, the net change in HO volume was negative (<0 cm³/year) for a specific body region. There were more palovarotene-treated versus untreated subjects (47% and 24% in Study 301 and the NHS, respectively) with negative changes in new HO volume in at least one body region at the last measured timepoint. Net negative changes for total body HO also occurred more frequently in Study 301 compared to the NHS (29% in Study 301 versus 5% in the NHS).

Literature reports indicate that shrinkage of HO lesions may occur in untreated FOP patients, as well as in nongenetic forms of HO. While the mechanism is unknown, it is plausible that this may be related to resolution of edema in newer lesions with progressive calcification and consolidation to mature cortical bone, analogous to the remodeling of callus around a fracture (according to the Applicant's response to IR submission to the NDA on August 5, 2021).

Because negative HO volume changes were reported more frequently in Study 301 than in the NHS, the Applicant contends that palovarotene treatment may cause HO regression. However, it

is important to note that all HO volume measurements in these studies were by body region, therefore, shrinkage in individual lesion(s) could be offset or masked by increasing size of other lesions within the same region. NHS subjects generally had more HO lesions that were growing in size, thus negative changes would tend to be underestimated in these untreated patients to a greater extent than in palovarotene recipients. Because of the lack of data on individual HO lesions in these studies, there is insufficient evidence to conclude that the negative HO volume data resulted from palovarotene-related regression of existing lesions as seen radiographically (e.g., due to consolidation of the lesion or decreased inflammation), in addition to inhibition of new HO formation.

The HO volume calculations were in part dependent on subjective assessments and varying orientation of axial slices on different CT scans; however, given the processes of double read and adjudication, measurement error is unlikely to explain some of the larger HO volume declines observed. Moreover, measurement error would apply equally to scans from treated and untreated subjects, therefore this mechanism alone cannot explain the disproportionate number of treated subjects with net negative HO.

It is possible that in at least some instances, negative new HO volume changes are likely to reflect actual shrinkage of lesions, possibly as a natural process of lesion maturation or due to a decrease in inflammation, rather than a decrease in HO itself. However, the data are insufficient to conclude that palovarotene promotes this process. Regardless of the exact mechanism, there does not appear to be a plausible rationale for excluding negative HO changes from analyses. On the other hand, if the reduction in volume was due to consolidation or a decrease in the underlying inflammatory process rather than inhibition of the growth of new HO, it is unclear whether the occurrence of negative new HO should be viewed as a treatment benefit, given that neither lesion consolidation nor decrease in inflammation has been associated with improvement in functional status in patients with FOP.

Conclusion

The clinical implication of the occurrence of negative new HO volumes in Studies 301, 202B/C and the NHS remains unclear. However, there is no convincing evidence that these data could have created a bias in favor of palovarotene, or that exclusion (i.e., zeroing out) of negative HO data from analyses, as in the prespecified primary analysis of Study 301, was justified from a clinical perspective.

6.3.4. Consistency of Phase 2 and Phase 3 Whole-Body HO Data

Issue

Phase 2 efficacy data pertaining to chronic/flare-up dosing was not consistent with phase 3 data.

Background

During the phase 2 extension Study 202, chronic daily dosing of palovarotene was introduced in 202 Parts B and C, with higher doses (20/10 mg) for flare-ups, and efficacy was assessed using annual whole-body HO. In 202 Part C, the primary endpoint was the annualized change from

baseline in whole-body HO volume, similar to Study 301. However, 202C was a smaller study which was not powered to demonstrate efficacy via comparisons to the NHS.

Assessment

No interim analyses were planned for Study 202, and the original NDA included only descriptive summaries of the 202B/C data, which showed large apparent discrepancies between overall new HO volume (raw data) for Study 202B (mean 28.0 cm³/year) and Study 202C (mean 24.3 cm³/year), compared to Study 301 (mean 9.4 cm³/year) and the NHS (23.7 cm³/year). Because the chronic/flare-up treatment protocol was similar for Studies 202 and 301, and essentially identical for Studies 202C and 301, concerns were raised about consistency of these efficacy data.

The original NDA highlighted differences between the Study 202B protocol versus the 202C/301 protocol as a reason for the discordant results. Specifically, the 202B protocol required documentation of at least two flare-up symptoms within the previous 7 days to initiate flare-up dosing and did not allow resetting of the flare-up treatment cycle for intercurrent flare-ups at a new site, marked worsening of the initial symptoms, or trauma considered likely to lead to a flare-up. As a result, flare-up dosing was used more sparingly in Study 202B compared to 202C and 301. The Applicant conducted a review of potential flare-up symptoms and treatments in 202B, purportedly showing that multiple subjects had, in retrospect, remained untreated or undertreated for certain flare-up symptoms (and thus remained at the 5 mg chronic daily dose without flare-up dosing), and in some cases accrued large volumes of new HO at the site of the symptoms. FDA reviewers requested additional information regarding undertreatment of flares in 202B, but ultimately, did not find these data or rationale convincing and determined that the 202B efficacy data cannot be reliably interpreted.

The study populations of Studies 202 and 301 differed in certain aspects: most of the subjects in Study 202 began treatment in Study 201 because of an acute flare-up, so they may have had a more active disease state compared to subjects in Study 301, in which enrollment required the absence of a recent flare-up. In addition, subjects began chronic treatment in 202B or 202C without regard to the timing of their last flare-up. Therefore, subjects with flare-up symptoms within 1 month of chronic treatment baseline (thus, experiencing possible residual HO formation at the flare-up site) were excluded from analyses to align with Studies 301 and NHS. With these exclusions, the mean new HO volume for 202C subjects (unadjusted data) declined somewhat, to 19.0 cm³/year.

Study 202C subjects were also older than Study 301 and NHS subjects, with more advanced disease, and had already undergone treatment with palovarotene under various regimens prior to 202C, whereas the Study 301 subjects were treatment-naïve at enrollment. In order to increase comparability between the Study 202C and NHS populations, FDA requested matched and propensity score weighted analyses, which suggested similar efficacy to that observed in Study 301 (See Section [6.2.2.4](#)).

In addition, data from 202C subjects following the extended treatment pause were requested by FDA. The new HO volume data showed a pattern similar to Study 301 subjects, with an initial increase from the pre-pause treatment to the treatment interruption phase, followed by a decline after treatment re-start.

Conclusion

Based on additional data and analyses, FDA reviewers have concluded that the differing outcomes of Studies 301 and 202C do not present a major concern. When differences in study populations were partially accounted for in matched pair and propensity score weighting analyses, Study 202C versus NHS comparisons were favorable to palovarotene treatment, and consistent with the Study 301 versus NHS data. In addition, data on 202C subjects who restarted treatment following the 2019 to 2020 treatment pause show substantially smaller volumes of new HO compared to the pre-pause period, which were similar to an analogous group in Study 301.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The preclinical safety of palovarotene was adequately assessed in a comprehensive nonclinical development program that was submitted and reviewed with the original NDA and included general, reproductive, and genetic toxicity studies. Dedicated rodent carcinogenicity studies to assess the carcinogenic potential of palovarotene have not been conducted; instead, the Applicant assessed the carcinogenic potential of palovarotene using a weight of evidence (WoE) approach outlined in an amendment to International Council for Harmonization S1B(R1). The nonclinical review team in consultation with the CDER Executive Carcinogenicity Assessment Committee (ECAC) concluded that the carcinogenic potential of palovarotene in humans is uncertain and assessment in a 2-year rat carcinogenicity study, in addition to a mouse *in vivo* carcinogenicity study, would add value to the assessment of human carcinogenic risk. Carcinogenicity bioassays were not considered necessary prior to submission and review of a marketing application because of the unmet medical need for the severely debilitating nature of heterotopic ossification in patients with FOP. However, while a determination of potential clinical benefit could be compared to known risks identified in the development program and unknown long term carcinogenic risk, characterization of carcinogenic potential will still be important given that FOP patients are anticipated to use palovarotene chronically.

The uncertainty of palovarotene carcinogenic potential is mainly related to 1) complex target pharmacology (e.g., activation of the target transcription factor promotes cellular proliferation and RAR γ acts as tumor promotor in some animal models, and RAR γ is abundant in many human cancers); 2) positive carcinogenic outcomes associated with the retinoid class from activating the same drug target; and 3) histopathological changes of concern (epithelial hyperplasia and chronic inflammatory changes in the skin and stomach), which occurred at clinically relevant exposures with inadequate alternative mechanistic explanation in the 6-month rat study and which were supported by similar findings (skin) in cynomolgus monkeys (see Section [13](#)). Therefore, rodent carcinogenicity studies in two species to assess the carcinogenic potential from long-term oral exposure to palovarotene are being recommended as post marketing requirements.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Retinoids are associated with numerous class-related adverse effects. For this application, the two most serious safety concerns are PPC and embryo-fetal toxicity, which have been reported with other retinoids and are discussed in Sections [7.7.2](#) and [7.7.3](#), respectively. Reduced bone mineral density appears to be associated with palovarotene and other retinoids and is discussed in Section [7.7.4](#). Other potential retinoid class effects include neuropsychiatric effects, including depression, suicidality, seizures and pseudotumor cerebri; mucocutaneous adverse effects; serious skin reactions such as Stevens-Johnson syndrome; musculoskeletal effects including arthralgia and back pain; hypersensitivity reactions; acute pancreatitis; hepatotoxicity; elevated triglycerides; inflammatory bowel disease; hearing impairment; and eye abnormalities including decreased night vision.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Palovarotene was approved to treat patients with FOP in Canada in January 2022, but no patients have yet been treated with commercially supplied drug, therefore, no postmarketing data are available. Palovarotene has not been approved in any other country to date.

7.4. FDA Approach to the Safety Review

The bulk of the FOP/palovarotene safety data comes from patients exposed to the 5 mg chronic (nonflare) dose or the 20/10 mg flare-up regimen (all doses weight adjusted when appropriate) in Studies 202B, 202C and 301. This review focuses primarily on pooled safety data from these studies for each of these two regimens in the Applicant's intended target population of females ≥ 8 years of age and males ≥ 10 years of age (referred to as $\geq 8/10$), which represents 139 of the total 164 FOP subjects who received palovarotene in any study (the FOP-FAS). Safety data for younger children (ages $< 8/10$) are generally consistent with the intended target population, with the possible exception of PPC, as discussed below. Palovarotene exposure related to lower-dose flare-up regimens (10/5 mg and 5/2.5 mg) was relatively limited and is not discussed in this review, except for data related to new flare-ups.

The $\geq 8/10$ safety data presented here were compiled by Clinical Data Scientist staff from Studies 202B/202C/301 from the integrated summary of safety (ISS) datasets in the first NDA resubmission (April 29, 2022), using the cutoff date of July 31, 2021. Subsequent safety updates were submitted on August 10, 2022, and on February 16, 2023 (with this second NDA resubmission) and are of interest primarily for updated bone safety information related to PPC and growth.

The NDA includes extensive safety data related to non-FOP indications: pediatric patients with multiple osteochondromas; six phase 1 and 2 studies in adults with chronic obstructive pulmonary disease (COPD); and 12 single- and multiple-dose studies in healthy volunteers.

In addition to routine safety assessments (adverse events [AEs], concomitant medications, vital signs, electrocardiogram, physical exam, safety labs), the FOP palovarotene studies included

frequent pregnancy testing, the Columbia-Suicide Severity Rating Scale (C-SSRS), and assessments related to bone safety and growth; the latter are discussed in Section 7.7.1. Treatment-emergent adverse events (TEAEs) were protocol-defined as AEs that developed or worsened after administration of the first dose to 7 days after the last dose of study drug and were coded using the Medical Dictionary for Regulatory Activities version 22.0. AEs were not collected systematically in the NHS because there was no treatment. As discussed in the previous Integrated Review of this NDA, no major data quality or integrity issues were identified that would preclude performing the safety review.

7.5. Adequacy of the Clinical Safety Database

The NDA 215559 safety database for palovarotene is adequate to evaluate the proposed FOP indication and dosage regimens. The FOP phase 2 and 3 studies enrolled a relatively large proportion of the known patients with this disease globally. Although comparison safety data in untreated FOP patients is very limited, there is substantial placebo-controlled data available for palovarotene in prior COPD studies (adults) and a multiple osteochondromas study (pediatric), and the safety profile of retinoids as a drug class is well known from extensive experience with other retinoids.

A total of 164 patients with FOP received at least one dose of palovarotene, including 139 patients in the Applicant's intended target population (age $\geq 8/10$ years). The following table [below](#) summarizes demographic characteristics for subjects in this target population who received, in any phase 2 or phase 3 study, the chronic palovarotene (PVO) 5 mg regimen (N=131), the PVO 20/10 flare-up regimen (N=105), or any PVO regimen (N=139).

Table 27. Baseline Demographic and Clinical Characteristics, Age at First Entry $\geq 8/10$ Years (FOP-FAS)

Characteristic	Chronic PVO 5 mg (Nonflare Dosing) (N=131)	PVO 20/10 mg (Flare-Up Dosing) (N=105)	PVO Total (All Exposed Subjects*) (N=139)
Sex, n (%)			
Female	64 (49)	50 (48)	69 (50)
Male	67 (51)	55 (52)	70 (50)
Age, years			
Mean (SD)	18.9 (9.3)	18.6 (8.9)	19.1 (9.4)
Median (min, max)	16 (8, 61)	16 (9, 61)	16 (8, 61)
Age group, years, n (%)			
<14	40 (31)	33 (31)	42 (30)
≥ 14	91 (70)	72 (69)	97 (70)
Race, n (%)			
Asian	6 (5)	5 (5)	7 (5)
Black or African American	0	0	2 (1)
Multiple	5 (4)	3 (3)	6 (4)
Not Available	0	0	6 (4)
Other	1 (1)	0	1 (1)
Unknown	9 (7)	7 (7)	9 (7)
White	102 (78)	83 (79)	106 (76)
Missing	8 (6)	7 (7)	8 (6)

Characteristic	Chronic PVO 5 mg (Nonflare Dosing) (N=131)	PVO 20/10 mg (Flare-Up Dosing) (N=105)	PVO Total (All Exposed Subjects*) (N=139)
Ethnicity, n (%)			
Hispanic or Latino	19 (15)	15 (14)	22 (16)
Not Hispanic or Latino	94 (72)	75 (71)	99 (71)
Not Reported	18 (14)	15 (14)	20 (14)
Country of participation, n (%)			
Argentina	5 (4)	3 (3)	5 (4)
Australia	8 (6)	4 (4)	8 (6)
Brazil	5 (4)	4 (4)	5 (4)
Canada	4 (3)	4 (4)	4 (3)
Spain	4 (3)	3 (3)	4 (3)
France	17 (13)	14 (13)	19 (14)
Great Britain	12 (9)	12 (11)	12 (9)
Italy	6 (5)	4 (4)	6 (4)
Japan	2 (2)	2 (2)	2 (1)
Sweden	6 (5)	5 (5)	6 (4)
United States	63 (48)	51 (49)	71 (51)

Source: adsl.xpt; Software: R

*Includes all exposed subjects 201, 202A, 202B, 202C, 301

Subjects may overlap between study arms. Large numbers of subjects with missing race/ethnicity data were mainly due to legal restrictions in France

All doses reduced by weight in subjects who were <90% skeletally mature by x-ray

Abbreviations: FOP-FAS, fibrodysplasia ossificans progressive full analysis set; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects with given characteristic; PVO, Palovarotene; SD, standard deviation

The following table [below](#) summarizes the duration of exposure for chronic 5 mg daily dosing (mean 79 weeks), flare-up 20/10 mg dosing (mean 35 weeks), and for any palovarotene dose (mean 102 weeks) among the FOP target population ($\geq 8/10$) subjects as of the July 31, 2021 ISS data cutoff.

Table 28. Duration of Exposure, Age at First Entry $\geq 8/10$ Years (FOP-FAS)

Parameter	Chronic PVO 6 mg (Nonflare Dosing) (N=131)	PVO 20/10 mg (Flare-Up Dosing) (N=105)	PVO Total (All Exposed Subjects*) (N=139)
Duration of treatment, weeks			
Mean (SD)	78.9 (50.4)	35.1 (25.8)	102.4 (59.4)
Median (Q1, Q3)	71.3 (44.9, 92.9)	28.1 (14.5, 46.7)	82.6 (72.9, 130.7)
Min, max	0.9, 224.7	0.3, 134.1	4.1, 242.3
Total exposure (person years)	198.1	68.6	272.7

Parameter	Chronic PVO 6 mg (Nonflare Dosing) (N=131)	PVO 20/10 mg (Flare-Up Dosing) (N=105)	PVO Total (All Exposed Subjects*) (N=139)
Patients treated, by duration, n (%)			
>0 to 3 months	9 (7)	24 (23)	8 (6)
>3 to 6 months	6 (5)	24 (23)	4 (3)
>6 to 9 months	11 (8)	19 (18)	3 (2)
>9 to 12 months	12 (9)	15 (14)	2 (1)
>12 to 18 months	38 (29)	13 (12)	38 (27)
>18 to 24 months	29 (22)	5 (5)	45 (32)
>24 to 30 months	8 (6)	1 (1)	4 (3)
>30 to 42 months	9 (7)	1 (1)	13 (9)
>42 to 54 months	9 (7)	0	21 (15)
>54 to 66 months	0	0	1 (1)
Missing	0	3 (3)	0

Source: adsl.xpt, adex.xpt; Software: R

*Includes all exposed subjects 201, 202A, 202B, 202C, 301

Subjects may overlap between study arms. All doses reduced by weight in subjects who were <90% skeletally mature by x-ray
Abbreviations: FOP-FAS, fibrodysplasia ossificans progressive full analysis set; Max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; PVO, palovarotene; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.6. Safety Results

7.6.1. Safety Results

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary

The following table [below](#) presents an overview of treatment-emergent adverse events for the $\geq 8/10$ - year-old FOP study population during treatment with the chronic 5 mg or the flare-up 20/10 mg regimen in Studies 202B, 202C or 301. There were no deaths during treatment or related to a TEAE. Serious AEs were reported in 24% of subjects while receiving the chronic 5 mg regimen, and in 23% of subjects while receiving the 20/10 mg flare-up regimen. These two regimens were also similar with regard to overall AEs (97% versus 94%) and AEs leading to drug interruption or discontinuation. However, AEs leading to dose reduction were more frequent among subjects receiving the 20/10 mg flare dosing compared to 5 mg chronic daily dose (43% versus 8%).

Table 29. Studies 202B/202C/301: Overview of Treatment-Emergent Adverse Events, Age at First Entry $\geq 8/10$ Years (FOP-FAS)

Event Category	Chronic PVO 5 mg (Non-Flare Dosing) (N=131) n (%)	PVO 20/10 mg (Flare-up Dosing) (N=105) n (%)
SAE	31 (24)	24 (23)
SAEs with fatal outcome	0	0
Life-threatening SAEs	0	0
AE leading to permanent discontinuation of study drug	6 (5)	5 (5)
AE leading to dose modification of study drug	29 (22)	52 (50)
AE leading to interruption of study drug	22 (17)	20 (19)
AE leading to reduction of study drug	10 (8)	45 (43)
Any AE	127 (97)	99 (94)
Severe and worse	22 (17)	20 (19)
Moderate	59 (45)	53 (51)
Mild	46 (35)	26 (25)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that developed or worsened after administration of the first dose of study drug to the end of dosing as follows: (first dose date) $\leq$ (AE start date) $\leq$ (last dose date) +7 days.

Severity as assessed by the investigator.

Subjects may overlap between study arms.

Abbreviations: AE, adverse event; FOP-FAS, fibrodysplasia ossificans progressiva full analysis set; N, number of subjects in treatment arm; n, number of subjects with at least one event; PVO, palovarotene; SAE, serious adverse event

7.6.1.2. Deaths

No deaths were reported during palovarotene treatment or for 30 days post-treatment in the FOP-FAS, including the post-pause period per the most recent safety update. As discussed in the previous Integrated Review for this NDA, one FOP subject from Study 301 died 2.5 months after discontinuing palovarotene, attributed to restrictive lung disease from complications of FOP. In addition, there was one death of a FOP NHS subject who never received palovarotene.

There have been no deaths reported in the multiple osteochondroma or healthy volunteer study populations from other programs. Deaths reported in the COPD program were generally related to age and underlying disease; none were assessed as related to study treatment by the Investigator.

7.6.1.3. Serious Treatment-Emergent Adverse Events

Serious adverse events (SAEs) were frequently reported in all FOP palovarotene studies, including 24% of subjects during chronic dosing and 23% of subjects during flare-up dosing within the $\geq 8/10$ target population. The most frequently reported system organ class of SAEs was musculoskeletal and connective tissue disorders, which in addition to PPC included events that could be associated with retinoids or with the underlying disease FOP, such as arthralgia, back pain and pain in extremity. The next most frequently reported system organ class of SAEs was infections, especially pneumonia, cellulitis and COVID; FOP patients are known to be at increased risk for pneumonia, right-sided heart failure and thoracic insufficiency, and 16% of NHS subjects experienced pneumonia. There were SAEs of tonic chronic seizure, epilepsy, syncope and myoclonus reported in one phase 2/3 subject each. While other retinoids may be associated with seizure, numerous NHS and Study 301 subjects reported a prior history of

seizures. Overall, many of the reported SAEs (with the exception of PPC) appear to be more likely related to the disease rather than treatment, but this is difficult to determine in the absence of a suitable control group in these studies.

For further details, see the previous NDA Integrated Review (December 23, 2022, in DARRTS), which included a list of all SAEs reported in the $\geq 8/10$ subset of the FOP-FAS through the July 31, 2021, cutoff date. Because numerous subjects in Studies 202C and 301 restarted palovarotene after the treatment pause at various dates in 2020 to 2021, additional SAEs are included in safety updates through the most recent cutoff (April 27, 2022). The new events are most notable for a substantial increase in the number of SAEs of COVID-19 infection, and do not change the safety profile of palovarotene in the FOP population.

The labeled prescribing information for other retinoids (e.g., isotretinoin, soriatane, bexarotene) includes warnings regarding certain AEs that appear to be class-related: hepatotoxicity, pancreatitis, hyperlipidemia, serious skin reactions (e.g., Stevens Johnsons syndrome) and intracranial hypertension (pseudotumor cerebri) (Teva 1982; Stiefel 1996; Ligand 1999). In FOP clinical studies of palovarotene, there were no reported instances of serious or severe AEs in these categories. Therefore, the clinical judgment of reviewers is that current evidence does not support labeled warnings/precautions for these conditions, but rather these will be included in section 6: Adverse Reactions based on assumed class effects.

7.6.1.4. Adverse Events Leading to Treatment Discontinuation

Among FOP subjects age $\geq 8/10$ years, treatment was discontinued due to an AE in 6/131 subjects (4.6%) during treatment with chronic 5 mg dosing, and in 5/105 subjects (4.8%) during treatment with 20/10 mg flare-up dosing. The only AE resulting in >1 treatment discontinuation was dry skin (1 subject with each regimen). The other AEs causing discontinuation during chronic dosing were furuncle, amylase increased, lipase increased, epiphyses premature fusion, myoclonus, intentional self-injury, and erythema. The other AEs causing discontinuation during flare-up dosing were cellulitis, hemophilus infection, localized infection, malnutrition and mobility decreased.

7.6.1.5. Treatment-Emergent Adverse Events

Mucocutaneous adverse effects such as dry skin, rash, pruritus, alopecia and dry mouth were the most frequently reported adverse effects, similar to previous experience with other retinoids and hypervitaminosis A. The previous NDA Integrated Review included summaries of TEAEs in the $\geq 8/10$ population according to the most frequent preferred terms and by System Organ Class/ Narrow FDA Medical Dictionary for Regulatory Activities query (FMQ).

The following table [below](#) represents the most common ($\geq 10\%$ incidence) adverse reactions, where this term is defined in PLR labeling regulations as “those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event” [21 CFR 201.57(c)(7)]. Most of the adverse reactions included in the table represent narrow FMQ groupings of >1 preferred term, which are listed in the table footnotes. Many of these reactions are characteristic of retinoids, and in most cases the incidence in chronic versus flare-up dosing was similar.

Table 30. Studies 202B/202C/301: Subjects With Adverse Reactions by FDA Medical Query (Narrow) Occurring at ≥10% Frequency, Age at First Entry ≥8/10 Years (FOP-FAS)

Adverse Reaction (PT or FMQ*)	Chronic PVO 5 mg (Non-flare Dosing) (N=131)	PVO 20/10 mg (Flare-Up Dosing) (N=105)
	n (%)	n (%)
Dry skin	80 (61)	60 (57)
Dry mouth	52 (40)	35 (33)
Rash	60 (46)	56 (53)
Pruritis	46 (35)	51 (49)
Arthralgia	47 (36)	32 (31)
Alopecia	32 (24)	31 (30)
Erythema	25 (19)	34 (32)
Headache	25 (19)	20 (19)
Back pain	22 (17)	12 (11)
Myalgia	15 (12)	9 (9)
Hypersensitivity	13 (10)	21 (20)
Paronychia	13 (10)	12 (11)
Peripheral edema	12 (9)	20 (19)
Fatigue	7 (5)	12 (11)

Source: FDA Clinical Data Scientist staff, derived from ISS datasets in NDA resubmission (April 29, 2022), cutoff date July 31, 2021

*Preferred terms included in FMQ-based adverse reactions:

Dry mouth = lip dry, dry mouth, dry throat

Rash = rash, skin exfoliation, blister, dermatitis, rash generalized, rash maculopapular, skin reaction, rash macular, rash popular, urticaria, dermatitis contact, rash erythematous, rash pruritic, rash pustular, vessel puncture site rash, viral rash

Pruritis = pruritus, pruritus generalized, ear pruritus, eyelids pruritus, nasal pruritus, pruritus allergic, pruritus genital, rash pruritic, vulvovaginal pruritus, eye pruritus, lip pruritus

Alopecia = alopecia, madarosis

Erythema = erythema, generalized erythema, flushing, rash erythematous

Headache = headache, migraine, sinus headache

Back pain = back pain, flank pain, sciatica

Myalgia = myalgia, musculoskeletal discomfort

Hypersensitivity = drug eruption, hypersensitivity, pruritus allergic, drug hypersensitivity

Peripheral edema = peripheral swelling, edema peripheral

Fatigue = fatigue, lethargy, asthenia, malaise

Abbreviations: FDA, Food and Drug Administration; FMQ, FDA medical dictionary for regulatory activities query; FOP-FAS, fibrodysplasia ossificans progressiva full analysis set; ISS, integrated summary of safety; N, number of subjects in treatment arm; n, number of subjects with given adverse reaction; NDA, new drug application; PT, preferred term; PVO, palovarotene

Severe mucocutaneous AEs were reported in 51% of FOP subjects and included skin exfoliation (31%), drug eruption (i.e., retinoid dermatitis, 18%) and blisters (7%). Mucocutaneous events were the most common reason for dose reductions, especially at the higher 20/10 mg flare-up doses; in almost all cases, subjects were able to continue treatment with lower doses and/or supportive measures such as skin lotions, lip balm, artificial tears, etc.

Because of the association of retinoids with depression and potential suicidality, the C-SSRS was administered to all study participants age ≥8 years in Study 301 as well as the NHS. There was no evidence of an increase in suicidal thoughts or behavior. The FMQ for depression identified 11% of subjects, and one subject discontinued treatment after 1 month due to “non-suicidal/intentional self-injury.”

Hearing impairment is a common feature of FOP and was reported by 43% of NHS subjects. Audiometry in Study 301 confirmed high rates of hearing loss at baseline; the incidence and type of abnormal clinically significant findings at 12 months was similar to baseline. Hearing impairment TEAEs were reported in 12% of palovarotene-treated subjects in the FOP-FAS, with similar incidence during chronic and flare-up treatment (7% versus 8%, respectively); none of these events were considered severe or led to discontinuation of treatment. AEs of hearing

impairment were much less frequent in subjects with multiple osteochondroma or COPD, with no imbalances between palovarotene and placebo.

7.6.1.6. Laboratory Findings

As discussed in the previous Integrated Review, several FOP subjects developed minor triglyceride elevations, and one healthy subject in a phase 1 drug-drug interaction study was hospitalized with acute pancreatitis with elevated lipase, probably due to interaction with the CYP3A inhibitor ketoconazole. There were no other clinically meaningful changes in hematology or serum chemistry evaluations.

7.6.1.7. Assessment of Drug-Induced Liver Injury

Moderate transaminase elevations were observed in several palovarotene-treated FOP subjects, particularly with the higher 20/10-mg doses, consistent with a retinoid effect. No subjects met Hy's Law criteria.

7.6.1.8. Vital Signs

As previously reviewed, there were no consistent or clinically meaningful changes from baseline in blood pressure or heart rate associated with palovarotene treatment.

7.7. Key Safety Review Issues

7.7.1. Increased Rate of Reported Flare-Ups During Palovarotene Treatment; Potential for Retinoid-Induced Myositis

Issue

Increased rate of reported flare-ups during palovarotene treatment; potential for retinoid-induced myositis.

Background

The rate of new FOP flare-up episodes was assessed in the NHS and palovarotene studies and is relevant to both efficacy and safety. Flare-up incidence and rate were designated in phase 3 as secondary efficacy endpoints to assess whether chronic palovarotene treatment may suppress the initiation of new flare-ups, in addition to potentially suppressing formation of new HO. However, retinoids, and vitamin A in toxic doses, 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, sometimes associated with strenuous physical activity. Because FOP flare-ups are frequently triggered by local inflammation or trauma and are characterized by ossification of muscle and other soft tissues, there is a theoretical concern for induction or exacerbation of flare-ups by palovarotene.

Assessment

In all FOP studies, subjects were instructed to call the study site immediately for potential flare-up symptoms, but the process by which flare-ups were treated and reported varied.

In the NHS, subjects reporting potential flare-ups were evaluated in clinic or monitored with weekly phone contacts. Subjects were also contacted by phone every 6 months between the yearly clinic visits but were not systematically asked about new flare-ups at visits and did not record symptoms in diaries.

In the early phase 2 Studies 201/202A/B, flare-ups were treated if they met the following criteria: the subject had at least two out of six pre-defined symptoms (pain, soft tissue swelling, decreased ROM, stiffness, redness and warmth), it was within 7 days of symptom onset, symptoms were consistent with the subject's previous flare-up symptoms, and flares were confirmed by the investigator. Flare-ups that were not treated (i.e., not meeting these criteria, or intercurrent flare-ups at a different location during flare-up treatment) were recorded not as flare-ups per se, but as AEs under the Medical Dictionary for Regulatory Activities preferred term of "condition aggravated."

In the later phase 2 Study 202C and phase 3 Study 301, the criteria for initiating flare-up treatment were expanded such that only one symptom or a traumatic event likely to lead to a flare-up was required, if consistent with previous flare-ups and confirmed by the investigator, with no requirement to start treatment within 7 days of onset. Additionally, intercurrent (or markedly worsened) flare-ups were recorded and treated as new flare-ups.

Flare-Up Incidence and Rate in Phase 2 Studies

During the 12-week period of treatment/follow-up of the index flare-up in Study 201, new symptoms consistent with a flare-up (i.e., condition aggravated AEs) were reported by more subjects randomized to the palovarotene 10/5 mg regimen (13/21, 62%) in comparison to the 5/2.5 mg regimen (2/9, 22%) or placebo (3/10, 30%). In addition, some of the subjects treated with the 10/5 mg regimen experienced more than one new flare-up event within the 12-week observation period, therefore the rate of new events was highest in this treatment group. However, it should be noted that subjects in this 10/5 mg arm reported a greater number of flare-ups in the year prior to enrollment (4.6) compared to the placebo and 5/2.5 mg arms (2.3, 2.0). The majority of new events occurred at a new location rather than at the original flare-up location. Two of the events in the 10/5 group were categorized as SAEs of condition aggravated.

Table 31. Study 201: New Flare-Up Events Reported During Treatment of an Initial (Index) Flare-Up (FOP-F-FAS)

Parameter	Placebo	PVO 5/2.5 mg	PVO 10/5 mg
Number of treated (index) flare-ups	10	9	21
Number of index flare-ups that were followed by $\geq$ one new event within 12 weeks	3 (30%)	2 (22%)	13 (62%)
Total number of new events within 12 weeks	3	2	24
Number at new location/number worsening at original location	2/1	2/0	18/6
Time interval of onset of new events: Weeks 0-4/Weeks 5-8/Weeks 9-12	0/1/2	1/1/0	11/7/6

Source: Study 201 CSR, and RTQs submitted on August 23, 2022 and October 5, 2022

Abbreviations: CSR, clinical study report; FOP-F-FAS, fibrodysplasia ossificans progressiva flare-up full analysis set; PVO, palovarotene; RTQs, response to questions

To address the issue of a possible triggering of new flare-ups by higher palovarotene doses, the Applicant analyzed these events by regimen across the NHS and phase 2 studies (Table 32 below). Within the 12 weeks following an index flare-up, new events (i.e., condition aggravated AEs) were reported slightly more frequently when the index flare-up was treated with 10/5 mg or 20/10 mg compared to 5/2.5 mg or placebo/untreated flare-ups. Most of these new events occurred at a different location from the index flare-up.

Table 32. New Flare-Up Events Occurring Within 12 Weeks of a Treated or Imaged Flare-Up Across Studies (FOP-F-FAS)

Parameter	Untreated NHS	Placebo	PVO 5/2.5 mg	PVO 10/5 mg	PVO 20/10 mg
Number of treated or imaged (index) flare-ups	53	10	9	52	66
Number of index flare-ups that were followed by ≥1 new event within 12 weeks	12 (23%)	3 (30%)	2 (22%)	19 (37%)	24 (36%)
Total number of new events within 12 weeks	17	3	2	38	33

Source: ISS Table 14.9.7 (original March 31, 2021 NDA), RTQs submitted on August 23, 2022 and October 5, 2022

The FOP-F-FAS includes all subjects with at least one flare-up (from teleconferencing and imaged flare-ups) from the NHS and from treated flare-ups in the interventional studies 201, 202A and 202B. Numbers and percentages are based on number of flare-ups, not number of subjects.

Abbreviations: FOP-F-FAS, f brodyplasia ossificans progressiva flare-up full analysis set; ISS, integrated summary of safety; NDA, new drug application; NHS, natural history study; PVO, palovarotene; RTQs, response to questions

In subjects receiving the chronic/flare-up regimen in Study 202 Parts B and C, new flare-ups (or condition aggravated AEs) occurred at a higher rate during treatment with the 20/10 mg flare-up regimen compared to with the chronic 5 mg daily dosing (Table 33):

Table 33. Study 202, Parts B and C: Flare-Up Rate, by Dosing Period

Parameter	Chronic Dosing Period*	Flare-Up Dosing Period**
Study 202 Part B		
N at risk / n with ≥1 flare-up	44/28	28/14
Total number of flare-ups	64	28
Total number of subject dosing-months	641	142
Flare-up rate per subject-month exposure, mean (95% CI)	0.10 (0.08-0.12)	0.20 (0.12-0.27)
Study 202 Part C		
N at risk / n with ≥1 flare-up	43/30	33/17
Total number of flare-ups	47	68
Total number of subject dosing-months	488	233
Flare-up rate per subject-month exposure, mean (95% CI)	0.10 (0.07-0.12)	0.29 (0.22-0.36)

Source: IR/ISE Supplemental Tables 3a and 3b

*The chronic period includes treated and untreated (i.e., condition aggravated in Part B) flare-ups with a start date during chronic dosing. Any flare-up that occurred during chronic dosing that resulted in the start of flare-up dosing (i.e., treated flare-ups) was allocated to the chronic period.

**The flare-up period includes new flare-ups (or condition aggravated AEs in Part B) with a start date during the flare-up dosing.

Abbreviations: AE, adverse event; CI, confidence interval; IR, information request; ISE, integrated summary of effectiveness; N, number of subjects; n, number of subjects with specific parameter

Flare-Up Incidence and Rate in Phase 3 Study

Flare-ups were reported by a slightly greater proportion of palovarotene-treated versus untreated subjects in Study 301 versus NHS through month 12: 67% in Study 301 and 56% in the NHS, based on at least one relevant symptom. Among subjects with at least one flare-up event, the number of reported events per subject was also greater in Study 301 (mean 4.2, range 1 to 23) versus the NHS (mean 2.5, range 1 to 9). Therefore, among all patients (with or without flare-

ups), the rate of flare-ups per month of study participation was greater in Study 301 compared to the NHS (0.15 versus 0.07 per subject-month, respectively). Data were similar for the subset of 39 subjects who crossed over from the NHS to Study 301 ([Table 34](#)).

Table 34. Study 301 and NHS: Incidence and Rate of New Flare-Ups

Parameter	Untreated NHS	Palovarotene Study 301
All subjects, Principal Safety Set		
Proportion of subjects who reported at least one flare-up Through Month 12	62/111 (56%)	66/99 (67%)
Flare-up rate per subject-month of exposure (95% CI)	0.07 (0.06, 0.08)	0.15 (0.13, 0.17)
Subjects who transferred from NHS to Study 301 (N=39)		
Proportion of subjects who reported at least one flare-up Through Month 12, within each study	23/39 (59%)	26/39 (67%)
Flare-up rate per subject-month of exposure (95% CI)	0.08 (0.07, 0.10)	0.15 (0.12, 0.18)

Source: IR/ISE Supplemental tables E8.1, E8.2, E10.1 and E10.2 Based on ≥ one reported flare-up symptom

Abbreviations: CI, confidence interval; IR, information request; ISE, integrated summary of effectiveness; N, number of subjects; NHS, natural history study

As noted by the Applicant, these differences in flare-up rate may be explained, at least in part, by differences in reporting related to study design and conduct. Although Studies 301 and the NHS were conducted mostly at the same institutions, with similar adjunctive care (e.g., corticosteroids for certain flare-ups), NHS subjects generally had less frequent contact with study staff. Phone contacts were primarily every 6 months in the NHS; in Study 301, subjects were contacted every three months during chronic dosing and every 4 weeks during flare-up dosing. Study 301 subjects were asked to maintain daily symptom diaries, which were reviewed at clinic visits; NHS subjects did not use diaries and may have been less motivated to report symptoms that were not intended for any treatment. In addition, worsening of flare-ups was not systematically recorded in the NHS, unlike Study 301. A published survey of untreated FOP patients has reported an average rate of 0.16 flare-ups per month, (Pignolo et al. 2016), potentially supporting that these events may have been under-reported in the NHS.

In addition, among the 39 subjects who crossed over from the NHS to Study 301, the mean number of flare-ups recorded prospectively in the last 12 months of the NHS was 0.6; at the time of enrollment in Study 301, the same 39 subjects reported (retrospectively) a mean of 1.1 flare-ups during the previous 12 months (the same time period) (Table 20.1.35.1 in the integrated summary of effectiveness resubmission).

In Study 301, many subjects experienced multiple flare-ups, often in succession, whereby a new event within 12 weeks of the onset of the last event would restart the 20/10 dosing regimen before chronic dosing (5 mg) could resume. Thus, a flare-up “cycle” could include one or multiple flare-ups; the mean number of flare-ups per cycle in Study 301 was 2.2 and the maximum was 23. The table [below](#) compares the rates of new flare-ups occurring during chronic dosing (i.e., the first or index flare-up of a new cycle) and during flare-up dosing (any subsequent flare-ups within a cycle). The rate of reported new flare-ups was greater during the higher dosing periods (0.33 versus 0.12 events/month). Among these follow-on events within a flare-up cycle, 82 (42%) were categorized as worsening of the initial flare-up, and 114 (58%) were categorized as intercurrent flare-ups at a new location ([Table 35](#)).

Table 35. Study 301: Flare-Up Rate, by Dosing Period (PSS, N=99)

Parameter	Chronic Period*	Flare-Up Period**	Overall
Flare-up rate per subject-month of exposure (95% CI)	0.12 (0.10-0.14)	0.33 (0.28-0.38)	0.18 (0.16-0.20)

Source: IR/ISE Supplemental Table 4.1

*The chronic period includes flare-ups with a start date during chronic dosing. Any flare-up that occurred during chronic dosing that resulted in the start of flare-up dosing (i.e., treated flare-ups) was allocated to the chronic period.

**The flare-up period includes new flare-ups with a start date during flare-up dosing.

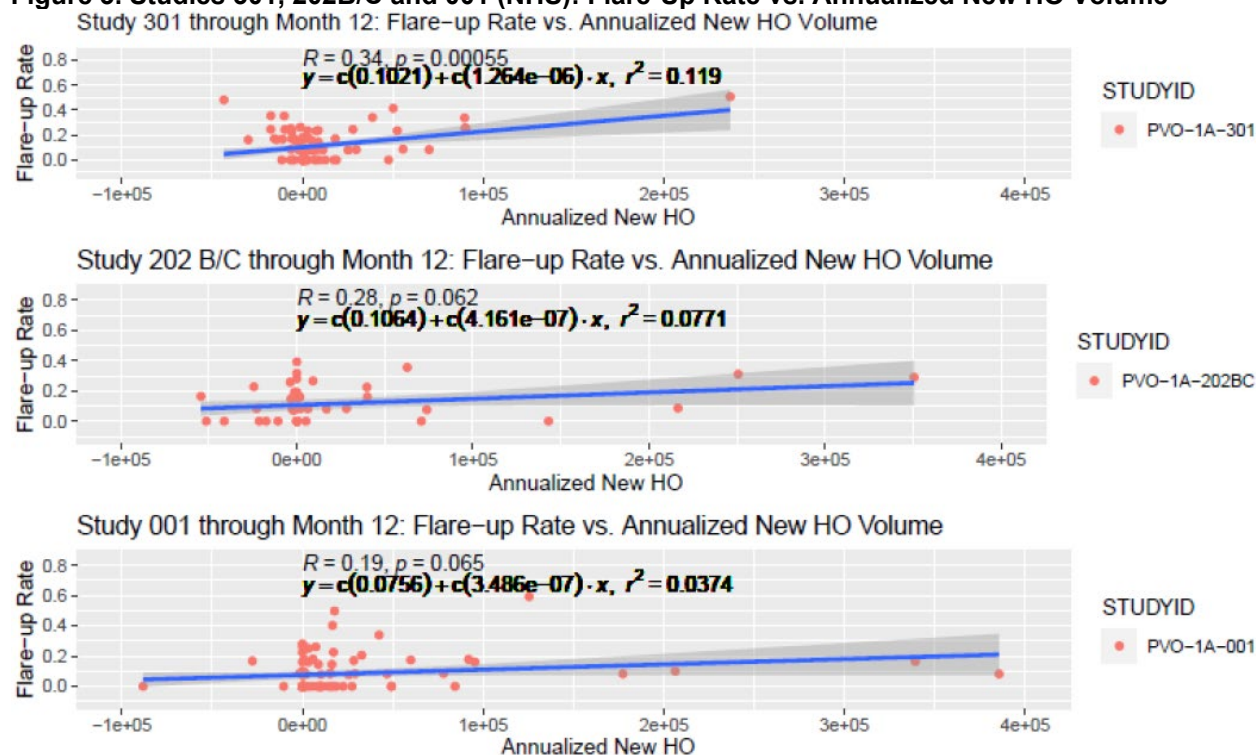
Abbreviations: CI, confidence interval; IR, information request; ISE, integrated summary of effectiveness; N, number of subjects; PSS, principal safety set

The clinical significance of the number of flare-ups in these studies with regard to disease progression is unclear. Subjects reporting at least one flare-up, compared to subjects reporting no flare-ups, developed larger quantities of new whole-body HO, both in the NHS (mean 38.1 versus 6.2 cm³) and in Study 301 (mean 11.7 versus 3.2 cm³). Otherwise, the number of flare-ups did not appear to be closely related to the quantity of new whole-body HO in these studies, but the high degree of variability of HO volume data makes assessment of these relationships challenging. Among the five subjects in either the NHS or Study 301 with annualized new HO >100 cm³/year, 3 of the 4 NHS subjects had reported only 1 or 2 flare-ups. The only Study 301 subject with >100 cm³/year of new HO (236.8 cm³/year) was an exception, having reported 13 flare-ups; however, other subjects reporting greater numbers of flares developed much less, or even negative, new HO.

Among the 39 subjects who transferred from the NHS to Study 301, the change in number of flare-ups for a given subject did not appear to predict the change in new HO. The two subjects with the largest increases in number of flare-ups between the NHS and Study 301 (one event to 18 events, and one event to 14 events, respectively) nevertheless had large declines in rates of new HO from the NHS to Study 301.

In response to FDA request, the Applicant analyzed the relationship between the rate of flare-ups and the volume of new HO. In each study (301, 202B/C, NHS), there was a positive relationship between flare rate and new HO volume, as would be expected based on the documentation of new HO at some flare-up sites ([Figure 3](#)). However, the correlations were modest even in Study 301. This is consistent with the primary analysis demonstrating significantly smaller quantities of new HO in treated subjects, despite the greater number of flare-ups. The correlation was weakest in the NHS, which may seem surprising given that flare-ups in this study were not treated; this may be related to the apparent under-reporting of flare-ups in the NHS.

Figure 3. Studies 301, 202B/C and 001 (NHS): Flare-Up Rate vs. Annualized New HO Volume



Source: NDA resubmission February 16, 2023, M1.11.4 Response to FDA CR Letter

Flare-ups defined as including AEs of condition aggravated

Abbreviations: AE, adverse event; CR, complete response; FDA, Food and Drug Administration; HO, heterotopic ossification; NDA, new drug application; NHS, natural history study; PVO, palovarotene; STUDYID, study identification; vs, versus

The Applicant also conducted an analysis of the association between the extent of palovarotene flare-up dosing (total number of weeks exposure) with annualized new HO, and again found a weak correlation, thus no clear evidence that flare-up dosing may be a risk factor for new HO.

Conclusion

Uncertainty remains as to why flare-ups were reported more frequently during palovarotene treatment, particularly during higher-dose treatment of an initial flare-up. Anecdotally, some patients with FOP are reported to experience clusters of flare-ups at different sites in a short time. In some cases, this might be related to a rebound in symptoms following the withdrawal of glucocorticoids often used to treat the acute symptoms. Potentially, retinoids could cause myositis resulting in a flare-up, or adverse effects such as myalgia or arthralgia that could be misinterpreted as symptoms of a new flare-up.

Also uncertain is whether the increase in reported flare-ups has any clinical significance with regard to disease progression. In both Study 301 and the NHS, subjects who reported at least one flare-up developed, on average, much larger quantities of new HO compared to subjects who reported no flare-ups. However, the data were highly variable. Overall, the rate of flare-ups, and the extent of palovarotene dosing, were not strong predictors of new HO in these studies. Given these uncertainties, this issue should be evaluated further in the postmarketing setting.

7.7.2. Premature Epiphyseal Closure in Growing Children With Potential for Adverse Effects on Growth

Issue

PPC was reported in many pediatric subjects treated with palovarotene, with potential for adverse effects on growth.

Background

Systemic retinoids, as well as vitamin A toxicity, have long been associated with a variety of adverse musculoskeletal effects. Among these are published case reports of PPC occurrence and impaired growth in children with prolonged exposure to various retinoids prescribed for the treatment of dermatologic conditions or cancer. Growth plate abnormalities and premature closure were also observed in juvenile rats exposed to palovarotene and were consistent with retinoid class effects (see Section 7.1). Prior to palovarotene studies, PPC had not been reported in patients with FOP.

Because of this potential risk, palovarotene studies for the FOP indication included a Bone Safety Management Plan in pediatric subjects (<18 years of age). Based on hand/wrist x-rays at screening to assess growth plates, subjects with <90% skeletal maturity, defined as bone age <12 years (girls) or <14 years (boys), received weight-adjusted dosing. In those with open growth plates, continued monitoring included scheduled PA hand/wrist and AP knee radiographs to monitor growth plates and bone age; measurements of standing height (stadiometry) and knee height (knee caliper); and use of whole-body CT scans to measure femur and tibia length. These assessments were conducted every 6 months in Study 301 and every 6 to 12 months in Study 202B/C. Growth assessments were conducted every 12 months in the NHS.

Study 301 began enrollment in November 2017. In 2019, multiple instances of PPC among pediatric subjects in this study were reported based on scheduled radiographs. In December 2019, a partial clinical hold was imposed for the dosing of any children under 14 years of age; dosing was never resumed except for children who subsequently reached age 14. Protocol Amendment 5 added an extended 2-year safety follow-up for pediatric subjects, including annual assessment of growth, hand/wrist radiograph and WBCT.

Assessment

Regarding bone safety, three pediatric age categories were evaluated in the ISS:

- <8 years (girls)/<10 years (boys), representing a prepubertal population;
- ≥8/10 to <14 years of age, representing an early adolescent population (generally early- to mid pubertal) which has, on average, attained approximately 80 to 90% of adult height; and
- ≥14 to <18 years, representing a late adolescent population.

In Study 301 at baseline, pediatric patients with FOP exhibited generally normal skeletal maturation: mean chronologic age and bone age by x-ray were closely matched (11.4 and 11.5 years, respectively), and all adolescents age ≥14 years had achieved ≥90% skeletal maturity, i.e., bone age ≥12 (girls) or ≥14 (boys). During palovarotene treatment, mean increase from baseline

in bone age was slightly greater than mean increase in chronologic age: mean ratios of Δ bone age/ Δ chronologic age were 1.2 to 1.4 at months 6, 12, 18 and 24. Individual changes were highly variable.

Standing height was also in the normal range at baseline in most children with FOP. [Table 36](#) presents mean height Z-scores, which ranged from -0.50 to +0.44 at baseline across the three pediatric age categories in Studies 301 and the NHS. Although there was great variability among individual subjects, these data showed a trend toward lower height Z-scores in adolescents compared to younger children at baseline; this may reflect the development of spinal deformities in some adolescents with FOP. At Month 12, mean height Z-scores declined moderately from baseline among palovarotene-treated subjects <14 years of age; there were slightly smaller mean declines among untreated NHS subjects. Differences in growth between treated and untreated subjects were most apparent in subjects who developed PPC, as discussed below.

Table 36. Study 301 and NHS (FOP-FAS): Mean Height Z-Score in Pediatric FOP Subjects

Parameter	NHS			Study 301 (Palovarotene-Treated)		
	<8/10	≥8/10 to <14	≥14 to <18	<8/10	≥8/10 to <14	≥14 to <18
Age group (years)						
Baseline, n	23	21	20	21	36	19
Baseline mean Z-score	0.44	0.09	0.18	0.34	-0.35	-0.50
Month 12, n	22	17	18	15	31	13
Mean change from baseline	-0.18	-0.30	-0.55	-0.57	-0.36	-0.02

Source: M2.7.4 (March 31, 2021 NDA submission), Table 32 Age groups are defined by subject age at study entry
Abbreviations: FOP, fibrodysplasia ossificans progressiva; FOP-FAS, fibrodysplasia ossificans progressive full analysis set; n, number of subjects; NDA, new drug application; NHS, natural history study

Across Studies 301 and 202B/C, there were 25 subjects in the youngest group (age <8/10 years at study entry) who were treated with palovarotene; among these, 14 (56%) developed PPC. There were 39 early adolescent subjects (age ≥8/10 to <14 years); among these, 13 (33%) developed PPC. Among 38 older adolescents (age ≥14 to <18 years) in these studies, none were reported to develop PPC; this may result from difficulty distinguishing premature versus physiologic epiphyseal closure in this age group. There was a similar distribution of females and males in subjects with and without PPC. Subjects who developed PPC had received weight-based dose reductions at enrollment based on bone age indicating <90% skeletal maturity.

With one exception, all cases of PPC first became apparent on x-rays of the knee (partial or complete closure of distal femur and/or proximal tibia growth plates), typically on the scheduled x-rays at month 12 of treatment. PPC appeared to be bilaterally symmetric and synchronous at other joints, based on a very limited number of subjects with bilateral or additional x-rays; this issue (i.e., proportionality of PPC) was not systematically evaluated. Advances in bone age at the hand/wrist were generally similar in subjects with and without PPC. In the ISS, the Applicant evaluated palovarotene exposure (cumulative dose, duration of chronic or flare-up dosing, area under the concentration [AUC] for concentration versus time curve) for pediatric subjects with and without PPC; no consistent trends were apparent.

[Table 37](#) shows that while palovarotene treatment was associated with trends of slower growth overall in comparison to NHS subjects, the subset that developed PPC accounted for most of the difference, especially among early adolescent subjects (age ≥8/10 to <14 years). In Study 301, mean standing height increase was 1.2 cm/year in this age group with PPC, compared to 3.5 cm/year in treated subjects without PPC and 4.2 cm/year in untreated subjects, and the proportion with growth velocity <4 cm/year was greater (86%, 54% and 41% in these respective

groups). It should be noted that this is a small subgroup (seven subjects age $\geq 8/10$ to <14 years with PPC).

Table 37. Study 301 and NHS (FOP-FAS): Standing Height Changes at Month 12

Variable	NHS (Untreated)		Study 301, No PPC		Study 301, With PPC	
	$<8/10$	$\geq 8/10$ to <14	$<8/10$	$\geq 8/10$ to <14	$<8/10$	$\geq 8/10$ to <14
n	n=22	n=17	n=4	n=24	n=11	n=7
Height mean change from baseline, cm	5.2	4.2	3.6	3.5	3.4	1.2
Growth velocity <4 cm/year	6 (27%)	7 (41%)	2 (50%)	13 (54%)	6 (55%)	6 (86%)
Growth velocity 4-5 cm/year	1 (5%)	4 (24%)	1 (25%)	2 (8%)	0	0
Growth velocity >5 cm/year	15 (68%)	6 (35%)	1 (25%)	9 (38%)	5 (46%)	1 (14%)

Source: M2.7.4 Table 39 (March 31, 2021 submission)

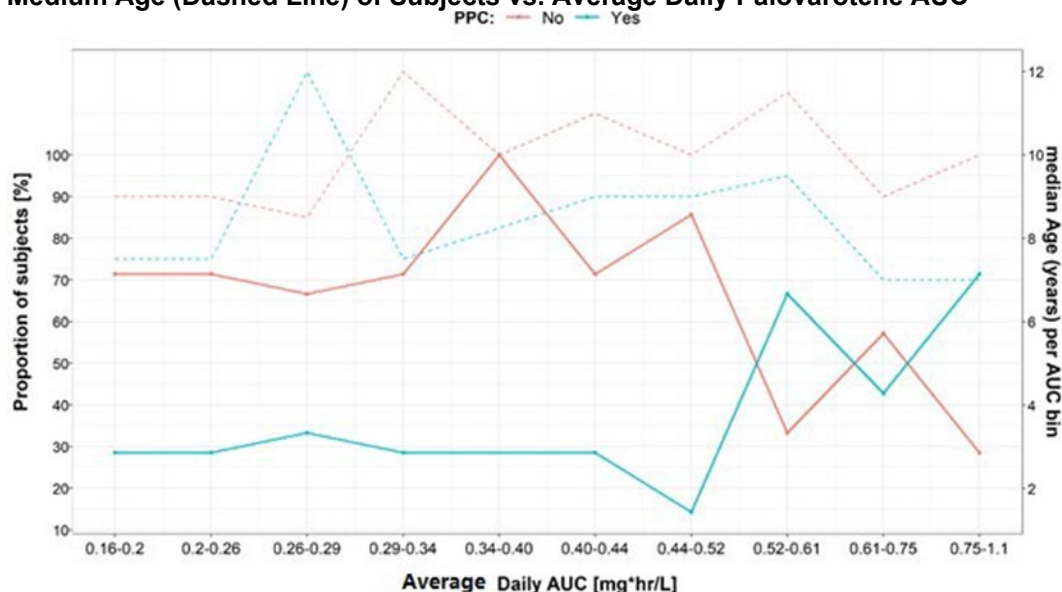
Abbreviations: FOP-FAS, fibrodysplasia ossificans progressiva full analysis set; n, number of subjects; NHS, natural history study; PPC, premature epiphyseal closure

Knee height and femur/tibia lengths (by CT) are presumed to be less susceptible than standing height to measurement difficulty in the presence of FOP-related deformities such as scoliosis. There were generally only small differences in these parameters between untreated NHS subjects and treated subjects without PPC. However, as with standing height, PPC was associated with trends of smaller gains in these growth parameters among subjects age $\geq 8/10$ to <14 years.

In addition to the risk of reduced stature based on growth slowing or arrest, PPC at the distal femur and/or proximal tibia has the potential to create leg length discrepancy due to asymmetric effects on the right and left leg, or abnormal knee angulation due to differential growth of medial and lateral aspects of the growth plate. These issues were systematically addressed in all pediatric subjects: the difference between right and left leg length was derived from the sum of femur and tibia lengths, as measured by whole-body CT scans, on each side; and knee angulation was measured on AP knee radiographs. These evaluations found no evidence of any differences between subjects in Studies 202B/C or 301 and the NHS overall or for subjects with or without PPC. For further details of these evaluations, refer to prior NDA Integrated Review (dated December 23, 2022, in DARRTS).

ER analyses were conducted to assess the impact of palovarotene exposure on PPC risks. The results show that the risk of PPC is increased at higher palovarotene AUCs ([Figure 4](#)). However, this result is likely to be driven by patients <8 years old. When only considering patients 8/10 to 13 years, there is absence of a clear relationship between the proportion of subjects with PPC and AUCs ([Figure 4](#)).

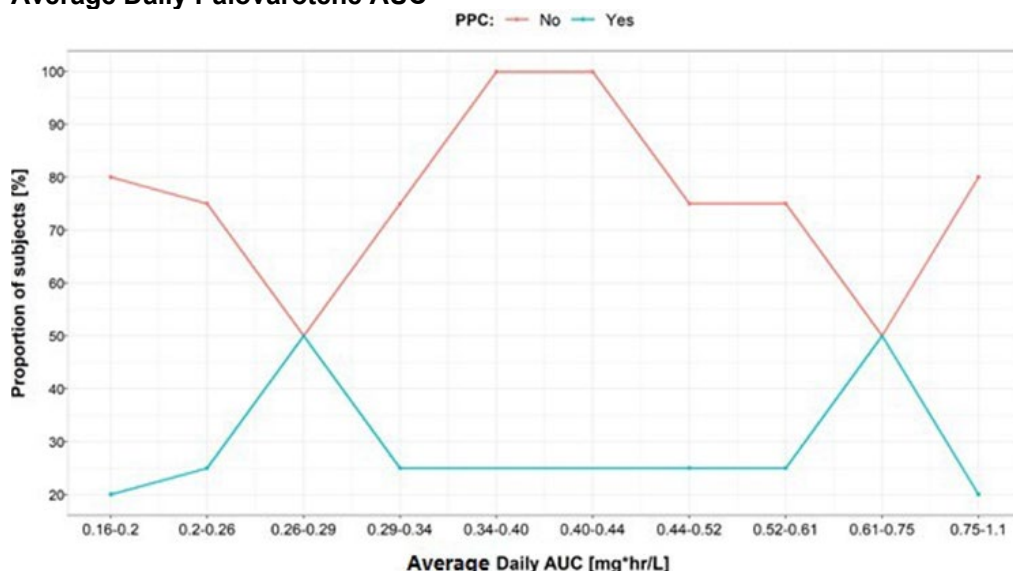
Figure 4. Plots of (1) Proportion of Subjects With or Without PPC Events (Solid Line) and (2) Medium Age (Dashed Line) of Subjects vs. Average Daily Palovarotene AUC



Source: Clinical pharmacology reviewer's analysis.

Abbreviations: AUC, area under the concentration versus time curve; PPC, premature epiphyseal closure

Figure 5. Plots of Proportion of Subjects (Girls 8 to 13 Years/Boys 10 to 13 Years) With PPC vs. Average Daily Palovarotene AUC



Source: Clinical pharmacology reviewer's analysis

Abbreviations: AUC, area under the concentration versus time curve; PPC, premature epiphyseal closure

In general, there is no ER relationship for palovarotene exposure and proportion of patients with PPC events for subjects greater than 8 years of age. Lowering the dose of palovarotene for patients younger than 12 years of age is not predicted to reduce risks of PPC. The review team acknowledges that this conclusion is limited by the small number of reported PPC events in the clinical studies.

Conclusion

The review team agrees with the Applicant that palovarotene treatment of pediatric patients with FOP is associated with a serious risk of PPC. Premature epiphyseal closure development was most apparent at the active growth plates of the knee (distal femur and proximal tibia), which is consistent with literature reports involving other retinoids. Premature epiphyseal closure was not generally associated with rapid advances in bone age as assessed by x-rays of the hand/wrist.

All patients with open growth plates are likely to be at risk of PPC. Younger children (<8/10 years) may be at greatest risk, but 33% of older pediatric patients (age ≥8/10 to <14 years) also showed evidence of PPC in the clinical studies. The Applicant could not identify specific risk factors or a safe level of palovarotene exposure to predict the occurrence of PPC. Because PPC involved the knee and appeared to be irreversible, reduced height is expected to result.

In addition to reduced stature, and potentially disproportionate growth (e.g., short legs relative to trunk), PPC of growth plates at the knee poses a potential risk of leg length discrepancy or abnormal knee angulation. Radiographs have shown no evidence of such effects in study subjects to date, but the duration of treatment and/or follow-up has been limited in most cases; longer-term data are needed.

PPC and impaired growth represent a major safety risk of palovarotene treatment in children with FOP and open growth plates, which will be further investigated in the planned postmarketing safety study. To mitigate this risk to the extent possible, the indicated population should be limited to girls over the age of 8 and boys over the age of 10. Although skeletal abnormalities are a known risk for the retinoid class of products and the finding is labeled as a Warning and Precaution, palovarotene is intended to be a chronically administered product unlike other retinoid agents. Additionally, the PPC risk for palovarotene occurred earlier and more frequently. Therefore, product labeling should include a Boxed Warning for PPC because this is a serious risk in the population of patients with open growth plates and careful monitoring can mitigate that risk. Therefore, the Boxed Warning will include recommendations for patient monitoring, including height measurements and imaging of growth plates.

7.7.3. Embryo-Fetal Toxicity (Retinoid Class Effect)

Issue

Embryo-fetal toxicity (retinoid class effect).

Background

Embryo-fetal toxicity has been reported with multiple retinoids and may result in irreversible fetal malformations, adverse pregnancy outcomes and stillbirths. The labeling of all approved retinoids (isotretinoin, acitretin, tretinoin, bexarotene) includes Boxed Warnings for pregnancy and teratogenicity.

Assessment

Embryo-fetal toxicity consistent with retinoid effects was observed in fetal rat studies of palovarotene (Section [7.1](#)).

The disease burden of FOP results in low reproductive fitness, and there are only rare reports of pregnancy in women with FOP (almost all known cases of FOP result from new spontaneous mutations). Maternal FOP poses life-threatening risks for both the mother and fetus, including cardio-respiratory complications, thromboembolism, delivery complications, fetal distress, and premature birth. Consensus guidelines for FOP advise of these life-threatening risks and urge serious consideration and family planning before attempting a pregnancy. As a result of the high-risk nature of pregnancy in women with FOP, reports of miscarriage are common amongst the small number of FOP pregnancies documented in case reports. The risk of embryo-fetal toxicity from palovarotene would potentially add to the incidence of these events in the population likely to use the drug.

Clinical studies of palovarotene included frequent pregnancy testing and contraception requirements as a precaution. To date, there are no reports of pregnancy or in utero exposure to palovarotene. Based on a phase 1 study showing very low palovarotene levels in semen, administration to a male is considered to be of low risk to female partners who become pregnant.

Conclusion

The risk of teratogenicity, and other pregnancy-related risks is a class warning for retinoid products. Therefore, the palovarotene label will contain a Boxed Warning for teratogenicity. The Applicant has proposed a risk management plan that does not include a risk evaluation and mitigation strategy with the goal of educating prescribers, pharmacists, and patients about the teratogenic potential of palovarotene. This is a reasonable approach based on the following: the FOP patient population is very small and is largely managed by experts in the disease; the pregnancy risks of FOP and importance of family planning discussions are already included in consensus guidelines; pregnancy is very infrequent in FOP patients due to low reproductive fitness; and off label use of palovarotene for other indications such as acne is not expected to occur.

7.7.4. Apparent Adverse Effects of Palovarotene on Vertebral Bone Mineral Density, Bone Mineral Content, and Fractures

Issue

Apparent adverse effects of palovarotene on vertebral bone mineral density (BMD), bone mineral content (BMC), and fractures.

Background

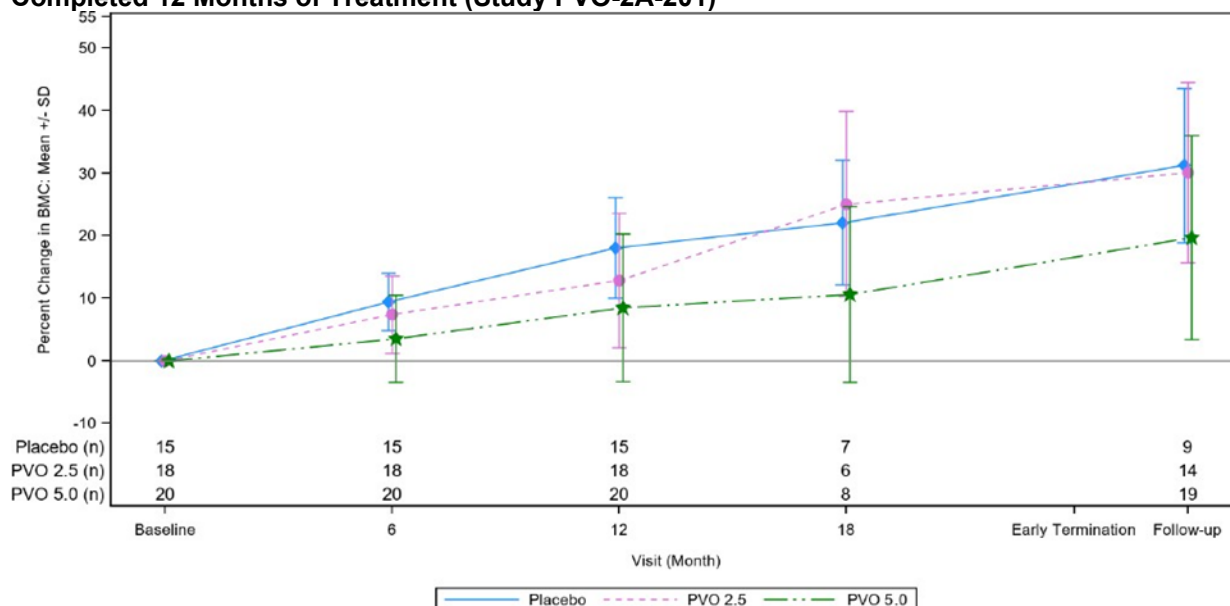
Literature reports indicate that retinoids and vitamin A toxicity may cause bone demineralization, osteoporosis, or “slender long bones” in children. Labeling for isotretinoin in the treatment of acne includes a Warning for negative effects on BMD seen in clinical trials. There is no definitive evidence of an increase in fractures related to retinoid use.

Assessment

Assessments of BMD and BMC by dual x-ray absorptiometry (DXA) were not included in the palovarotene FOP studies because of the likely confounding effects of extensive HO in overlying

soft tissues. However, DXA was conducted on subjects ages 2 to 14 years with multiple osteochondromas in study PVO-2A-201 under another program. Although treatment duration was limited in most subjects due to early termination of the trial, there were discernable trends of reduced BMC accrual in the palovarotene 5 mg treatment group compared to the 2.5 mg and placebo groups. [Figure 6](#) shows that lower BMC in the 5 mg group appeared to persist at the follow-up visit 6 months after discontinuation of the drug.

Figure 6. Lumbar Spine BMC, Percent Change From Baseline, in Subjects With MO Who Completed 12 Months of Treatment (Study PVO-2A-201)



Source: Study PVO-2A-201 CSR Figure S27B.1C

Abbreviations: BMC, bone mineral content; CSR, clinical study report; MO, multiple osteochondromas; n, number of subjects; PVO, palovarotene; SD, standard deviation

Because of this adverse BMC trend in the multiple osteochondroma trial, the FOP DMC requested retrospective re-evaluation of the WBCT scans from FOP patients in Studies 301 (palovarotene treated) and the NHS (untreated) for the assessments related to vertebral structural integrity listed below. It should be noted that these measures have not been validated by FDA for assessment of fractures or estimation of fracture risk in clinical trials; standard radiographs are considered the gold standard for assessment of vertebral fractures. In addition, the populations of Studies 301 and the NHS differed in age and possibly other factors due to the lack of randomization.

Biomechanical CT (BCT) analysis was conducted at L1, L2 or adjacent vertebrae (i.e., T12 if either L1 or L2 was not evaluable) to derive the following parameters:

- Estimated bone compressive strength (Newtons) by finite element analysis
- Trabecular volumetric BMD (mg/cm³) of the central vertebral body
- BMC (g) of the entire vertebral body

The Applicant analyzed the data for changes from baseline, with adjustments for covariates, and reported nominally significant associations of palovarotene treatment with lower values for each of these parameters.

Vertebral fracture analysis of T4 through L4 vertebrae was conducted using automated placement of six points to outline vertebral morphometric shape, which were used to calculate deformity ratios for grading using established criteria of Genant:

- Normal (Grade 0; deformity <20%)
- Mild (Grade 1; deformity $\geq 20\%$ to <25%)
- Moderate (Grade 2; deformity $\geq 25\%$ to <40%)
- Severe (Grade 3; deformity $\geq 40\%$)

The prevalence of these fractures on baseline imaging was 21.5% in palovarotene-treated subjects (Study 301) and 23.6% of untreated subjects (NHS). At 12 months, 28.4% of palovarotene-treated subjects (Study 301) and 11.6% of untreated subjects (NHS) were found to have at least one new-onset vertebral fracture that was not present at baseline. For the target $\geq 8/10$ -year-old population, these proportions were 24.2% and 11.8%, respectively. The 12-month incidences of at least one new-onset moderate/severe fracture (Grade 2 or 3) were 8.6% (palovarotene) and 4.7% (untreated) overall, or 9.1% and 4.4% for the $\geq 8/10$ population. The report indicates that all of these apparent fractures were asymptomatic.

The Applicant also analyzed clinical fracture AEs in the FOP-FAS: normotopic bone fractures were reported in 13/164 subjects (7.9%), including 2/23 subjects (8.7%) in the placebo arm.

Conclusion

The results of the BCT analysis suggest that palovarotene treatment may be associated with decreases in vertebral bone strength, BMC and BMD. Prior vertebral fractures appeared to be highly prevalent at baseline in FOP studies given the young age of the population, which may be disease related, and new abnormalities occurred at a higher rate in palovarotene-treated versus untreated patients over 12 months. These effects are consistent with some data involving other retinoids, but do not establish a definitive causal association due to the post hoc nature of the analyses, use of nonvalidated measures, and differences between the populations of the two nonrandomized studies. This issue will be further explored in the planned postmarketing study.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Age, Sex, Race, and Health Status

Based on a population PK analysis of palovarotene plasma concentration data from 577 subjects, age (2 to 85 years), sex, race (Asian, black, white, and other), and health status (healthy volunteers, FOP, chronic obstructive pulmonary disease, and multiple osteochondromas) were not significant covariates on the PK of palovarotene. According to the population PK analysis, body weight (13 to 130 kg) has a significant impact on palovarotene PK, resulting in increasing exposure with decreasing weight at the same dose.

Renal Impairment

Renal excretion is a minor elimination route of palovarotene based on the mass balance study. No dedicated PK study was conducted in subjects with renal impairment. According to the Applicant's population PK analyses, there was no evidence that serum creatinine affected palovarotene PK. However, since severe renal impairment may potentially affect the drug's hepatic metabolism, there is a concern of increased exposure in severely renally impaired patients. While no dose adjustment is needed for patients with mild-to-moderate renal impairment, the use of palovarotene in patients with severe renal impairment is not recommended.

Hepatic Impairment

No dedicated PK study was conducted in subjects with hepatic impairment. Population PK analyses suggest that there was no significant difference in the PK of palovarotene in subjects with mild (Child-Pugh A, N=66) hepatic impairment compared to subjects with normal hepatic function. The effect of moderate (Child-Pugh B) hepatic impairment on the PK of palovarotene is not conclusive based on the population PK analyses as only a limited number of subjects (N=5) with moderate hepatic impairment were included. The effect of severe (Child-Pugh C) hepatic impairment on the PK of palovarotene has not been evaluated. Given that 97.1% of radioactivity was recovered in feces in the mass balance study and that palovarotene is extensively metabolized by CYP enzymes, palovarotene exposure may likely be increased in subjects with moderate or severe hepatic impairment.

Therefore, the use of palovarotene is not recommended for subjects with moderate and severe hepatic impairment. A postmarketing requirement will be issued to conduct a hepatic impairment study and evaluate the effect of moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment on the PK of palovarotene to inform the dosing recommendations in subjects with hepatic impairment.

More details on intrinsic factors of palovarotene can be found in the Integrated Review in DARRTS dated December 23, 2022.

8.2. Extrinsic Factors

8.2.1. Food Effect

The Applicant proposed taking palovarotene capsules with food, preferably at the same time each day. The capsules may be swallowed whole or opened and the contents emptied onto a teaspoon of soft food. This proposal is supported by the food effect data and the administration instructions from Study 301.

Following oral administration of two 10 mg palovarotene capsules after a high-fat breakfast, palovarotene maximum plasma concentration (C_{max}) and AUC_{0-inf} were 15% and 39% higher, respectively, when compared to exposures under fasting conditions. Following administration of the palovarotene capsules by sprinkling the contents onto one teaspoon of apple sauce after a high-fat breakfast, both AUC and C_{max} were comparable to when the capsules were swallowed whole after a high-fat breakfast.

The review team adds several examples of soft food such as apple sauce, low-fat yogurt, or warm oatmeal under the administration instruction section of the label, if patients choose to take palovarotene with soft food. The stability of palovarotene when mixed with low-fat yogurt and warm oatmeal was found to be acceptable from a chemistry, manufacturing, and controls perspective. In addition, the Study 301 protocol did not specify any soft food, which allows multiple soft food options with palovarotene. The review team also recommends adding “do not administer with grapefruit, pomelo, or juices containing these fruits” under administration instructions, as palovarotene should not be taken concomitantly with strong/moderate CYP3A inhibitors. This is also consistent with the dosing instruction in the study protocol of Study 301.

8.2.2. Drug Interactions

Effect of CYP3A Inhibition and Induction on Palovarotene PK

Study 17041B showed that co-administration of ketoconazole 400 mg QD (a strong CYP3A4 inhibitor) and palovarotene 1 mg QD caused an increase of palovarotene AUC by 3.1-fold. Study NP17040 showed co-administration of rifampin 600 mg QD (a strong inducer of CYP3A4, 2C8, 2C19 and several transporters) and palovarotene 1 mg QD caused a decrease of palovarotene AUC by 89%. The review team agrees that the Applicant’s PBPK analyses are adequate to evaluate the effects of the moderate CYP3A inhibitor erythromycin on the PK of palovarotene. The simulated geometric mean ratios of AUC_{0inf} and C_{max} for palovarotene in the absence and presence of erythromycin (500 mg QID) are 2.54 (90%CI of 2.39, 2.69) and 1.64 (90% CI of 1.59, 1.69), respectively.

The review team therefore recommends that 1) palovarotene should not be taken with a strong or moderate CYP3A4 inhibitor; and 2) if concomitant use with moderate CYP3A inhibitor is unavoidable, the dose of palovarotene should be reduced by half. In addition, the review team concludes that the PBPK analyses are inadequate to evaluate the effect of the moderate CYP3A inducer efavirenz on the PK of palovarotene and agreed with the Applicant’s proposal to avoid concomitant use with strong to moderate CYP3A inducers.

In Study NP21025, a single oral dose of 40 mg prednisone decreased the AUC of co-administered palovarotene by 14%. However, maximum induction of CYP3A4 was not achieved with a single dose of prednisone. The results from Study NP21025 cannot be used to justify that co-administration of multiple-dose prednisone does not affect the PK of palovarotene. Population PK analyses of the PK data of 59 subjects concomitantly taking prednisone did not detect the use of prednisone as a significant covariate on the PK of palovarotene. Therefore, the review team agrees that no dose adjustment is needed for palovarotene in patients who concomitantly use prednisone.

Effect of Palovarotene on Other Drugs

Palovarotene is not expected to impact the PK of prednisone (5 mg QD of palovarotene) and midazolam (20 mg QD of palovarotene).

In Vitro Drug Interaction Characterizations of Palovarotene

Cytochrome P450 (CYP) Enzymes: Palovarotene is an inducer of CYP3A4 and CYP2B6, but not CYP1A2, CYP2C8, CYP2C9 and CYP2C19. Palovarotene is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.

Uridine diphosphate (UDP)-glucuronosyl transferase (UGT) Enzymes: Palovarotene is not an inhibitor or a substrate of UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9 or UGT2B7.

Transporter Systems: Palovarotene is not an inhibitor of P-gp, OAT1, OAT3, OCT2, MATE1, MATE2 K, BCRP, OATP1B1, OATP1B3, OCT1, and BSEP. Palovarotene is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, or OCT1.

More details on extrinsic factors of palovarotene can be found in the Integrated Review in DARRTS dated December 23, 2022.

8.3. Plans for Pediatric Drug Development

Palovarotene is indicated for the treatment of adults and children (females 8 years and older, and males 10 years and older) with FOP. A six-week toxicity study was conducted in juvenile rats with oral palovarotene administered daily at 0.1, 0.5 or 1.2 mg/kg/day from postnatal Weeks 3 through 9 (prior to the closure of epiphyses, which normally occurs between Weeks 15 to 16).

Palovarotene adversely affected skeletal growth and development resulting in abnormal bone size, shape, mass and/or geometry in juvenile rats treated at ≥ 0.5 mg/kg/day (below the clinical exposure, based on AUC). Palovarotene caused dose-related thinning/closure of the physis, physeal hypertrophy and chondrodysplasia in multiple bones, decreased endochondral ossification and hypertrophic hyaline cartilage, and hypertrophy and chondrodysplasia in articular cartilage. Additionally, decreased bone density, avascular necrosis in the femoral head and neck region, and microfractures were notable at 1.2 mg/kg/day. These changes occurred with correlating decreases in bone formation markers, radiological changes (abnormal shape, diffuse bone loss, increased/decreased physis thickness, and increased space between bones). No recovery for effects on thinning/closure of the physis or chondrodysplasia were observed at ≥ 0.5 mg/kg/day; partial to complete recovery of decreased bone growth were seen in animals at 0.5 mg/kg/day.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

8.4.1. Animal Data

The Applicant conducted fertility and early embryonic development studies in male and female rats and an embryofetal development study in a single species (rat). The Agency agreed that there was no benefit in conducting an embryo-fetal development study in pregnant animals of a second species, as palovarotene adversely affected fetal development in pregnant rats, which was consistent with the retinoid class known to carry fetal development risks. Refer to the Integrated Review dated December 23, 2022 in DARRTS for additional details regarding the outcomes and conclusions of these studies.

9. Product Quality

Approval

The Office of Pharmaceutical Quality review team has assessed NDA 215559 with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, the Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective. For additional details, see prior Integrated Review dated December 23, 2022 in DARRTS.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

The clinical studies (NHS, 201, 202A/B/C, 301) were conducted in accordance with the ethical principles of the Declaration of Helsinki, and that are consistent with the International Council for Harmonization Good Clinical Practice and FDA regulations.

The original NDA submitted on March 31, 2021, was withdrawn on August 21, 2021, due to issues of data quality and integrity involving missing WBCT scan readings, which were identified during the review cycle and required extensive updating of the datasets and efficacy analyses. The resubmission includes a Data Integrity Quality Review Report which outlines the steps that were taken to assure the accuracy and reliability of the data. During this second review cycle, no additional issues involving data quality or integrity were identified.

Financial disclosure information was provided (in the original NDA submission) for the covered clinical studies 001, 201, 202A/B/C and 301, as defined by 21 Code of Federal Regulations (CFR) 54.2(e), which establish the effectiveness and safety of palovarotene (See Section [23](#)). No concerns are raised about the integrity of the data.

11. Advisory Committee Summary

An Advisory Committee meeting was held on June 28, 2023, to discuss the substantial evidence of effectiveness for palovarotene in the treatment of pediatric and adult patients with FOP. The committee was asked to consider if the available evidence provided by the Applicant demonstrates that palovarotene has effectiveness in treating FOP, and whether or not any potential benefit of this product outweigh its risks, both known and potential.

With Respect to Voting Question 1:

Does the evidence from Study 301 of palovarotene's treatment effect show the drug is effective in patients with fibrodysplasia ossificans progressiva (FOP)? Provide the rationale for your vote.

The Committee Vote Was:

Yes: 10 No: 4

The majority of the Committee members (10 of 14) voted "Yes," that the evidence from Study 301 demonstrates that palovarotene is effective in patients with FOP. The members that voted yes stated that, although palovarotene failed to meet its primary endpoint, the post hoc analyses and external control NHS were consistent and supported evidence of disease management in the treated population. The four members who voted "No" cited insufficient evidence to demonstrate effectiveness, no symptomatic improvement in treated subjects, statistical design flaws, and inappropriate post hoc analyses as factors that contributed to the data being unreliable and inconclusive regarding efficacy. These members recommended that additional studies be conducted to measure endpoints related to patient function and quality of life.

With Respect to Voting Question 2:

Do the benefits of palovarotene outweigh its risks for the treatment of patients with FOP?

- If you voted yes, provide the rationale for your vote.
- 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.

The Committee Vote Was:

Yes: 11 No: 3

The majority of the Committee members (11 of 14) voted "Yes," that the benefits of palovarotene outweigh its risks for the treatment of patients diagnosed with FOP. The members that voted yes highlighted the rarity and severity of FOP, as well as the lack of current treatment alternatives, as important factors in their vote. They added that the risk of delaying access to an approved treatment in favor of gathering more conclusive evidence is outweighed by the unmet medical need in patients with FOP. The members who voted "Yes" acknowledged that the magnitude of effectiveness shown by palovarotene could be small based on the confidence intervals but emphasized that these benefits can positively impact the quality of life of those affected by this debilitating disorder. They recommended that patient selection criteria be carefully specified to mitigate palovarotene's safety risks as well as patient/family-provider discussion to ensure risks are communicated. They also recommended monitoring bone mineral density in patients, screening for premature epiphyseal closure in pediatric patients, and creation of a patient registry to better understand the FOP patient population and HO volume changes over time. The three members who voted "No" stated that Study 301 did not provide enough evidence of effectiveness in patients with FOP, thus the risk: benefit ratio could not be considered favorable. They recommended that the Applicant conduct additional studies to better characterize if palovarotene provide clinically meaningful benefit in patients with FOP, and if so, what specific patient population (e.g., severity of disease and ages) might benefit most from palovarotene.

III. Additional Analyses and Information

12. Summary of Regulatory History

Refer to Integrated Review in DARRTS, dated December 23, 2022, for a summary of the product development leading up to the original NDA submission on March 31, 2021, and withdrawal of the NDA on August 12, 2021.

Palovarotene is a new molecular entity. On April 29, 2022, Ipsen resubmitted their NDA for palovarotene for the ‘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 (FOP). On December 23, 2022, FDA issued a Complete Response (CR) letter, which conveyed that Ipsen had not demonstrated efficacy of palovarotene, thus the anticipated clinical benefit in the treatment of pediatric and adult patients with FOP, specifically a benefit of palovarotene to prevent the formation of new heterotopic ossification (HO) (the proposed indication), had not been established.

The CR letter further conveyed a number of major review issues that remained unresolved including: 1) the appropriateness of reliance on post hoc analyses to support efficacy; 2) the acceptability of the external control group (natural history study [NHS]) for evaluation of efficacy of the chronic/flare-up dosing regimen; 3) the uncertain implications of the observed negative new HO volume data; 4) the lack of demonstration of efficacy of flare-up-only dosing in the phase 2 studies, and inconsistency in the efficacy data pertaining to chronic/flare-up dosing between phase 2 and 3 data; 5) the potential for increased incidence of flare-ups with palovarotene treatment, particularly with higher doses, which is a concern pertaining to both the efficacy and safety of the drug in patients with FOP; and 6) the unclear plan for demonstration of substantial evidence of effectiveness to support approval.

To address the review issues, FDA recommended that additional data and data analyses, as well as any other available data that may support the efficacy of palovarotene, be submitted. Refer to the CR letter in DARRTS, dated December 23, 2022, for the specific additional data and data analyses requested.

On February 16, 2023, Ipsen submitted a complete response to the deficiencies outlined in the CR letter.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

A comprehensive nonclinical development program consisting of in vitro and in vivo pharmacology and toxicology studies was conducted and reviewed under the original NDA review cycle (see Integrated Review, December 23, 2022).

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Carcinogenicity

No rodent carcinogenicity studies were conducted with palovarotene. The Applicant conducted and submitted a weight-of evidence (WoE)-based risk assessment of palovarotene carcinogenic potential using the available nonclinical data and published information in the public domain. Based on this, the Applicant argued that palovarotene is unlikely to pose a carcinogenic hazard to patients and concluded rodent carcinogenicity studies (neither rat nor mouse) would not contribute any significant value to the human risk assessment. The following WoE factors were used to support the Applicant's conclusion:

1. Maximum duration of patient treatment and patient population (FOP).
2. The absence of preneoplastic or neoplastic lesions in palovarotene's nonclinical chronic toxicology program or in human data.
3. The lack of association between carcinogenicity risk and activation of retinoic acid receptor gamma (RAR γ) in the publicly available literature.
4. Low carcinogenicity potential identified for other marketed retinoids.
5. The absence of hormonal or immunosuppression effects.
6. No signal of genotoxicity.
7. Reduction of unnecessary use of animals in testing.
8. To remain consistent with worldwide regulatory assessments of applications, based on EMA and Health Canada acceptance of the Applicant's proposal to not conduct all routine rodent carcinogenicity studies.

The nonclinical review team disagreed with the Applicant's WoE carcinogenicity conclusions. A brief discussion of WoE factors supporting the nonclinical review team's conclusions are given below:

1. Palovarotene pharmacology and RAR γ target biology

Palovarotene is a retinoic acid receptor (RAR) agonist with selectivity towards the retinoic acid receptor gamma subtype (RAR γ), without clinically relevant off-target activity. RAR belongs to the nuclear receptor superfamily, which act as ligand-activated transcription factors, and plays a critical role in cellular proliferation, differentiation, and apoptosis. Published studies describe RAR γ as a transcription factor for both tumor oncogenes and tumor suppressor genes, depending on the type of cancer studied (Soprano and Soprano 2002; Brown and Petrie 2021). RAR γ overexpression has been reported in several human tumors including liver, colon, stomach, renal, ovarian, and some cases of acute myeloid leukemia (Yan et al. 2010; Huang et al. 2013; Zhu and Luo 2016; Huang et al. 2017; Conserva et al. 2019; Petrie et al. 2020; Xiu et al. 2022).

Upregulation of RAR γ was correlated with cancer cell proliferation, metastasis, chemoresistance and poor survival of cancer patients. On the other hand, retinoids inhibit the development of different types of tumors (e.g., epithelial tumors associated with the skin, respiratory tract, stomach lung and mammary gland) (Jiang et al. 1999; Altucci and Gronemeyer 2001; Pettersson et al. 2002; Bogos et al. 2008; Bettoli et al. 2013). In fact, there are U.S. listed retinoids approved for the treatment of blood and skin related malignancies. The exact molecular mechanism of the retinoid-mediated anticancer effect is not known but is thought to be mediated primarily through induction of apoptosis and promotion of cell differentiation (Chen et al. 2014; Jin et al. 2022).

Overall, the WoE suggested complex biology of the target RAR γ in tumor development and progression, thus there is significant potential for a target-based malignancy risk of RAR γ cooperating with an oncogene pathway. The palovarotene data available to date has not addressed this.

Carcinogenicity Information With the Retinoid Class

Positive tumor outcomes were reported with most of the tested retinoids in rodent carcinogenicity studies at clinically relevant exposures. In rats, pheochromocytoma in the adrenal gland was observed with oral isotretinoin (1- and 5-fold clinical dose based on body surface area comparisons) and adapalene (≥ 2 -fold maximum recommended human dose, body surface area). In mouse, topical tretinoin gel caused cutaneous squamous carcinoma/papilloma in females and liver tumors in males. Blood vessel tumors (hemangiomas and hemangiosarcomas at several sites) were noted with etretinate (a metabolite of acitretin) in male but not female mice at 0.5-fold maximum recommended human dose (body surface area). Moreover, photocarcinogenesis and tumor promotion were reported with approved retinoids. The human relevance of observed nonclinical tumor profiles within the retinoid drug class is unknown.

Potential Evidence of Carcinogenicity From Nonclinical Studies With Palovarotene

Palovarotene was evaluated in chronic, repeat dose toxicity studies in rats and dogs for up to 26- and 39/52-weeks, respectively. In the chronic rat study, there were preneoplastic and inflammatory findings noted in the skin (hypergranulosis, epithelial hyperplasia (acanthosis), chronic inflammation and ulceration) and forestomach (epithelial degeneration/dyskeratosis and acute keratin layer inflammation) at clinically relevant doses. The rat skin changes were consistent with similar skin findings in monkeys. The epithelial hyperplasia findings, which were not species-specific, suggest carcinogenic potential in long-term rodent carcinogenicity studies.

Conclusion

The nonclinical review team, with concurrence from the Executive CDER Carcinogenicity Assessment Committee, concluded that the cancer risk to humans is uncertain and therefore carcinogenicity studies in rats and mice would add value to human carcinogenesis risk assessment. Therefore, the nonclinical review team recommends the conduct of rodent carcinogenicity studies in two species as a postmarketing requirement to adequately assess the clinical carcinogenicity risk from long-term oral exposure to palovarotene.

14. Clinical Pharmacology

14.1. In Vitro Studies

There were no new data submitted under this review. Please refer to the Integrated Review in DARRTS dated December 23, 2022, for details.

14.2. In Vivo Studies

There were no new data submitted under this review. Please refer to the Integrated Review in DARRTS dated December 23, 2022, for details.

14.3. Bioanalytical Method Validation and Performance

Two validated LC-MS/MS methods were used to determine plasma and seminal fluid concentrations of palovarotene. The established benchtop stability, storage stability and freeze-thaw stability cover the maximum storage periods for corresponding clinical studies. For more details, please refer to the Integrated Review in DARRTS dated December 23, 2022.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

Please refer to the Integrated Review in DARRTS dated December 23, 2022, for details.

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

Please refer to this section in the previous Integrated Review, which contains the protocol synopsis for the phase 3 pivotal study, PVO-1A-301.

16. Efficacy

[Table 38](#) lists the efficacy studies conducted by the Applicant for the palovarotene FOP program.

Table 38. Studies Conducted for Palovarotene Treatment in Subjects With FOP

Study	Design	Population	Dose	Endpoints
PVO-1A-001	Natural history study	n=114	No treatment	HO by WBCT every 12 months
PVO-1A-201	R, DB, placebo-controlled 12-week study 6 weeks flare-up treatment, followed by 6 weeks observation	Subjects ≥6 years with FOP and active flare-up n=40 enrolled	Flare-up only dosing Placebo (n=10) 10 mg for 2 weeks, then 5 mg for 4 weeks (n=21) 5 mg for 2 weeks then 2.5 mg for 4 weeks (n=9)	Single flare-up site evaluated Primary: Percentage of subject responders, defined by no or minimal new HO (≤3 on 0-6 scale) at the flare-up site versus baseline as assessed by plain radiograph at Week 6.
PVO-1A-202, A	Single arm, open-label extension of Study 201 Treatment of 2 new flare-ups Duration of treatment, 6 weeks	Subjects from 201 n=40 enrolled	Flare-up only dosing: 10/5	Up to two flare-up sites assessed Primary: Percentage of subject responders as assessed by plain radiographs at the follow-up visit. Percentage of subject responders at up to two, new, distinct flare-up sites compared to baseline as assessed by CT at flare-up Week 6.
PVO-1A-202, B	Open-label, single arm	Subjects ≥6 years with FOP n=54 (subjects from Part A and 18 new subjects)	Adults: Chronic dosing of 5 mg daily with flare-up dosing of 20 mg for 4 weeks then 10 mg for 8 weeks Children: no chronic 5 mg, flare-up only dose	Primary: Proportion of flare-ups with no new HO ("responders") at Week 12.

Study	Design	Population	Dose	Endpoints
PVO-1A-202, C	Open-label, single arm	Subjects from Part B n=46	Adults: chronic dosing of 5 mg daily with flare-up dosing of 20 mg for 4 weeks then 10 mg for 8 weeks Children: chronic dose allowed with flare-up dosing	Primary: Annualized change in new HO volume as assessed by WBCT
PVO-1A-301	Single arm, open-label with NHS as external control	Adult and pediatric subjects ≥4 years of age with FOP n=107	Chronic dosing of 5 mg daily with flare-up dosing of 20 mg for 4 weeks then 10 mg for 8 weeks	Primary: Annualized change in new HO volume as assessed by WBCT

Source: compiled by reviewer

Abbreviations: CT, computed tomography; DB, double-blind; FOP, fibrodysplasia ossificans progressiva; HO, heterotopic ossification; n, number of subjects; NHS, natural history study; PVO, palovarotene; R, randomized; vs, versus; WBCT, whole-body computed tomography

Details regarding select efficacy assessments used in the palovarotene FOP program are shown in the tables and figures below.

The analog scoring scale used by the Applicant to measure new HO on plain radiographs in patients with FOP is shown in [Table 39](#).

Table 39. Analogue Scoring Scale to Measure New HO on Plain Radiograph

Score ^a	Description	Measurement Requirements (Longest Diameter of HO/Normotopic Bone)
0	No HO	No measurement
1	Single or multiple spicules (punctate) or islands (noncontiguous) of HO	No measurement
2	Coalescing islands or reticular complexes of bone	No measurement
3	Single contiguous HO with longest dimension $\leq 1/2$ diameter of reference normotopic bone ^b in any projection	$\leq 50\%$
4	Single contiguous HO with longest dimension $> 1/2$ but ≤ 1 diameter of reference normotopic bone ^b in any projection	$> 50\%$ but $\leq 100\%$
5	Single contiguous HO with longest dimension > 1 but ≤ 2 diameter of reference normotopic bone ^b in any projection	$> 100\%$ but $\leq 200\%$
6	Single contiguous HO with longest dimension > 2 diameters of reference normotopic bone ^b in any projection	$> 200\%$
NE	HO lesion is not evaluable (comments required)	No measurement

Source: Clementia -PVO-1A-201 and PVO-1A-202 Independent Review Charter

^a Score is based on highest grade feature

^b Reference normotopic bone for the indicated location of HO is defined as follows:

Proximal / Upper Extremity – humeral shaft

Distal Upper Extremity = radial shaft

Hip/Proximal Lower Extremity – width of femoral neck

Knee – femoral shaft

Distal Lower Extremity – tibial shaft

Ankle – tibial shaft

Foot - metatarsal

Abbreviations: HO, heterotopic ossification; NE, not evaluable; PVO, palovarotene

The Cumulative Analogue Joint Involvement Scales for assessing disease severity in patients with FOP is shown in [Table 40](#).

Table 40. Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP

The examiner should evaluate the following: Neck – flexion/extension; rotation; lateral bending [0–2] Thoraco-lumbar spine – forward flexion; chest expansion with deep breathing [0–2] Jaw – mouth opening [0–2] Shoulders – abduction [0–2 for each shoulder] Elbows – flexion/extension [0–2 for each elbow] Wrists – dorsiflexion/volarflexion [0–2 for each wrist] Hips – flexion (standing, sitting, or supine) [0–2 for each hip] Knees – flexion/extension [0–2 for each knee] Ankles – dorsiflexion/plantarflexion [0–2 for each ankle]
Scores for each assessed area: 0=normal to <10% deficit 1=10% - 90% deficit 2≥90% deficit
Possible scores: Axial=0–6 Upper limbs=0–12 Lower limbs=0–12 Total=0–30
The examiner MUST also note and record if the patient: • Can walk [yes/no] • Uses a wheelchair [yes/no] • Needs SOME help with activities of daily living [yes/no] • Needs COMPLETE help with activities of daily living [yes/no]

Source: Bone 101 (2017): 123-128.

Forearm rotation (pronation/supination), subtalar motion, and finger/toe motion are not assessed. The CAJIS for each region is based on the greatest limitation in ANY aspect of assessed function. For example, if forward flexion of the thoracic and lumbar spine is not possible but chest expansion is only minimally affected (or vice versa) then the score for the thoracic and lumbar spine would be a 2 (maximal).

Abbreviations: CAJIS, cumulative analogue joint involvement scale; FOP, fibrodysplasia ossificans progressiva

The components of the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale are shown in [Figure 7](#).

Figure 7. The PROMIS Global Health Scale

The PROMIS Global Health short form consists of 10 questions on the adult form and nine questions each on the subject-completed and proxy-completed pediatric form, scored on varying scales.

For the adult form, Global Physical Health and Global Mental Health scores range from 4 (worse health) to 20 (better health).

In the calculation of the Global Physical and Mental Health scores, questions were rescaled as shown in [Table 6](#).

Table 6. Rescaled Global Physical and Mental Health Scores

Parameter(s)	Raw Score	Rescaled Score
7	0	5
	1 to 3	4
	4 to 6	3
	7 to 9	2
	10	1
8 and 10	1	5
	2	4
	3	3
	4	2
	5	1

Source: Appendix 16.1.9 Statistical Analysis Plan Version 2 Table 7

Notes: For the pediatric form, only a total score was calculated, with values ranging from 7 (worse health) to 35 (better health). If a subject was missing some (but not more than three) of the contributing question scores, the total score was calculated as the average observed score multiplied by the number of expected question scores. Global Physical Health scores and Global Mental Health scores were also converted to T-scores.

A T-score of 50 is normal. A T-score <50 indicates worse health while a T-score >50 indicates better health.

Abbreviations: PROMIS, patient reported outcomes measurement information system

Details of additional statistical analyses performed for the purposes of contributing to the demonstration of the efficacy of palovarotene in the treatment of FOP are shown in the tables below.

To investigate robustness of the weighted linear mixed effects (wLME) results to the impact of extreme large values of annualized new HO, the Applicant performed a threshold analysis with a threshold of 100 cm³/year. In this analysis, the values of annualized new HO greater than 100 cm³/year were replaced with the threshold 100 cm³/year ([Table 41](#)).

Similar analyses with different thresholds from 90 cm³/year (new HO >90 cm³/year set to 90 cm³/year) to 30 were performed ([Table 42](#)). These analyses indicate that the difference in the original wLME analysis was not likely driven by extreme large values of subjects in NHS.

Table 41. wLME for Annualized New HO Volume (No Square-Root Transformation and Negatives Included) for Palovarotene-Treated and Untreated Subjects, Replacing Annualized New HO >100 cm³/Year With 100 cm³/Year (Principal FAS)

Method	Study 301 (N=97)	NHS (N=101)	Difference (95% CI)	Nominal p-value
Threshold analysis (HO volumes >100 cm ³ set to 100 cm ³)	8.7	17.7	-9.1(-15.8, -2.3)	0.01

Source: Table 25 in ISE. Results were from a mixed model with dependent variable annualized new HO and independent variables including fixed effects of treatment and baseline total HO/baseline age and a random subject effect. Wilcoxon p-value 0.0003

Abbreviations: CI, confidence interval; FAS, full analysis set; HO, heterotopic ossification; ISE, integrated summary of effectiveness; N, number of subjects; NHS, natural history study; wLME, weighted linear mixed effect model

Table 42. Sensitivity Analyses on Influence of Large Values

Threshold (cm ³)	Study 301	NHS	Difference	LCL	UCL	Nominal p-Value
100 (Table 25 in ISE)	8.686	17.742	-9.057	-15.848	-2.266	0.01
90	8.5	17.3	-8.8	-15.4	-2.2	0.01
70	8.0	15.6	-7.6	-13.5	-1.7	0.0125
50	7.0	13.6	-6.5	-11.4	-1.7	0.01
30	4.8	10.3	-5.5	-9.1	-1.8	0.004

Source: FDA reviewers' analyses

Analyses of New HO with different thresholds from 90 cm³ (new HO >90 cm³/year set to 90 cm³/year) to 5 cm³/year New HO values exceeding threshold value were set to the threshold value. Results were from a mixed model with dependent variable annualized new HO and independent variables including fixed effects of treatment and baseline total HO/baseline age and a random subject effect.

Abbreviations: FDA, Food and Drug Administration; HO, heterotopic ossification; ISE, integrated summary of effectiveness; LCL, lower confidence limit; NHS, natural history study; UCL, upper confidence limit

17. Clinical Safety

Please refer to previous Integrated Review for detailed adverse event summary tables.

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable.

21. Other Drug Development Considerations

Not applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Inspections of the following clinical site investigators were conducted: Dr. Edward Hsiao (Studies 001, 201, 202, 301); Dr. Mona Al Mukaddam (Studies 001, 202, 301); and Dr. Edna Mancilla (Study 301). Dr. Hsiao was issued a Form 483 (VAI) regarding several late-reported severe adverse events; these were all reported and there were no concerns raised regarding data integrity. The other two inspections were NAI.

23. Labeling: Key Changes and Considerations

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft ([Table 43](#)). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

23.1. Approved Labeling Types

Upon approval of this [application/efficacy supplement], the following labeling documents will be FDA-approved:

- Prescribing Information
- Medication Guide
- Container Labels
- Carton Labeling

24. Postmarketing Requirements and Commitments

1. Conduct a clinical trial to evaluate the impact of hepatic impairment on the pharmacokinetics of palovarotene in subjects with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment relative to healthy adult subjects with normal hepatic function, in accordance with the study design described in guidance for industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. (May 2003) Submit the subject-level datasets with the final report.
2. Conduct a carcinogenicity study in rats to assess the carcinogenic potential from long-term oral exposure to palovarotene.
3. Conduct a carcinogenicity study in mice to assess the carcinogenic potential from long-term oral exposure to palovarotene.
4. Conduct a prospective observational registry study with safety objectives of comparing palovarotene exposed and unexposed patients with fibrodysplasia ossificans progressiva (FOP). Evaluate risks of increased flare-up episodes, alterations in growth, and bone fractures. The registry should also collect information on women exposed to palovarotene during pregnancy to assess for adverse events related to pregnancy through the first year postpartum, and birth and developmental outcomes through the infant's first year of life. Begin safety data collection within 90 days of protocol agreement. After protocol finalization, the PMR progress report should be submitted annually as part of the NDA annual report that also includes an evaluation of the effectiveness of meeting the registry study's safety objectives. Collect 10-year safety data from a minimum of 100 subjects, approximately half of whom will be pediatric patients (8 years to less than 18 years of age for girls and 10 years to less than 18 years of age for boys), and approximately two-thirds of whom will be exposed to palovarotene.

25. Financial Disclosure

There were no investigators with disclosable financial interests/arrangements in the covered clinical studies 201, 202A/B/C, 301 or NHS; refer to previous review for details.

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Guidance for Industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003)

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27. Review Team

Table 44. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Noreen Cabellon, MS
Nonclinical reviewer	Lydia Haile, PhD
Nonclinical team leader	David Carlson, PhD
OCP reviewer(s)	Xiaomeng Xu, PhD
OCP team leader(s)	Li Li, PhD
Clinical reviewer	Stephen Voss, MD
Clinical team leader	Theresa Kehoe, MD; Shannon Sullivan, MD, PhD
Statistical analyst	Emily Nguyen, MS
Biometrics reviewer	Alexander Cambon, PhD
Biometrics team leader	Feng Li, PhD
Cross-disciplinary team leader	Theresa Kehoe, MD
Division director (pharm/tox)	Todd Bourcier, PhD
Division director (OCP)	Jaya Vaidyanathan, PhD
Division director (OB)	Mark Rothmann, PhD
Division director (clinical)	Theresa Kehoe, MD
Office director (or designated signatory authority)	Lisa Yanoff, MD

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 45. Additional Reviewers of Application

Office or Discipline	Name(s)
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OSI	
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OSE/DMEPA	Corwin Howard, PharmD Madhuri Patel, PharmD
OSE/DRM	Cristen Lambert, PharmD Yasmeen Abou-Sayed, PharmD Laura Zendel, PharmD
OSE/DPV	Amy Chen, PharmD Ali Niak, MD Daniel Woronow, MD
DPMH	Ethan Hausman, MD Shetarra Walker, MD John Alexander, MD
Other	

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication error Prevention and Analysis; DPMH: Division of Pediatrics and Maternal Health; DPV, Division of Pharmacovigilance; DRM, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

27.1. Reviewer Signatures

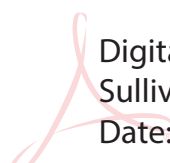
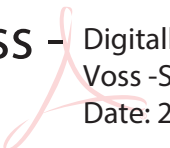
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Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Signatory Authority	Lisa B. Yanoff, MD Office of Cardiology, Hematology, Endocrinology, and Nephrology Enter Division	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: All sections	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: {See appended electronic signature page}				
Clinical Cross-Disciplinary Team Lead	Theresa E. Kehoe, MD Office of Cardiology, Hematology, Endocrinology, and Nephrology DGE	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: All sections	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: {See appended electronic signature page}				

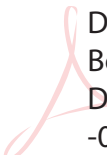
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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Team Leader	Shannon Sullivan, MD, PhD Office of Cardiology, Hematology, Endocrinology, and Nephrology DGE	☒ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: All sections	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Shannon D. Sullivan -S  Digitally signed by Shannon D. Sullivan -S Date: 2023.08.10 16:36:21 -04'00'				
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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
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Signature/date/time stamp: Elisabeth Hanan -S Digitally signed by Elisabeth Hanan -S Date: 2023.08.10 16:52:19 -04'00'				
Regulatory Project Management Regulatory Project Manager	Noreen Cabellon, MS Office of Regulatory Operations DROCHEN	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 12.0	Based on my assessment of the application: ☐ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature/date/time stamp: Noreen N. Cabellon -S Digitally signed by Noreen N. Cabellon -S Date: 2023.08.10 16:57:05 -04'00'				

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacology/Toxicology Division Director	Todd Bourcier, PhD Office of Cardiology, Hematology, Endocrinology, and Nephrology DPTCHEN	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5, 7, 8, 13	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature/date/time stamp: Todd M. Bourcier -S  Digitally signed by Todd M. Bourcier -S Date: 2023.08.09 12:20:00 -04'00'				
Pharmacology/Toxicology Supervisor	David Carlson, PhD Office of Cardiology, Hematology, Endocrinology, and Nephrology DPTCHEN	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5, 7, 8, 13	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
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Signature/date/time stamp: Jayabharath Vaidyanathan -S  Digitally signed by Jayabharath Vaidyanathan -S Date: 2023.08.09 12:51:04 -04'00' On behalf of Li Li				
Clinical Pharmacology Reviewer	Xiaomeng Xu, PhD Office of Clinical Pharmacology Division of Cardiometabolic and Endocrine Pharmacology	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
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Clinical Pharmacology/Pharmacometrics Primary Reviewer	Xiaolei Pan, PhD Office of Clinical Pharmacology Division of Pharmacometrics	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.2 , 6.1 , 8.1 , 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biometrics Division Director	Mark Rothmann, PhD Office of Biostatistics Division of Biometrics II	☐ Benefit-Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 6.2.1, 6.2.2.4, 6.3	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Whether approval or not, this is not a slam dunk. Additionally, I cannot comment on any potential deficiency outside my expertise.
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Biometrics Team Leader	Feng Li, PhD Office of Biostatistics Division of Biometrics II	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.2.1, 6.2.2.4, 6.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
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NDA 215559
Sohonos (Palovarotene)

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
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Biometrics Statistical Analyst	Emily Nguyen, MS Office of Biostatistics Division of Analytics and Informatics	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 6.2.1	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
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NDA 215559
Sohonos (Palovarotene)

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
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NDA 215559
Sohonos (Palovarotene)

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Other Reviewer	Po-Yin Chang, PhD Office of Surveillance and Epidemiology Division of Epidemiology I	☐ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☐ Additional Information and Analyses Sections: 6.3.2	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
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Include “IA” for authors who contributed to the Interdisciplinary Assessment and add “Abbreviations: IA, Interdisciplinary Assessment” as a table note.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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LISA B YANOFF
08/16/2023 08:37:07 AM

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	215559
Priority or standard	Priority
Submit date(s)	4/29/2022
Received date(s)	4/29/2022
PDUFA goal date	12/29/2022
Division/office	Division of General Endocrinology (DGE)
Review completion date	12/22/2022
Established/proper name	Palovarotene
(Proposed) proprietary name	Sohonos
Pharmacologic class	Retinoic acid receptor gamma (RAR γ) selective agonist
Code name	Retinoid
Applicant	Ipsen Biopharmaceuticals, Inc.
Dosage form(s)/formulation(s)	Capsules 1 mg, 1.5 mg, 2.5 mg, 5 mg, 10 mg
Dosing regimen	Chronic dosing, 5 mg daily; flare-up dosing, 20 mg daily for 4 weeks, followed by 10 mg daily for 8 weeks for a total of 12 weeks (20/10 mg flare-up treatment); doses are weight-adjusted for patients < 60 kg
Applicant proposed indication(s)/ population(s)	Prevention of heterotopic ossification (HO) in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva (FOP)
Proposed SNOMED indication	82725007 Progressive myositis ossificans (disorder)
Regulatory action	Complete response
Approved dosage (if applicable)	N/A
Approved indication(s)/ population(s) (if applicable)	N/A
Approved SNOMED term for indication (if applicable)	N/A

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Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BA	bioavailability
CAJIS	Cumulative Analogue Joint Involvement Scale
CMC	chemistry, manufacturing, and controls
CRCL	creatinine clearance
DMC	data monitoring committee
ECG	electrocardiogram
EFD	embryo-fetal development
EOP2	end-of-phase 2
ETA	interindividual random effect
FDA	Food and Drug Administration
FMQ	FDA Medical Dictionary for Regulatory Activities query
FOP	fibrodysplasia ossificans progressiva
FOP-PFQ	FOP-Physical Function Questionnaire
GCP	good clinical practice
GLP	good laboratory practice
HO	heterotrophic ossification
IC ₅₀	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IND	investigational new drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MRHD	maximum recommended human dosage
NDA	new drug application
NHS	natural history study
NOAEL	no observed adverse effect level
OCF	Office of Clinical Pharmacology
OPQ	Office of Pharmaceutical Quality
PD	pharmacodynamic
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PT	preferred term
QD	once daily
REMS	risk evaluation and mitigation strategy
ROM	range of motion
SAE	serious adverse event

NDA 215559

Sohonos, palovarotene capsules

SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TK	toxicokinetic
T _{max}	time to maximum concentration
TQT	thorough QT
ULN	upper limit of normal
WBCT	whole-body computed tomography

I. Executive Summary

1. Summary of Regulatory Action

Fibrodysplasia ossificans progressiva (FOP) is a rare and severely disabling disease caused by a gain-of-function mutation in the activin A type I receptor ACVR1 (ALK2), which renders ALK2 constitutively active to bone morphogenetic protein ligands, drives ectopic chondrogenesis and osteogenesis, and leads to heterotrophic ossification (HO) in connective tissue, joints, and muscle.

Palovarotene is an orally bioavailable retinoic acid receptor (RAR) gamma (RAR γ) selective agonist (retinoid) that appears to interfere with ALK2-mediated bone formation indirectly by dampening bone morphogenetic protein signaling, leading to blockade of chondrogenic and osteogenic differentiation, reprogramming of progenitor cells into nonskeletal lineage, and prevention of abnormal endochondral bone formation in animal models.

Approximately 800 confirmed cases of FOP have been reported globally. Patients with FOP develop extraskeletal bone formation in muscles, tendons and ligaments known as beginning in early childhood. HO is episodic, with some events starting with soft tissue inflammation (flare-up). The accumulation of extraskeletal bone is cumulative and irreversible, causing restriction of movement, deformities, and severe disability. Chronic complications may include chest wall deformity (thoracic insufficiency syndrome), ankyloses of the temporo-mandibular joints resulting in severe tooth decay and malnutrition, and localized skin breakdown. Most patients use mobility assistance by their 20's due to HO around the hips, and survival is shortened (median 56 years), usually by cardio-respiratory failure and pneumonia.

Patients with FOP face a high unmet medical need, as there are no approved therapies and no therapies have been shown to treat or slow progression of HO formation and reduce overall disease burden. Current conventional therapy for FOP is aimed at symptom relief by decreasing inflammation and treating chronic pain. Symptomatic treatment with high dose steroids is often used to treat symptom “flares,” however, short term burst steroid therapy has no benefit in reducing the overall burden of HO or slowing disease progression. Attempts at surgical excision of lesions usually leads to reactivation of disease and new HO.

In support of this application, the Applicant conducted a phase 2, randomized, double-blind, placebo-controlled study in patients with FOP (Study 201), with a phase 2 open-label single arm extension study (Study 202), as well as a single arm, open-label, externally controlled phase 3 study (Study 301). The external control group for Study 301 was a 36-month natural history study (NHS), also conducted by the Applicant, in pediatric and adult patients with FOP.

The proposed dosing regimen includes chronic daily treatment (5 mg), with higher-dose treatment (20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks), with extension if needed, during symptomatic “flare-up” episodes (referred to herein as “20/10 mg” flare-up dosing). All proposed doses are adjusted based on body weight in skeletally immature patients under 18 years of age. This dosing regimen was used in Study 301. A “flare-up only” dosing

regimen is proposed as an alternative treatment option for patients who are unable to tolerate chronic daily treatment, even at reduced doses. This option would consist of the same treatment for flare-ups (20/10 mg), with no chronic treatment during clinically quiescent periods (i.e., between flare-ups). The 20/10 mg “flare-up only” regimen, and 5/2.5 mg and 10/5 mg flare-up-only regimens, were used in Studies 201 and 202.

The primary endpoint for Studies 201/202 was the incidence of new HO at the flare-up site 12 weeks after flare-up initiation. The primary endpoint for Study 301 was annualized change in new whole-body HO volume, and the key secondary endpoint was proportion of subjects with any new HO. Additional secondary endpoints in Study 301 included the number of body regions with new HO, the proportion of subjects reporting flare-ups, and the rate of flare-ups per subject-month. Exploratory endpoints included change from baseline in range of motion (ROM) assessed by CAJIS (Cumulative Analogue Joint Involvement Scale) for FOP, change from baseline in physical function using age-appropriate forms of the FOP-PFQ (FOP Physical Function Questionnaire), and change from baseline in physical and mental function for subjects ≥ 15 years old and mental function for subjects < 15 years old using age-appropriate forms of the PROMIS (Patient Reported Outcomes Measurement Information System) Global Health Scale.

HO volume was assessed by whole-body CT scans based on prespecified body regions in Study 301 and NHS subjects using appropriate adjudication. Whole-body CT scans from Study 202 Parts B and C were read by the same imaging contractor as in Study 301 and the NHS; however, there were differences in methodology between the phase 2 and phase 3 studies. Specific inconsistencies in CT read methodology included the following: in Study 202B/C, CT scans were read by a single radiologist without concurrent comparison to any control group; CT assessments of HO volume were performed using 15 body regions in 202B/C compared to 9 body regions in 301; and 202B/C did not include systematic evaluation of intrareader agreement, similar to the random rereads conducted in Study 301/NHS.

Both Studies 201/202 and Study 301 failed their respective prespecified primary efficacy analyses. In addition, none of the secondary or exploratory endpoints in Study 301 showed statistically significant differences between palovarotene-treated and untreated/control subjects and thus did not provide supportive evidence of the efficacy of palovarotene in the treatment of FOP.

Key Efficacy Issues

The Applicant relied on post hoc analyses from Study 301 to support effectiveness. The following key efficacy issues were identified during the review.

Appropriateness of Reliance on Post Hoc Analyses To Support Efficacy

Post hoc analyses are generally considered hypotheses generating and usually not appropriate for providing substantial evidence of effectiveness. However, in this specific setting, the Agency acknowledged that the prespecified primary analysis had a bias against palovarotene. Therefore, the U.S. Food and Drug Administration (FDA) statistical team considered it was reasonable to look at alternative, more appropriate analyses. Various post hoc analyses performed by the review team suggested that there could have been a nominally significant difference between the primary outcomes of Study 301 and NHS subjects if appropriate analyses had been used.

However, this finding relied on an unverifiable assumption that no other unmeasured confounding factors could have substantially impacted the study results.

In additional post hoc analyses, the Applicant pooled treated subjects from Study 201/202 and Study 301 and compared HO volumes to all untreated control patients from Study 201 and the NHS. These analyses pose multiple statistical challenges for the following reasons: multiple different dosing regimens were used in phase 2 and phase 3; different criteria for treating flares were used in phase 2 versus phase 3 (such that flares were generally undertreated in Study 201/202); a large variability in “placebo” response was observed in the NHS, in which change in HO volume ranged from ~-91000 to +39000; the methods used to determine changes in HO volume by whole-body CT scan differed between the phase 2 and phase 3 trials; and some patients carried over from the NHS to one of the intervention trials, which may have introduced selection bias.

Use of an External Control Group (NHS) for Evaluation of Efficacy of the Chronic/Flare-up Regimen

When an external control is used, there will be a lack of assurance of comparability between treated and untreated subjects given the lack of randomization. Compared to Study 301, NHS subjects were older and had more severe disease severity at baseline. The FDA statistical team performed various analyses to assess the impact of baseline imbalances in selected covariates. However, these analyses could not address the impact of unmeasured and unknown confounding. Furthermore, some NHS subjects were enrolled into Study 301 or other intervention studies after some period of observation in the NHS. The possibility of subject selection bias could not be ruled out. The submission did not address these concerns adequately.

Uncertain Clinical Implications of Negative New HO Volume Data

Based on the natural history of disease progression in FOP, in which HO accumulates gradually over time, the clinical significance of negative HO volumes remains unclear. Whether negative HO volume as assessed by CT scan represents “noise” due to inflammation occurring at an initial flare-up site, or a natural process of bone consolidation as the transition from cartilaginous tissue to bone occurs, or some other physiologic mechanism, remains unknown. Therefore, how to account for negative HO volume change in a study assessing effects of a drug on total HO volume, in which negative HO volumes were seen in both treated and untreated subjects, was not made evident or justified by the Applicant.

Phase 2 Studies: Efficacy of Flare-up-Only Dosing Was Not Established; Efficacy Data Pertaining to Chronic/Flare-up Dosing Were Generally Not Consistent With Phase 3 Data

The primary efficacy endpoint in phase 2 was the proportion of flare-ups resulting in significant new HO (Studies 201, 202A, 202B), and this endpoint was not met with palovarotene treatment compared to placebo. Thus initially, only flare-up dosing (without chronic dosing) was given in phase 2, in contrast to phase 3 (Study 301), in which patients were treated with both chronic and flare-based dosing. Complicating the phase 2 analyses, Studies 202B and 202C subsequently added chronic daily 5 mg dosing to the flare-based regimen, and the primary endpoint was changed to reduction in annualized new whole-body HO volume compared to untreated NHS patients (similar to the primary endpoint for Study 301). Although the data comparing chronic + flare dosing in Studies 202B/202C and Study 301 to the NHS could be informative, particularly

in the subsets of patients who received consistent dosing regimens, Study 202C was ongoing at the time of this NDA submission and these comparisons were not presented.

Additional factors that further complicate such analyses include the following: 1) the rate of annualized new HO in Study 202B ($\sim 29 \text{ cm}^3/\text{year}$) was much higher than in Study 301 ($\sim 9 \text{ cm}^3/\text{year}$) and the NHS ($\sim 24 \text{ cm}^3/\text{year}$), suggesting that these patient populations may have had different baseline disease severities; 2) a subset of patients were enrolled de novo into Study 202B, whereas others were initially enrolled in Study 201 after an acute flare-up and then transferred to Study 202B/C; 3) patients in Study 202B/C were 3 to 5 years older compared to patients in Study 301 and the NHS; and 4) Study 202B and Study 301 had different criteria defining a “flare,” such that some flares in Study 202B were untreated compared to Study 301.

In addition, subgroup analyses suggested that patients in Study 202B, who were undertreated for flare-up symptoms that did not meet the stricter flare-defining criteria, had a higher mean volume of new HO ($33.5 \text{ cm}^3/\text{year}$) compared to patients in Study 202B whose flare symptoms were treated ($-3.0 \text{ cm}^3/\text{year}$) because they met the stricter flare-defining criteria. This finding is inconsistent with the data specific to 202 Part C, in which all flare-up symptoms were treated but rates of new HO remained high. Further, the data from Study 202B/C for patients who received chronic 5 mg dosing and experienced no flare symptoms or flare-based dosing suggest that chronic dosing had no effect to prevent new HO, as these patients had high levels of new HO ($\sim 29 \text{ cm}^3/\text{year}$) despite continuous 5 mg dosing; this is inconsistent with the Study 301 and NHS data, in which patients who did not require flare-based dosing had low volumes of new HO ($\sim 3 \text{ cm}^3/\text{year}$ in Study 301 and $\sim 7 \text{ cm}^3/\text{year}$ in the NHS, respectively).

Because of these inconsistencies of the Study 202B/C versus Study 301 data and the complicating factors of interim protocol changes and differences in study populations, a more complete assessment of palovarotene efficacy in FOP will require further analyses of the 202B/C data, including (but not limited to) comparisons to untreated NHS subjects; control of covariates; comparisons including additional data collected after the original cut-off date submitted in the NDA; and analyses comparing whole-body CT data from Study 202C and Study 301 to the NHS.

Risk Assessment

Safety risks associated with palovarotene include those directly associated with the retinoid drug class of medications, as well as risks seen specifically in patients with FOP. Boxed Warnings and Warnings and Precautions contained in the retinoid class product labels include teratogenicity, psychiatric disorders, pseudotumor cerebri, serious skin reactions, pancreatitis, lipid abnormalities (hypertriglyceridemia), hearing impairment, hepatotoxicity, inflammatory bowel disease, skeletal abnormalities including decreased bone mineral density, hyperostosis and premature epiphyseal closure, and vision impairment.

Regarding the risk of premature physeal closure (PPC) seen with the retinoid class, treatment with palovarotene caused PPC in subjects with open growth plates despite lower, weight-based dosing in younger patients. Potentially, this could result in significant adverse effects on growth, especially in younger age groups. The Applicant proposed an indication that would allow most patients with at least 80% skeletal maturity (bone age 8 years in girls and 10 years in boys) to receive palovarotene for the prevention of HO despite the risk of PPC, given the severity of the disease.

Palovarotene is a known teratogen as a member of the retinoid class; however, there are only rare reports of pregnancy in women with FOP, and consensus guidelines urge serious consideration before women with FOP attempt pregnancy given that pregnancy is extremely high risk. As a precaution, clinical studies of palovarotene have included frequent pregnancy testing and contraception requirements, and to date, there are no reports of pregnancy or in utero exposure to palovarotene. The Applicant proposed a Boxed Warning in labeling to mitigate this risk.

Regarding effects on bone mineral content, bone density and fractures, results of a biomechanical CT and vertebral fracture analysis suggest that palovarotene treatment may be associated with decreases in vertebral bone strength, BMC and BMD, and a higher risk of new onset morphometric vertebral fractures. These effects are consistent with some data involving other retinoids and are consistent with the BMD findings by DXA in osteochondroma subjects. However, the data do not establish a definitive causal association due to the post hoc nature of the analyses, use of non-validated measures and differing amounts of follow-up data between the nonrandomized populations of Study 301 and the NHS.

There is an unresolved concern that palovarotene for patients with FOP could increase the incidence of HO flare-ups. FOP flare-up episodes were reported by a greater proportion of palovarotene-treated subjects in Study 301 compared to untreated subjects in the NHS and at a higher frequency (0.15 versus 0.07 per month), and within Study 301, new flare-ups were reported at higher rates during cycles of flare-up treatment (0.33 new events per month versus 0.12 per month during chronic dosing). Most of the new flare-ups occurred at sites distant from the initial site. Similarly, data from Studies 201/202 showed higher rates of new flare-ups during flare-up dosing with palovarotene 10/5 mg or 20/10 mg (0.18 to 0.29/month) in comparison to placebo or NHS untreated subjects (0.11 to 0.12/month), or chronic 5 mg dosing (0.10/month). However, flare-ups appear to have been under-reported in the NHS, so the validity of these findings remains unclear. The potential risk of an increase in HO flares during treatment with palovarotene was not identified by the Applicant nor was this risk included in proposed product labeling. Additional analyses will be necessary to better determine the potential for palovarotene treatment to worsen disease severity and posing a safety risk by increasing HO formation.

Conclusions

Overall, the Applicant has not demonstrated substantial evidence of the effectiveness of palovarotene in the treatment of pediatric or adult patients with FOP. As the benefit has not been established, a meaningful benefit-risk assessment cannot be performed. Thus, the data submitted in NDA 215559 do not support approval of palovarotene for prevention of HO in pediatric or adult patients with FOP, and the application will receive a Complete Response. A potential path forward for the Applicant to attempt to demonstrate substantial evidence of the effectiveness of palovarotene for the treatment of FOP would include additional data analyses comparing similarly treated subjects from the phase 2 and phase 3 trials and the NHS in order to resolve the numerous review issues pertaining to efficacy discussed above, particularly the inconsistencies and discrepancies in the results between the phase 2 and phase 3 trials. It is recommended that such analyses include all patients and trial data until study close-out for the intervention trials and the NHS so that the Agency can make the most informed decision about a benefit-risk assessment for palovarotene in patients with FOP in a future resubmission.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Fibrodysplasia ossificans progressiva (FOP) is a rare, severely disabling disease caused by a gain-of-function mutation in the activin A type I receptor ACVR1 (ALK2). The most common mutation (>90%) is arginine 206 to histidine (R206H), which renders ALK2 constitutively active to bone morphogenetic protein ligands, drives ectopic chondrogenesis and osteogenesis, and leads to heterotrophic ossification (HO) in connective tissue, joints, and muscle. Approximately 800 confirmed cases of FOP have been reported globally. Patients with FOP develop extraskeletal bone formation in muscles, tendons and ligaments, known as HO, beginning in early childhood. HO is episodic, with some events starting with soft tissue inflammation (flare-up). The accumulation of extraskeletal bone is cumulative and irreversible, causing restriction of movement, deformities, and severe disability. Complications include chest wall deformity (thoracic insufficiency syndrome), ankyloses of the temporo-mandibular joints resulting in severe tooth decay and malnutrition, and localized skin breakdown. Most patients use mobility assistance by their 20's due to HO around the hips. Survival is shortened (median 56 years), most often by cardio-respiratory failure and pneumonia. There are currently no approved therapies for the treatment of FOP, thus patients face a high unmet medical need to control their disease. Palovarotene is an orally bioavailable retinoic acid receptor (RAR) gamma (RARγ) selective agonist (retinoid) that appears to interfere with ALK2-mediated bone formation indirectly via dampening bone morphogenetic protein signaling. This is thought to lead to blockade of chondrogenic and osteogenic differentiation, reprogramming of progenitor cells into nonskeletal lineage, and prevention of abnormal endochondral bone formation.	FOP is a rare and serious debilitating condition caused by a gain-of-function mutation in the ALK2 receptor that manifests starting in early childhood. Patients with FOP face a high unmet medical need as no therapies have been shown to treat or slow progression of FOP, specifically the formation of HO and the resulting morbidity associated with chronic HO accumulation. Palovarotene is a retinoic acid receptor (RAR) gamma (RARγ) selective agonist (retinoid) that appears to interfere with ALK2-mediated bone formation and is thus being developed for the treatment of FOP.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	There are currently no approved treatments for patients with FOP. Current conventional therapy for FOP is aimed at symptom relief by decreasing inflammation and chronic pain. Attempts at surgical excision of lesions usually leads to reactivation of disease and new HO. Symptomatic treatment with high dose steroids is often used to treat symptom “flares,” however, short term burst steroid therapy has not benefit in reducing the overall burden of HO or slowing disease progression. There are currently no approved therapies for the treatment of FOP.	FOP is a rare disease with no approved therapies, thus only supportive care can be used to decrease pain and inflammation.
Benefits	In support of the proposed indication, the Applicant conducted a phase 2 randomized, placebo-controlled, double-blind study in patients with FOP (Study 201) with a phase 2 open-label single arm extension study (Study 202), and a single arm, open-label, externally controlled, phase 3 study (Study 301). The external control group for Study 301 was a 36-month natural history study (NHS) conducted by the Applicant in patients with FOP. The proposed dosing regimen includes chronic daily treatment (5 mg), with higher dose treatment (20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks, with extension if needed, referred to as “20/10 mg”) during symptomatic “flare-up” episodes of FOP (all proposed doses are adjusted based on body weight in skeletally immature patients under 18 years of age). This dosing regimen was used in Study 301. A “flare-up only” dosing regimen is proposed as an alternative treatment option for patients who are unable to tolerate chronic daily treatment, even at reduced doses. This option would consist of the same treatment of flare-ups (20/10 mg), with no chronic treatment during clinically quiescent periods (i.e., between flare-ups). The 20/10 “flare-up only” regimen, along with a 5/2.5 mg and a 10/5 mg regimen, were used in Studies 201 and 202. The primary endpoint for Study 201/202A/202B was the incidence of new HO at the flare-up site 12 weeks after flare-up initiation. The primary endpoint for Study 301 was annualized change in new whole-body HO volume, and the key secondary endpoint was proportion of subjects with any new HO. Additional secondary endpoints in Study 301 included the number of body regions with new HO, proportion of subjects reporting flare-ups, and the rate of flare-ups per subject-month. Exploratory endpoints included change from baseline in ROM (range of motion) assessed by CAJIS (Cumulative Analogue Joint Involvement Scale for FOP), change from baseline in physical function using age-appropriate forms of the FOP-PFQ (FOP Physical Function Questionnaire), and change from baseline in physical and mental function using age-appropriate forms of the PROMIS (Patient Reported Outcomes Measurement Information System) Global Health Scale.	Both the phase 2 randomized, placebo-controlled trials (Studies 201/202) and the externally controlled phase 3 trial (Study 301) failed to meet their respective prespecified primary efficacy endpoints. The Applicant submitted post hoc analyses from Study 301 to support the effectiveness of palovarotene in treating FOP. However, the validity and acceptability of these post hoc analyses using an external control group (with multiple differences compared to the treated group with respect to demographics and disease status) are questionable. Furthermore, the post hoc analyses included negative new HO volume data, which was seen in both treated and untreated patients. The clinical significance of a decrease in HO volume over time in patients with FOP is unclear, as HO volume is known to accumulate over time as the disease progresses. Additionally, none of the secondary or exploratory endpoints in Study 301 supported a benefit of treatment with palovarotene over nontreated subjects. The data from the placebo-controlled phase 2 studies (202B/C) also failed to support the efficacy of either chronic or flare-based dosing of palovarotene in the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	HO volume was assessed by whole-body CT scans based on prespecified body regions in study 301 and NHS subjects using appropriate adjudication. Whole-body CT scans from Study 202 B/C were read by the same imaging contractor as in Study 301 and the NHS; however, there were differences in methodology between the phase 2 and phase 3 studies. Specific inconsistencies in CT read methodology included the following: in Study 202B/C, CT scans were read by a single radiologist without concurrent comparison to any control group; CT assessments of HO volume were performed using 15 body regions in 202B/C compared to 9 body regions in 301; and 202B/C did not include systematic evaluation of intrareader agreement, similar to the random rereads conducted in Study 301/NHS. Both Studies 201 and 301 failed the prespecified primary efficacy analysis. In addition, none of the secondary or exploratory endpoints in Study 301 showed a difference between palovarotene-treated and control/untreated patients. Thus, the Applicant relied on post hoc analyses from Study 301 to support the effectiveness of palovarotene in this NDA submission. The following key efficacy issues were identified during the FDA review: • <u>Appropriateness of reliance on post hoc analyses to support efficacy.</u> Post hoc analyses are generally considered hypotheses generating and usually not appropriate for providing substantial evidence of effectiveness. However, in this specific setting, the Agency acknowledged that the prespecified primary analysis had a bias against palovarotene. The FDA statistical team thus considered it is reasonable to look at alternative, more appropriate analyses. Various post hoc analyses performed by the review team suggested that there could have been a nominally significant difference between the primary outcomes of Study 301 and NHS subjects if appropriate analyses had been used. However, this finding relied on an unverifiable assumption that no other unmeasured confounding factors could have substantially impacted the study results. In additional post hoc analyses, the Applicant pooled treated subjects from Study 201/202 and Study 301 and compared HO volumes to all untreated control patients from Study 201 and the NHS. These analyses pose multiple statistical challenges for the following reasons: multiple different dosing regimens were used in phase 2 and phase 3; different criteria for treating flares were used in phase 2 versus phase 3 (such that flares may have been undertreated in Study 201/202); large variability in “placebo” response from the NHS, in which change in HO volume ranged from ~ -91000 to +39000, was seen; methods used to determine changes in HO volume by whole-body CT scan differed between the	treatment of FOP. In addition, multiple complications with respect to these data were identified during the review and will require clarification and additional analyses to be potentially interpretable. These include incompleteness of the phase 2 trial data, which was ongoing at the time of the NDA submission; differences in study populations within phase 2 and compared to phase 3 and the NHS; interim changes in study design and study endpoints; and use of varying flare-up defining criteria used to initiate flare-based dosing.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	phase 2 and phase 3 trials; and a subset of patients carried over from the NHS to one of the intervention trials, which may have introduced selection bias. • <u>Use of an external control group (NHS) for evaluation of efficacy of the chronic/flare-up regimen.</u> When an external control is used, there will be a lack of assurance of comparability between treated and untreated subjects given the lack of randomization. Compared to Study 301, NHS subjects were older and had worse disease severity at baseline. The FDA statistical team performed various analyses to assess the impact of baseline imbalance in selected covariates. However, these analyses could not address the impact of unmeasured and unknown confounding. Furthermore, some NHS subjects were enrolled into Study 301 or other intervention studies after some period of observation in the NHS. The possibility of subject selection bias could not be ruled out. The submission did not address these concerns adequately. • <u>Uncertain clinical implications of negative new HO volume data.</u> Based on the natural history of disease progression in FOP, in which HO accumulates gradually over time, the clinical significance of negative HO volumes remains unclear. Whether negative HO volume as assessed by CT scan represents “noise” due to inflammation occurring at an initial flare-up site, or a natural process of bone consolidation as the transition from cartilaginous tissue to bone occurs, or some other physiologic mechanism, remains unknown. Therefore, how to account for negative HO volume change in a study assessing effects of a drug on total HO volume, in which negative HO volumes were seen in both treated and untreated subjects, was not made evident or justified by the Applicant. • <u>Phase 2 studies: Efficacy of flare-up-only dosing was not established; efficacy data pertaining to chronic/flare-up dosing were generally not consistent with phase 3 data.</u> The primary efficacy endpoint in phase 2 was the proportion of flare-ups resulting in significant new HO (Studies 201, 202A, 202B), and this endpoint was not met with palovarotene treatment compared to placebo. Thus initially, only flare-up dosing (without chronic dosing) was given in phase 2, in contrast to Study 301, in which patients were treated with both chronic and flare-up dosing. Complicating the phase 2 analyses, Studies 202B and 202C subsequently added chronic daily dosing to the flare-based regimen, and the primary endpoint was changed to reduction in annualized new whole-body HO volume compared to untreated NHS patients (similar to the primary endpoint for Study 301). Although the data comparing chronic + flare dosing in Studies 202B/202C to the NHS could be informative, especially given that the dosing was consistent across these studies,	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Study 202C was ongoing at the time of this NDA submission and none of these data were presented. Further complicating these analyses, the rate of annualized new HO in Study 202B (~29 cm³/year) was much higher than in Study 301 (~9 cm³/year) and the NHS (~24 cm³/year), suggesting that these patient populations may have had different baseline disease severities; a subset of patients were enrolled de novo into Study 202B, whereas others were initially enrolled in Study 201 after an acute flare-up and then transferred to Study 202B/C; patients in Study 202B/C were 3-5 years older compared to Study 301 and the NHS; and Study 202B and 301 had different criteria defining a “flare,” such that some flares in 202B were untreated compared to 301. Subgroup analyses suggested that patients in Study 202B who were undertreated for flare-up symptoms had a significantly higher mean volume of new HO (33.5 cm³/year) compared to patients in Study 202B whose flare symptoms were treated because they met the stricter flare-defining criteria (~3.0 cm³/year). This finding is inconsistent with the limited data specific to Part C, in which all flare symptoms were treated but rates of new HO were high. The data from Study 202B/C from patients who received chronic 5 mg dosing but no flare symptoms or flare-based dosing suggest that chronic dosing had no effect to prevent new HO, as these patients had high levels of new HO (~29 cm³/year) despite continuous 5 mg dosing; this is inconsistent with Study 301 and NHS data, in which patients who did not require flare-based dosing had low volumes of new HO (~3 cm³/year in Study 301 and ~7 cm³/year in the NHS, respectively). Because of these inconsistencies of the Study 202B/C versus Study 301 data and the complicating factors of protocol changes and differences in study populations, a more complete assessment of palovarotene efficacy in FOP will require additional analyses of the 202B/C data, including (but not limited to) comparisons to untreated NHS subjects; control of covariates; comparisons that include additional data collected after the original cut-off date submitted in the NDA; and analyses comparing whole-body CT data from Study 202C and Study 301 to the NHS, given that the 202C and 301 treatment regimens were the same.	

Risk and Risk Management	Palovarotene is a member of the retinoid class of medications and carries the risks associated with the class. Boxed Warnings and Warnings and Precautions contained in the retinoid class product labels include teratogenicity; psychiatric disorders; pseudotumor cerebri; serious skin reactions; pancreatitis and hepatotoxicity; hypertriglyceridemia; hearing impairment; inflammatory bowel disease; skeletal abnormalities, including decreased bone mineral density, hyperostosis and premature epiphyseal closure; and vision impairment, including corneal opacities and decreased night vision. Palovarotene may also be associated with risks that are specific to patients with FOP. Of major concern is the potential for increased incidence of flare-ups with palovarotene treatment. FOP flare-up episodes were reported by a greater proportion of palovarotene-treated subjects in Study 301 compared to untreated subjects in the NHS, and at a higher frequency (0.15 versus 0.07 per month). However, flare-ups appear to have been under-reported in the NHS based on the study design. In addition, within Study 301, flare-ups were reported at higher rates during cycles of flare-up treatment (0.33 new events per month, versus 0.12 per month during chronic dosing). Similarly, data from Studies 201/202 showed higher rates of new flare-ups during flare-up dosing with 10/5 mg (0.26/month), 20/10 mg (0.18-0.20/month) and 20/10 mg (0.29/month), in comparison to flare-up dosing with 5/2.5 mg (0.08/month), placebo/NHS (0.11-0.12/month), or chronic 5 mg dosing (0.10/month). • <u>Premature Epiphyseal closure</u>: Systemic retinoids have long been associated with a variety of adverse skeletal effects, including premature physeal closure (PPC) and impaired growth in children. Growth plate abnormalities and premature closure were also observed in juvenile rats exposed to palovarotene and were consistent with retinoid class effects. Treatment with palovarotene caused PPC in subjects with open growth plates. This occurred despite the weight-based dosing in younger patients. There were trends of slower growth (standing height and femur/tibia length) among some though not all subjects with PPC, and no evidence of reversibility although long term data were limited. The Applicant proposes an indication that would allow most patients with at least 80% skeletal maturity (bone age 8 years in girls and 10 years in boys) to receive palovarotene despite the risk of PPC given the severity of the disease. • <u>Teratogenicity</u>: Embryo-fetal toxicity has been reported with multiple retinoids and may result in irreversible fetal malformations, adverse pregnancy outcomes and stillbirths. The labeling of all approved retinoids (isotretinoin, acitretin, tretinoin, bexarotene) includes a Boxed Warning for pregnancy and teratogenicity. Embryo-	Palovarotene is associated with multiple significant risks related to its mechanism of action as a retinoid derivative (e.g., teratogenicity, premature epiphyseal closure, etc.), as well as specific risks associated with its use in patients with FOP (e.g., potential increase in incidence of “flares”). The Applicant proposed enhanced labeling to communicate the risks of teratogenicity and PPC in a Boxed Warning, Warning and Precaution, and contraindication of pregnancy, along with educational materials for prescribers, pharmacists, patients and their caregivers. To mitigate the risk of PPC associated with palovarotene use in growing children, the Applicant proposed a lower, weight-based dosing regimen for pediatric subjects and to limit treatment to pediatric patients who have achieved at least 80% of their final adult height, which is approximately >8 years of age in girls and >10 years in boys. The potential risk of increase in disease “flares” with flare-based treatment will need to be further investigated to determine the validity of this finding.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	fetal toxicity consistent with retinoid effects was observed in fetal rat studies of palovarotene. There are only rare reports of pregnancy in women with FOP, and pregnancy in women with FOP poses life-threatening risks for both the mother and fetus. Reports of miscarriage are fairly common amongst the small number of FOP pregnancies documented in case reports. The risk of embryo-fetal toxicity from palovarotene would add to the incidence of these events in the population likely to use the drug. As a precaution, clinical studies of palovarotene included frequent pregnancy testing and contraception requirements. To date, there are no reports of pregnancy or in utero exposure to palovarotene. • <u>Psychiatric disorders</u>: Treatment with retinoids have been associated with depression, psychosis, and suicidal ideation. Psychiatric adverse events, including depressed mood, suicidal ideation, depression, mood changes, and memory/attention impairment were reported overall in 25 (18%) subjects in the phase 2 and 3 trials. • <u>Effects on bone mineral content, bone density and fractures</u>: The data submitted suggest that palovarotene treatment may be associated with decreases in vertebral bone strength, BMC and BMD, and a higher risk of new onset morphometric vertebral fractures. These effects are consistent with data involving other retinoids and are consistent with the BMD findings in osteochondroma subjects. However, the data do not establish a definitive causal association due to the post hoc nature of the analyses, use of nonvalidated measures and differing amounts of follow-up data between the nonrandomized populations of Study 301 and the NHS. Vertebral fracture assessment (VFA) has not been validated for assessment of vertebral fractures in clinical trials, and the data collected on vertebral density and estimated strength are exploratory measures that have not been demonstrated to predict fracture risk.	

Abbreviations: ALK2, activin receptor-I like kinase-2; BMC, bone mineral content; BMD, bone mineral density; CAJIS, Cumulative Analogue Joint Involvement Scale for FOP; CT, computed tomography; DXA, dual energy x-ray absorptiometry; FOP, fibrodysplasia ossificans progressiva; FOP-PFQ, fibrodysplasia ossificans progressiva Physical Function Questionnaire; HO, heterotrophic ossification; NHS, natural history study; PPC, premature physal closure; PROMIS, Patient Reported Outcomes Measurement Information System; R206H, arginine 206 to histidine mutation; RAR, retinoic acid receptor; RAR γ , retinoic acid receptor gamma; REMS, Risk Evaluation and Mitigation Strategy; ROM, range of motion; VFA, vertebral fracture assessment; wLME, Weighted Linear Mixed Effects

2.2. Conclusions Regarding Benefit-Risk

Fibrodysplasia ossificans progressiva is a rare and severely disabling disease caused by a gain-of-function mutation in the activin A type I receptor ACVR1 (ALK2), which renders ALK2 constitutively active to bone morphogenetic protein ligands, drives ectopic chondrogenesis and osteogenesis, and leads to HO in connective tissue, joints, and muscle.

Palovarotene is an orally bioavailable retinoic acid receptor (RAR) gamma (RAR γ) selective agonist (retinoid) that appears to interfere with ALK2-mediated bone formation indirectly by dampening bone morphogenetic protein signaling, leading to blockade of chondrogenic and osteogenic differentiation, reprogramming of progenitor cells into nonskeletal lineage, and prevention of abnormal endochondral bone formation in animal models.

Approximately 800 confirmed cases of FOP have been reported globally. Patients with FOP develop extraskeletal bone formation in muscles, tendons and ligaments known as heterotopic ossification beginning in early childhood. HO formation is episodic, with some events starting with soft tissue inflammation (flare-up). The accumulation of extraskeletal bone is cumulative and irreversible, causing restriction of movement, deformities, and severe disability. Chronic complications may include chest wall deformity (thoracic insufficiency syndrome), ankyloses of the temporo-mandibular joints resulting in severe tooth decay and malnutrition, and localized skin breakdown. Most patients use mobility assistance by their 20's due to HO around the hips, and survival is shortened (median 56 years), usually by cardio-respiratory failure and pneumonia.

Patients with FOP face a high unmet medical need, as there are no approved therapies and no therapies have been shown to treat or slow progression of HO formation and reduce overall disease burden. Current conventional therapy for FOP is aimed at symptom relief by decreasing inflammation and chronic pain. Symptomatic treatment with high dose steroids is often used to treat symptom "flares," however, short term burst steroid therapy has no benefit in reducing the overall burden of HO or slowing disease progression. Attempts at surgical excision of lesions usually leads to reactivation of disease and new HO.

Potential Benefit of Palovarotene in the Treatment of FOP

In support of this application, the Applicant conducted a phase 2, randomized, placebo-controlled, double-blind study in patients with FOP (Study 201), with a phase 2 open-label single arm extension study (Study 202), and a single arm, open-label, externally controlled phase 3 study (Study 301). The external control group for Study 301 was a 36-month natural history NHS, also conducted by the Applicant, in pediatric and adult patients with FOP.

The proposed dosing regimen includes chronic daily treatment (5 mg), with higher-dose treatment (20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks, with extension if needed, referred to as "20/10 mg") during symptomatic "flare-up" episodes (all proposed doses are adjusted based on body weight in skeletally immature patients under 18 years of age). This dosing regimen was used in Study 301. A "flare-up only" dosing regimen is proposed as an alternative treatment option for patients who are unable to tolerate chronic daily treatment, even at reduced doses. This option would consist of the same treatment of flare-ups (20/10 mg), with no chronic treatment during clinically quiescent periods (between flare-ups). The 20/10 "flare-up only" regimen, along with 5/2.5 and 10/5 regimens, were used in Studies 201 and 202.

The primary endpoint for Studies 201/202A/202B was the incidence of new HO at the flare-up site 12 weeks after flare-up initiation. The primary endpoint for Study 301 was annualized change in new whole-body HO volume, and the key secondary endpoint was proportion of subjects with any new HO. HO volume was assessed by whole-body CT scans based on prespecified body regions using appropriate adjudication. CT scans from Study 202 B/C were read by the same imaging contractor as in Study 301 and the NHS; however, there were differences in the precise methodology for assessing changes in HO by whole-body computed tomography (WBCT) between the phase 2 and phase 3 studies.

Additional secondary endpoints in Study 301 included the number of body regions with new HO, the proportion of subjects reporting flare-ups, and the rate of flare-ups per subject-month. Exploratory endpoints included change from baseline in ROM (range of motion) assessed by CAJIS (Cumulative Analogue Joint Involvement Scale for FOP), change from baseline in physical function using age-appropriate forms of the FOP-PFQ (FOP Physical Function Questionnaire), and change from baseline in physical and mental function using age-appropriate forms of the PROMIS (Patient Reported Outcomes Measurement Information System) Global Health Scale.

Both Studies 201/202 and Study 301 failed to meet the prespecified primary efficacy endpoints. In addition, none of the secondary or exploratory endpoints in Study 301 showed statistically significant differences between palovarotene-treated and untreated/control subjects and thus did not provide supportive evidence of efficacy of this product in the treatment of FOP.

Due to failure to achieve the prespecified primary endpoints, the Applicant relied on post hoc analyses from Study 301 to support the effectiveness of palovarotene. The following key efficacy issues were identified during the review.

- Appropriateness of reliance on post hoc analyses to support efficacy

Post hoc analyses are generally considered hypotheses generating and are usually not appropriate for providing substantial evidence of effectiveness. However, in this specific setting, the Agency acknowledged that the prespecified primary analysis had a bias against palovarotene. The FDA statistical team considered it is reasonable to look at alternative, more appropriate analyses. Various post hoc analyses performed by the review team suggested that there could have been a nominally significant difference between the primary outcomes of Study 301 and NHS subjects if appropriate analyses had been used; however, this finding relied on an unverifiable assumption that no other unmeasured confounding factors could have substantially impacted the study results.

In additional post hoc analyses, the Applicant pooled treated subjects from Study 201/202 and Study 301 and compared HO volumes to all untreated control patients from Study 201 and the NHS. These analyses pose multiple statistical challenges for the following reasons: 1) multiple different dosing regimens were used in phase 2 and phase 3; 2) different criteria were used for treating flares in phase 2 versus phase 3 (such that flares were generally undertreated in Study 201/202); 3) a large variability in the “placebo” response was observed in the NHS, in which change in HO volume ranged from ~ -91000 to +39000; and 4) the methods used to determine changes in HO volume by whole-body CT scan differed between the phase 2 and phase 3 trials; and 5) a subset of patients carried over from the NHS to one of the intervention trials, which may have introduced selection bias.

- Use of an external control group (NHS) for evaluation of efficacy of the chronic/flare-up regimen

When an external control is used, there will be a lack of assurance of comparability between treated and untreated subjects given the lack of randomization. Compared to Study 301, NHS subjects were older and had worse disease severity at baseline. The FDA statistical team performed various analyses to assess the impact of baseline imbalance in selected covariates. However, these analyses could not address the impact of unmeasured and unknown confounding. Furthermore, some NHS subjects were enrolled into Study 301 or other intervention studies after some period of observation in the NHS and the possibility of subject selection bias could not be ruled out. The submission did not address these concerns adequately.

- Uncertain clinical implications of negative new HO volume data

Based on the natural history of disease progression in FOP, in which HO accumulates gradually over time, the clinical significance of negative HO volumes remains unclear. Whether negative HO volume as assessed by CT scan represents “noise” due to inflammation occurring at an initial flare-up site, or a natural process of bone consolidation as the transition from cartilaginous tissue to bone occurs, or some other physiologic mechanism, remains unknown. Therefore, how to account for negative HO volume change in a study assessing effects of a drug on total HO volume, in which negative HO volumes were seen in both treated and untreated subjects, was not made evident or justified by the Applicant.

- Phase 2 studies: efficacy of flare-up-only dosing was not established; efficacy data pertaining to chronic/flare-up dosing were generally not consistent with phase 3 data

The primary efficacy endpoint in phase 2 was the proportion of flare-ups resulting in significant new HO (Studies 201, 202A, 202B), and this endpoint was not met with palovarotene treatment compared to placebo. Thus initially, only flare-up dosing (without chronic dosing) was given in phase 2, in contrast to phase 3 (Study 301), in which patients were treated with both chronic and flare-based dosing. Complicating the phase 2 analyses, Studies 202B and 202C subsequently added chronic daily dosing to the flare-based regimen, and the primary endpoint was changed to reduction in annualized new HO volume compared to untreated NHS patients (similar to the primary endpoint for Study 301). Although the data comparing chronic + flare dosing in Studies 202B/202C and Study 301 to the NHS could be informative, particularly in the subset of patients who received consistent dosing regimens, Study 202C was ongoing at the time of this NDA submission and thus these comparisons were not presented. Additional factors that further complicate such analyses include the following: 1) the rate of annualized new HO in Study 202B ($\sim 29 \text{ cm}^3/\text{year}$) was much higher than in Study 301 ($\sim 9 \text{ cm}^3/\text{year}$) and the NHS ($\sim 24 \text{ cm}^3/\text{year}$), suggesting that these patient populations may have had different baseline disease severities; 2) a subset of patients were enrolled de novo into Study 202B, whereas others were initially enrolled in Study 201 after an acute flare-up and then transferred to Study 202B/C; 3) patients in Study 202B/C were 3 to 5 years older compared to patients in Study 301 and the NHS; and 4) Study 202B and Study 301 had different criteria defining a “flare,” such that some flares in Study 202B were untreated compared to Study 301.

In addition, subgroup analyses suggested that patients in Study 202B, who were undertreated for flare-up symptoms based on stricter flare-defining criteria, had a higher mean volume of new HO ($33.5 \text{ cm}^3/\text{year}$) compared to patients in Study 202B whose flare symptoms were treated ($-3.0 \text{ cm}^3/\text{year}$) because they met the stricter flare-defining criteria. This finding is inconsistent with the data specific to 202 Part C, in which all flare-up symptoms were treated but rates of new HO remained high. Further, the data from Study 202B/C for patients who received chronic 5 mg dosing but no flare-up symptoms or flare-based dosing suggest that chronic dosing had no effect to prevent new HO, as these patients had high levels of new HO ($\sim 29 \text{ cm}^3/\text{year}$) despite continuous 5 mg dosing; this is inconsistent with the Study 301 and NHS data, in which patients who did not require flare-based dosing had low volumes of new HO ($\sim 3 \text{ cm}^3/\text{year}$ in Study 301 and $\sim 7 \text{ cm}^3/\text{year}$ in the NHS, respectively).

Because of these inconsistencies of the Study 202B/C versus Study 301 data and the complicating factors of interim protocol changes and differences in study populations, a more complete assessment of palovarotene efficacy in FOP will require further analyses of the 202B/C data, including (but not limited to) comparisons to untreated NHS subjects; control of covariates; comparisons including additional data collected after the original cut-off date submitted in the NDA; and analyses comparing whole-body CT data from Study 202C and Study 301 to the NHS.

Conclusions on Benefit: Overall, the data submitted fail to adequately demonstrate substantial evidence of the effectiveness of palovarotene for the treatment of adult or pediatric patients with FOP.

Risks Associated with Treatment of Patients with FOP with Palovarotene

Safety risks associated with palovarotene include those associated with the retinoid drug class of medications, as well as risks specific to the FOP patient population. Boxed Warnings and Warnings and Precautions contained in the retinoid class product labels include teratogenicity; psychiatric disorders; pseudotumor cerebri; serious skin reactions; pancreatitis and hepatotoxicity; hypertriglyceridemia; hearing impairment; inflammatory bowel disease; skeletal abnormalities, including decreased bone mineral density, hyperostosis and premature epiphyseal closure; and vision impairment.

Regarding the risk of PPC seen with the retinoid class, treatment with palovarotene caused premature growth plate closure in subjects with open growth plates. This occurred despite the weight-based palovarotene dosing in younger patients. The Applicant proposed an indication that would allow most patients with at least 80% skeletal maturity (bone age 8 years in girls and 10 years in boys) to receive palovarotene for the prevention of HO despite the risk of premature epiphyseal closure, given the severity of the disease.

Palovarotene is a known teratogen as a member of the retinoid class, however, there are only rare reports of pregnancy in women with FOP, and pregnancy is considered very high risk when it does occur. As a precaution, clinical studies of palovarotene included frequent pregnancy testing and contraception requirements, and to date, there are no reports of pregnancy or in utero exposure to palovarotene. The Applicant proposed a Boxed Warning and contraindications to pregnancy in product labeling to mitigate the risk of teratogenicity.

Regarding effects on bone mineral content, bone density and fractures, vertebral fracture analysis (VFA) suggest that palovarotene treatment may be associated with decreases in vertebral bone strength, BMC and BMD, and a higher risk of new onset morphometric vertebral fractures. These effects are consistent with data involving other retinoids and are consistent with the BMD findings by DXA in osteochondroma subjects. However, the data do not establish a definitive causal association due to the post hoc nature of the analyses, use of nonvalidated measures (e.g., VFA) and differing amounts of follow-up data between the nonrandomized populations of Study 301 and the NHS.

Specific risks of palovarotene to patients with FOP include a potential increased incidence of HO flare-ups. FOP flare-up episodes were reported by a greater proportion of palovarotene-treated subjects in Study 301 compared to untreated subjects in the NHS, and at a higher frequency (0.15 versus 0.07 per month). Within Study 301, flare-ups were reported at higher rates during cycles of flare-up treatment (0.33 new events per month, versus 0.12 per month during chronic dosing). Similarly, data from Studies 201/202 showed higher rates of new flare-ups during flare-up dosing with palovarotene 10/5 mg or 20/10 mg (0.18 to 0.29/month) in comparison to placebo or untreated NHS (0.11 to 0.12/month), or chronic 5 mg dosing (0.10/month). However, flare-ups appear to have been under-reported in the NHS based on the study design, so the validity of these findings remains unclear based on the Applicant's submitted data.

The potential risk of an increase in HO flares during treatment with palovarotene was not identified by the Applicant nor was this risk included in proposed product labeling. Additional analyses will be necessary to better determine the potential for palovarotene treatment to worsen disease severity by increasing HO formation.

Conclusions on Risk: Palovarotene is associated with significant risk due to the drug's mechanism of action as a member of the retinoid drug class, as well as specific risks associated with its use in patients with FOP.

Overall Benefit-Risk Assessment

Given the significant risks associated with palovarotene as a member of the retinoid drug class (e.g., teratogenicity, PPC, decrease in BMC, etc.) and the risks associated with use of palovarotene specifically in patients with FOP (namely, a potential for increased incidence of HO "flares" in treated versus untreated patients), and the lack of convincing evidence that either palovarotene chronic or flare-based dosing benefits patients with FOP by preventing HO formation or decreasing the progression of HO accumulation, the risk-benefit balance for use of this product to treat FOP is unfavorable.

II. Interdisciplinary Assessment

3. Introduction

Palovarotene is an orally administered retinoic acid receptor (RAR) gamma (RAR γ) selective agonist (retinoid) and is a new molecular entity. The Applicant proposes an indication for the prevention of cartilage and bone formation within soft tissues (heterotopic ossification (HO)) in adults and children (aged 8 years and above for females, and 10 years and above for males) with fibrodysplasia ossificans progressiva (FOP). FOP is a serious disease with no approved therapies. Palovarotene has been designated as a breakthrough therapy for this indication.

The proposed dosing regimen includes chronic daily treatment (5 mg), with higher-dose treatment (20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks, with extension if needed, referred to herein as “20/10 mg”) during symptomatic “flare-up” episodes of FOP (all proposed doses are adjusted based on body weight in patients under 18 years of age). This regimen was intended to be supported by a pivotal single-arm phase 3 study (PVO-1A-301) in which the primary endpoint was the volume (cm³) per year of new whole-body HO in palovarotene-treated adult and pediatric FOP subjects. The efficacy data were compared to data from an external control group from the FOP natural history study (PVO-1A-001, NHS) that was also conducted by the Applicant.

A “flare-up-only” regimen is proposed as an alternative treatment option for patients who are unable to tolerate chronic daily treatment, even at reduced doses. This option would consist of the same treatment of flare-ups (20/10 mg), with no chronic treatment during clinically quiescent periods (between flare-ups). This regimen is supported by phase 2 studies (Study PVO-1A-201, “Study 201,” and Study 202A/202B, “Study 202”) in which patients were treated only with the 20/10 mg and other flare-up regimens, with a primary endpoint of new HO at the flare-up site. Control data for the phase 2 trials were provided by evaluation of untreated flare-ups in placebo recipients and the NHS.

The review division agreed with the use of new HO at the one-year timepoint, as assessed by whole-body computed tomography (WBCT) scan, for the primary assessment of efficacy, given that the severe clinical manifestations of FOP generally result directly from HO accumulation. The submitted FOP studies (Phases 2 and 3, and the NHS) are considered fit-for-purpose for this assessing this endpoint.

An Advisory Committee was originally planned to consider a variety of clinical and statistical issues related to efficacy and the potential for increased incidence of HO flares with treatment that complicate benefit/risk considerations. However, after further review of that data, the Division determined that the Advisory Committee meeting was premature until additional data and data analyses could be completed by the Applicant; therefore, the Advisory Committee meeting was postponed.

The key review issues relevant to benefit and risk are identified in Section [3.1](#) below and discussed in detail in Sections [6.3](#) and [7.7](#), respectively.

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

- 3.1.1.1. Phase 3: Appropriateness of Reliance on Post Hoc Analyses To Support Efficacy**
- 3.1.1.2. Phase 3: Use of an External Control Group (NHS) for Evaluation of Efficacy of the Chronic/Flare-up Regimen**
- 3.1.1.3. Phase 3: Uncertain Clinical Implications of Negative New HO Volume Data**
- 3.1.1.4. Phase 2 Studies: Efficacy of Flare-up-Only Dosing Was Not Established; Efficacy Data Pertaining to Chronic/Flare-up Dosing Were Generally Not Consistent With Phase 3 Data**

3.1.2. Key Review Issues Relevant to Evaluation of Risk

- 3.1.2.1. Premature Physeal Closure in Growing Children, With Potential for Adverse Effects on Growth**
- 3.1.2.2. Embryo-Fetal Toxicity (Retinoid Class Effect)**
- 3.1.2.3. Increased Rate of Reported Flare-ups During Palovarotene Treatment; Potential for Retinoid-Induced Myositis**
- 3.1.2.4. Apparent Adverse Effects of Palovarotene on Vertebral Bone Mineral Density, Bone Mineral Content, and Fractures**

3.2. Approach to the Review

Table 3. Clinical Trials Submitted¹ in Support of Efficacy and/or Safety Determinations for Palovarotene

Trial Identifier	Trial Population	Trial Design	Regimen, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Enrolled	Number of Centers and Countries
PVO-1A-201 NCT 02190747	Subjects ≥6 years of age with clinically diagnosed classic FOP with symptomatic onset of a distinct flare-up in an appendicular area (upper or lower extremity), abdomen, or chest within 7 days of Study Day 1	Phase 2 Randomized Double-blind Placebo control Multicenter Adaptive dose finding	Treatment of FOP flare-ups: Cohort 1: Randomized 3:1 PVO 10 mg QD for 2 weeks, then 5 mg QD for 4 weeks (n=12); or Placebo for 6 weeks (n=4) Cohort 2: Randomized 3:3:2 PVO 10 mg QD for 2 weeks, then 5 mg for 4 weeks (n=9); PVO 5 mg QD for 2 weeks, then 2.5 mg QD for 4 weeks (n=9); or placebo for 6 weeks (n=6) Total number treated: 40 Placebo (10 subjects) 5/2.5 mg palovarotene (9 subjects) 10/5 mg palovarotene (21 subjects). Duration: 6 weeks treatment, then 6 weeks observation	Primary: Percentage of subject responders, defined by no or minimal new HO (≤3 on 0-6 scale) at the flare-up site versus baseline as assessed by plain radiograph at Week 6. Secondary: Proportion of subjects with new HO at flare-up site at Week 12 Volume of new HO at flare-up site at Week 12 by CT scan Soft tissue swelling (MRI) Range of motion Pain, swelling	Planned: 40 Actual: 40	2 centers in US 1 center in France 1 center in UK

Trial Identifier	Trial Population	Trial Design	Regimen, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Enrolled	Number of Centers and Countries
PVO-1A-202 (Part A) NCT 02279095	Subjects from Study PVO-1A-201	Phase 2 open-label extension of study PVO-1A-201 single arm	Treatment of up to 2 new flare-ups: Palovarotene 10 mg QD for 2 weeks, then 5 mg QD for 4 weeks Weight-based dosing when children 6+ years enrolled in Study PVO-1A-201. Duration of treatment (each flare-up): 6 weeks	Primary: Percentage of subject responders as defined by no or minimal new HO at the original flare-up site compared with baseline as assessed by plain radiographs at the follow-up visit. Percentage of subject responders as defined by no or minimal new HO at up to two, new, distinct flare-up sites compared with baseline as assessed by low-dose CT scan at Flare-up Week 6. Secondary: Volume of new HO at flare-up site at Week 12 by CT scan See footnotes ²	Planned: 40 Actual: 40	Centers: 4 Countries: 3

Trial Identifier	Trial Population	Trial Design	Regimen, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Enrolled	Number of Centers and Countries
PVO-1A-202 (Part B)	Subjects from Study PVO-1A-201 and up to 20 additional Adult Cohort subjects	Control Type: No control (single arm) No randomization Open label	Drug (established name): Palovarotene Dose: <u>Adult Cohort</u> (chronic/flare-up regimen): 5 mg QD for up to 24 months, with dose escalation for flare-up treatment to 20 mg QD for 4 weeks, then 10 mg QD for 8 weeks (total of 12 weeks or until flareup resolution if treatment extended beyond 12 weeks). <u>Pediatric Cohort</u> (flareup regimen only): same as flare-up dosing in the Adult Cohort except dosing is weight-adjusted. Number treated: 52 (34 from PVO-1A-202 Part A and 18 new) Duration: 12 weeks up to 24 months	Primary: Proportion of flare-ups with no new HO ("responders") at Week 12. Secondary: Volume of new HO at flare-up sites at Week 12 Volume of new HO by whole-body (less head) CT at Month 12 (Adult Cohort) See footnotes ³	Planned: 60 Actual: 54 (2 subjects untreated)	2 centers in US 1 center in France 1 center in UK
PVO-1A-202 (Part C)	Subjects from Study PVO-1A-202 Part B	Control Type: No control (single arm) No randomization Open label	Drug (established name): Palovarotene Dose: All subjects receive chronic/flare-up regimen from Part B (weight-adjusted for skeletally immature subjects). Part C is ongoing. Number treated: 46 (all continuing from PVO-1A-202 Part B) Duration: Up to 36 months	Primary: Annualized change in new HO volume as assessed by low dose WBCT scan, excluding head. Secondary: See footnotes ⁴	Planned: 48 Actual: 46	Centers: 4 Countries: 3

Trial Identifier	Trial Population	Trial Design	Regimen, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Enrolled	Number of Centers and Countries
PVO-1A-301 NCT 03312634	Adult and pediatric subjects ≥ 4 years of age with FOP	Control Type: Historical Control No randomization Open label	Drug (established name): Palovarotene Dose: 5 mg QD, with dose escalation for flare-up treatment to 20 mg QD for 4 weeks, then 10 mg QD for 8 weeks (total of 12 weeks; may be extended by 4-week intervals until flare-up resolves). Weight-based dosing according to 3 categories (20 to <40 kg, 40 to <60 kg, and ≥ 60 kg). Number treated: 107 Duration: Up to 48 months	Primary: Annualized change in new HO volume as assessed by low-dose WBCT, excluding head. Secondary: See footnotes ⁵	Planned: 110 Actual: 107	Centers: 16 Countries: 11

Source: Clinical Study Reports and adsl.xpt, and Clinical Reviewer

¹ Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

²Follow-up Component: Proportion of subjects across the seven HO scores (0 to 6) at the original flare-up site as assessed by plain radiographs at the follow-up visit; Flare-up Component: Proportion of subjects across the seven HO scores (0 to 6) at the new, distinct flare-up site as assessed by low-dose CT scan (or plain radiographs for subjects unable to undergo CT scan) at Flare-up Weeks 6 and 12 (Days 42 and 84). Additional secondary endpoints can be found in 202 CSR page 121.

³Flare-up based treatment: Change from baseline in amount of bone formation (volume) as assessed by low-dose CT scan (or area by plain radiographs for subjects unable to undergo CT scan) at Flare-up Week 12/EOT (Day 84/EOT). Chronic treatment: Change from baseline in whole-body burden of HO as assessed by low-dose WBCT scan, excluding head, at Study Months 12 and 24. Additional secondary endpoints can be found in 202 CSR page 122.

⁴Percent of subjects with new HO at Months 12, 24, 36, and overall; Change from baseline in ROM as assessed by CAJIS at Months 6, 12, 18, 24, 30, and 36; Change from baseline in physical function using age-appropriate forms of the FOP-PFQ at Months 6, 12, 18, 24, 30, and 36; Change from baseline in physical and mental function for subjects ≥ 15 years old and mental function for subjects <15 years old using age appropriate forms of the PROMIS Global Health Scale at Months 6, 12, 18, 24, 30, and 36.

⁵Proportion of subjects with any new HO at Month 12; Number of body regions with new HO at Month 12; Proportion of subjects reporting flare-ups at Month 12; Flare-up rate per subject-month exposure through Month 24.

Abbreviations: CT, computed tomography; FOP, fibrodysplasia ossificans progressiva; HO, heterotopic ossification; MRI, magnetic resonance imaging; n, number of subjects; PVO, palovarotene; QD, once daily; WBCT, whole-body computed tomography

4. Patient Experience Data

The FOP natural history study (NHS, PVO-1A-001) and the palovarotene intervention studies included patient-reported outcome measures related to physical function and a clinician-reported index of range of motion. Changes in these measures were found to correlate with more advanced age of FOP patients and with more severe disease but were insufficiently sensitive to show changes over the time scale of the clinical studies, with or without treatment. For this review, these data provided general supportive information but were not central to the regulatory decision.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☒	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☒	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☒	Patient-focused drug development meeting summary report	Held at FDA May 2019
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Retinoid
Mechanism of action	Binding of palovarotene to RAR γ antagonizes bone morphogenetic protein (BMP) / activin receptor-like kinase 2 (ALK2) downstream signaling by reducing BMP-mothers against decapentaplegic homolog (SMAD) 1/5/8 phosphorylation, potentially by promoting proteosome-mediated SMAD degradation. This leads to blockade of chondrogenesis, osteogenic differentiation, reprogramming of progenitor cells into nonskeletal lineage and prevents abnormal endochondral bone formation.
Active moieties	Parent drug palovarotene is the active moiety. The pharmacological activity of two metabolites, M3 and M4b, are approximately 1.7% and 4.2% as active as the parent drug based on an in vitro RAR γ transactivation assay.
QT prolongation	At a dose of 2.5 times the maximum recommended dose, palovarotene does not prolong the QT interval to any clinically relevant extent.
General Information	
Bioanalysis	Two validated LC-MS/MS methods were used to determine plasma and seminal fluid concentrations of palovarotene. The established benchtop stability, storage stability and freeze-thaw stability cover the maximum storage periods for corresponding clinical studies.
Healthy subjects versus patients	The PK data of healthy volunteers (N=238), FOP patients (N=123), chronic obstructive pulmonary disease (COPD) patients (N=198) and multiple osteochondromas (MO) patients (N=18) were included in population PK analyses. There was no evidence that disease status has a clinically relevant influence on the PK of palovarotene.
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	Drug exposure in FOP patients (Study PVO-1A-301): Parameter (Mean $\pm$ SD) Chronic dose, 5 mg once daily (QD) (N=41) or weight-based equivalent dose (N=29) AUC _{0-t} : 264 $\pm$ 98.4 ng*h/mL C _{max} : 40.6 $\pm$ 16.2 ng/mL CL/F: 17.8 $\pm$ 8.64 L/h Flare-up dose, 10 mg QD (N=26) or weight-based equivalent dose (N=22) AUC _{0-t} : 540 $\pm$ 226 ng*h/mL C _{max} : 78.4 $\pm$ 33.3 ng/mL CL/F: 17.0 $\pm$ 7.80 L/h Flare-up dose, 20 mg QD (N=24) or weight-based equivalent dose (N=29) AUC _{0-t} : 1060 $\pm$ 449 ng*h/mL C _{max} : 165 $\pm$ 72.7 ng/mL CL/F: 16.5 $\pm$ 7.43 L/h

Characteristic	Drug Information
Range of effective dosage(s) or exposure	Lowest effective flare-up dosing: 5 mg QD for 14 days followed by 2.5 mg QD for 28 days (5/2.5 mg regimen) Highest effective flare-up dosing: 20 mg QD for 28 days followed by 10 mg QD for 56 days (20/10 mg regimen)
Maximally tolerated dosage or exposure	Exposure of palovarotene in healthy adults following a single dose of 50 mg in fed state: AUC _{0-inf} =2370±662 ng*h/mL; C _{max} =328±92.2 ng/mL
Dosage proportionality	From Population PK analyses, palovarotene exhibited linear PK with dose-proportional increases in plasma exposure from 0.02 to 50 mg following QD dosing.
Accumulation	The accumulation ratios of palovarotene 5 mg QD, 10 mg QD and 20 mg QD over 28 days range from 1.04 – 1.16.
Time to achieve steady state	Based on trough palovarotene plasma concentrations, steady state is attained by Day 3 following QD dosing.
Bridge between to-be-marketed and clinical trial formulations	The proposed to-be-marketed (TBM) formulation is the same as the formulation used in FOP clinical studies. No bioequivalence (BE) study is needed to bridge the TBM formulation to the phase 3 trial formulation.
Absorption	
Bioavailability	Absolute or relative bioavailability of palovarotene has not been determined.
T _{max}	The median T _{max} in healthy adults under fasting state is 2 hours and a high fat meal delays median T _{max} to 4 hours.
Food effect (fed/fasted)	Compared with administration under fasted conditions, a high-fat, high-caloric breakfast increased exposure and delayed absorption of palovarotene:
Geometric least square mean and 90% CI	AUC _{0-∞} 139.7% (129.6%, 150.5%) C _{max} 116.5% (101.2%, 134.1%) T _{max} is delayed from 2 hours to 4 hours Plasma palovarotene AUC and C _{max} were comparable when either swallowed whole or the contents sprinkled onto applesauce following a high-fat, high-caloric breakfast.
Distribution	
Volume of distribution	Healthy adults (20 mg single dose): apparent volume of distribution of 237±90 L FOP patients: 131±87 L following chronic dosing 5 mg QD or equivalent (weight-based); 106±53 L following flare-up 10 mg QD or equivalent (weight-based) dosing; 109±61 L following flare-up 20 mg QD or equivalent (weight-based) dosing Following oral dose 20 mg QD for 5 days, palovarotene was detected in seminal samples at 3 hours post dose on Day 5; the mean semen concentration was 8.84 ng/mL and the mean semen/plasma concentration ratio was 0.0273.
Plasma protein binding	97.9% to 99.6%
Drug as substrate of transporters	In vitro data shows that palovarotene is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3 and OCT1. Substrate interaction assessments with renal transporters OAT1, OAT3, OCT2, MATE1 and MATE2-K transporters were not conducted because only 3.2% of dose was recovered in urine.

Characteristic	Drug Information Elimination
Mass balance results	Palovarotene and its four known major metabolites accounted for 40% of the total systemic exposure in plasma [palovarotene (14%), M3 (10%), M4b (7%), M2 (5%), and M4a (4%) based on AUC]. The pharmacological activity of M3 and M4b is approximately 1.7% and 4.2% of the activity of the parent drug based on an in vitro RARy transactivation assay. Over 13 days post dose, 97.1% and 3.2% radioactivity were recovered in feces and urine, respectively. Palovarotene and its four known major metabolites accounted for 67.2% of the dose in feces [M4a and M4b (32.2%), M2 (20.2%), M3 (12.4%), palovarotene (2.4%)].
Clearance	The apparent total body clearance (CL/F) across dose levels and across studies estimated by population PK analysis is 19.9 L/h. In FOP patients, the CL/F values across dose levels are 17.8 L/h (chronic dose), 17.0 L/h (low flare-up dose), and 16.5 L/h (high flare-up dose).
Half-life	In healthy subjects receiving 20 mg QD for 14 days, the mean steady-state $T_{1/2}$ was 8.7 hours. In FOP patients, the terminal $T_{1/2}$ values across dose levels are 4.9 h (chronic dose 5 mg QD or equivalent weight-based), 4.4 h (high flare-up dose 20 mg or equivalent weight-based), and 4.3 h (low flare-up dose 10 mg or equivalent weight-based).
Metabolic pathway(s)	Palovarotene is extensively metabolized by CYP3A4, 2C8 and 2C19, but primarily by CYP3A4. Five metabolites, M1 (6,7-dihydroxy), M2 (6-hydroxy), M3 (7-hydroxy), M4a (6-oxo), and M4b (7-oxo) were observed for palovarotene in clinical studies.
Primary excretion pathways (% dosage)	97.1% and 3.2% radioactivity were recovered in feces and urine, respectively.
	Intrinsic Factors and Specific Populations
Body weight	Based on population PK analysis, AUC and C_{max} were 8% and 12% higher for a 51 kg subject and 18% and 26% lower for a 98 kg compared to a 70 kg subject, respectively.
Age	According to population PK analysis of PK data from subjects aged 2-85 years, there was no evidence that age has a clinically relevant influence on the PK of palovarotene.
Renal impairment	A PK study was not conducted in subjects with renal impairment because only 3% of radioactivity was recovered in urine and there were no case reports of renal impairment in FOP patients enrolled in clinical studies. Population PK analysis suggests that serum creatinine or renal impairment status are not significant covariates on palovarotene PK.
Hepatic impairment	A PK study was not conducted in subjects with hepatic impairment. Per the Applicant, hepatic impairment was not reported in the FOP patients enrolled in the natural history study submitted with this application (N ~100). Population PK analyses suggest that there was no significant difference in the PK of palovarotene in subjects with mild (Child-Pugh A, N=66) hepatic impairment compared to subjects with normal hepatic function. The effect of moderate (Child-Pugh B) hepatic impairment on the PK of palovarotene is not conclusive based on the population PK analyses as only a limited number of subjects (N=5) with moderate hepatic impairment were included. The effect of severe (Child-Pugh C) hepatic impairment on the PK of palovarotene has not been evaluated. Given that 97.1% of radioactivity was recovered in feces in the mass balance study and that palovarotene is extensively metabolized by CYP enzymes, palovarotene exposure may likely be increased in subjects with moderate or severe hepatic impairment. Therefore, Applicant should conduct a hepatic impairment study and evaluate the effect of moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) on the PK of palovarotene to inform the dosing recommendations in subjects with hepatic impairment.

Characteristic	Drug Information
Inhibition/induction of metabolism	Drug Interaction Liability (drug as perpetrator)
	At clinically relevant plasma concentration, palovarotene did not significantly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Palovarotene did not pose a clinically relevant risk with respect to the inhibition of UGT enzymes. Palovarotene at clinically relevant concentration (0.32µM) did not induce CYP1A2, CYP2C8, CYP2C9 and CYP2C19 but induced CYP3A4 and CYP2B6 mRNA expression by 3.8-5.0 folds and 1.8-2.4 folds in vitro, respectively. In clinical study, palovarotene 20 mg QD did not induce CYP3A4-mediated metabolism of co-administered midazolam.
Inhibition/induction of transporter systems	Palovarotene is not an inhibitor of P-gp, OAT1, OAT3, OCT2, MATE1, or MATE2-K transporters. In vitro studies showed that palovarotene inhibited BCRP, OATP1B1, OATP1B3, OCT1, and bile salt export pump (BSEP) transporter with IC ₅₀ values of 9.69µM, 1.83µM, >3µM, >3µM, and 14.7µM, respectively. At the maximum recommended dose (20 mg QD), palovarotene does not pose a clinically relevant risk with respect to the inhibition of OATP1B1, OATP1B3, OCT1, or BSEP transporters.
Immunogenicity (not applicable)	

Source: Drafted by clinical pharmacology reviewer Peng Zou while employed at the FDA.

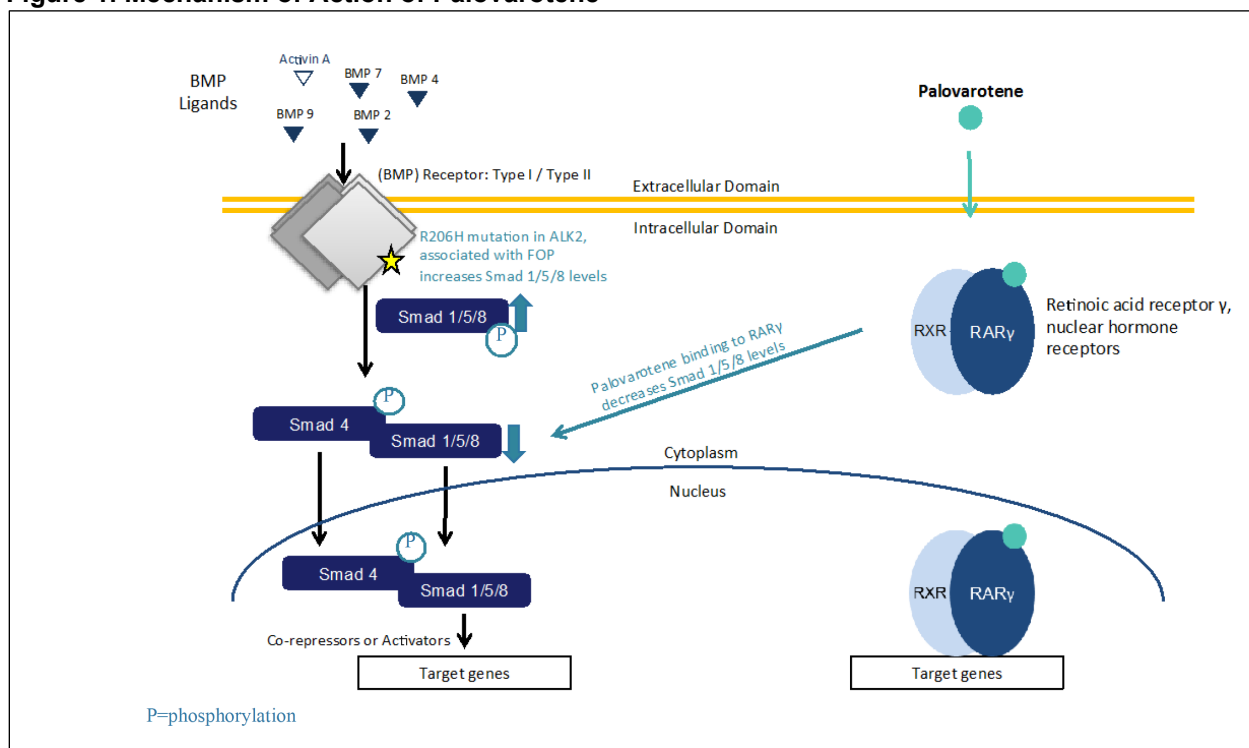
Abbreviations: ALK2, activin receptor-like kinase 2; AUC, area under the concentration versus time curve; BCRP, breast cancer resistance protein; BE, bioequivalence; BMP, bone morphogenetic protein; BSEP, bile salt export pump; CL/F, oral clearance; C_{max}, maximum observed concentration; COPD, chronic obstructive pulmonary disease; CYP, cytochrome P450; DDI, drug-drug interaction; FOP, fibrodysplasia ossificans progressiva; LC-MS/MS, liquid chromatography with tandem mass spectrometry; M1, 6,7-dihydroxy metabolite of palovarotene; M2, 6-hydroxy metabolite of palovarotene; M3, 7-hydroxy metabolite of palovarotene; M4a, 6-oxo metabolite of palovarotene; M4b, 7-oxo metabolite of palovarotene; M5, 8-carboxyl β-glucuronide of palovarotene; MATE1, multidrug and toxin extrusion 1; MATE2-K, multidrug and toxin extrusion 2-K; MO, multiple osteochondromas; OAT1, organic anion transporter 1; OAT3, organic anion transporter 3; OATP1B1, organic anion transporting polypeptide B1; OATP1B3, organic anion transporting polypeptide B3; OCT1, organic cation transporter 1; OCT2, organic cation transporter 2; PBPK, physiological based pharmacokinetics; PK, pharmacokinetics; popPK, population pharmacokinetics; QD, once daily; RAR, retinoic acid receptor; SD, standard deviation; SMAD BMP, suppressors of mothers against decapentaplegic homolog; TBM, proposed to-be-marketed; T_{max}, time to maximum observed concentration

5.1. Nonclinical Assessment of Potential Effectiveness

Proposed Mechanism of Action

In patients with FOP, abnormal bone formation, including ectopic chondrogenesis, osteogenesis, and heterotrophic ossification, are driven by a gain-of-function mutation in the bone morphogenetic protein (BMP) type I receptor ALK2 (ACVR1). Palovarotene is an oral retinoid with selectivity towards the gamma subtype of RAR (RAR γ). RAR γ receptor is expressed in chondrogenic cells and chondrocytes, where it operates as an unliganded transcriptional repressor in the absence of retinoid ligands. Binding of palovarotene to RAR γ antagonizes BMP/ALK2 downstream signaling by reducing SMAD1/5/8 phosphorylation, potentially by promoting proteasome-mediated SMAD degradation. This leads to blockade of chondrogenesis and osteogenic differentiation, reprogramming of progenitor cells into nonskeletal lineage, and prevention of abnormal endochondral bone formation. The Applicant also speculates that RAR γ agonist-mediated stimulation of canonical Wnt-b-signaling may also play an inhibitory role in chondro-progenitor cell differentiation. The BMP/ALK2 pathway and the mechanism of action of palovarotene are summarized in [Figure 1](#) below.

Figure 1. Mechanism of Action of Palovarotene



Source: Ipsen, from Type B meeting package June 27, 2017

Abbreviations: ALK2, activin receptor-like kinase-2; BMP, bone morphogenetic protein; FOP, fibrodysplasia ossificans progressiva; RAR γ , retinoic acid receptor gamma; RXR, retinoid X receptor; SMAD, suppressor of mothers against decapentaplegic

Nonclinical data from the series of in vitro and in vivo studies generated by the Applicant and from published research studies support the proposed mechanism of action of palovarotene and

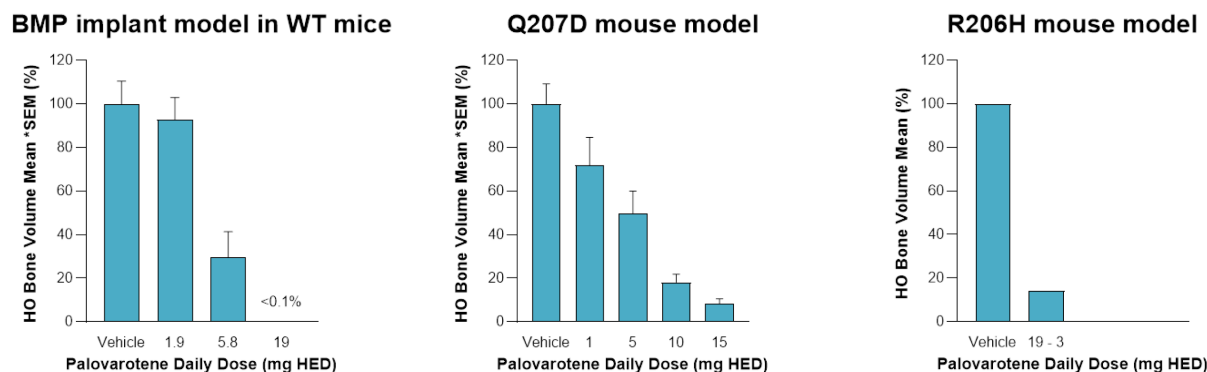
its efficacy in preventing HO formation in FOP. Palovarotene demonstrated specific RAR γ binding and functional selectivity towards RAR γ over RAR α and RAR β , with IC₅₀ and half maximal effective concentration (EC₅₀) values of 450nM and 8nM, respectively. In the initial proof of concept studies, pretreatment with a panel of RAR γ agonists, including palovarotene, inhibited BMP2-induced chondrogenic differentiation of cultured ADTC5 cells (chondrogenic cells) and led to the loss of skeletogenic potential of bone marrow derived mesenchymal stem cells. Similar findings were recapitulated in a BMP4 treated human FOP fibroblast cell line carrying human relevant gain of function R206H mutation of the ALK2 receptor. In these cell lines, palovarotene reduced (43 to 50%) the levels of phosphorylated Smad proteins (Smad1, Smad5 and Smad8). The effect of palovarotene on Smad proteins was absent in the presence of proteasome inhibitors, suggesting that palovarotene might promote proteasome mediated degradation of Smad proteins.

Key pharmacodynamic studies were conducted in BMP-implant and transgenic mouse FOP models (ALK2^{Q207D} and ALK2^{R206H} and Prrx1-R206H mice) (Figure 2). In the BMP-implant mouse model, injury-mediated HO was induced via implantation with matrigel containing skeletogenic factor rBMP2 inside calf muscle. The Applicant established that activation of the retinoid receptor is effective in preventing the formation of ectopic mineralized tissue masses at the operated sites when oral daily treatment with retinoids or palovarotene at 0.12 to 4 mg/kg (HED =0.6 to 19 mg) commences immediately following rBMP2 implantation and continues for 12 days. The strongest effect was seen with RAR γ selective agonists (CD1530 and palovarotene) as compared to pan-RAR and RAR α agonists. The inhibition of HO formation was abolished in RAR γ KO mice, suggesting that inhibition of chondrogenesis is mediated exclusively via RAR γ .

Activating mutations in ALK2 are embryo-lethal during embryonic development; therefore, chimeric or conditional gene expression models are routinely used. Palovarotene inhibition of HO was evaluated in ALK2^{Q207D} and ALK^{R206H} transgenic mouse models, which display abnormal HO formation in an inflammatory milieu. The ALK2^{Q207D} mice conditionally express the Q207D mutant encoding a constitutively active form of ALK2, whereas the ALK^{R206H} model contains a mildly activating gain-of-function mutation R206H in the ALK2 receptor. Only the R206H mutation occurs naturally in >97% of FOP patients and ALK2^{R206H} mice recapitulate many of the phenotypic features of FOP patients, including hind limb digit malformation, joint fusions, and extensive HO development. Both FOP mouse models require muscle injury/inflammation via cardiotoxin injection to elicit the HO response. Moreover, local, and global induction of transgene expression is achieved by injection with adenovirus expressing Cre in the ALK2^{Q207D} model and doxycycline in the ALK2^{R206H} model.

Administration of palovarotene to Ad-Cre/cardiotoxin-injected ALK2^{Q207D} mice (19-day old) starting from the day of muscle injury and for 15 consecutive days resulted in dose-dependent reduction in injury-induced HO volume (reduced 75% to 100%) at the injury site, with ED₅₀ of 2 mg/kg/day (HED =7 mg/day). Joint mobility was retained in 100% of treated animals while it was reduced in 70% of the control mice. Further investigation of the window of intervention indicated that treatment with palovarotene is most effective (up to 93.5% HO inhibition) when initiated early (prior to and up to 3-days post injury), but the effect was decreased to 71% inhibition with heterotopic bone volume by 7-day post injury. This suggests that palovarotene targets the chondrogenic phase of HO, preventing its progression to osteogenesis.

Figure 2. Microcomputed Tomography Analysis 2-Weeks Post Muscle Injury in Three Animal Models of FOP



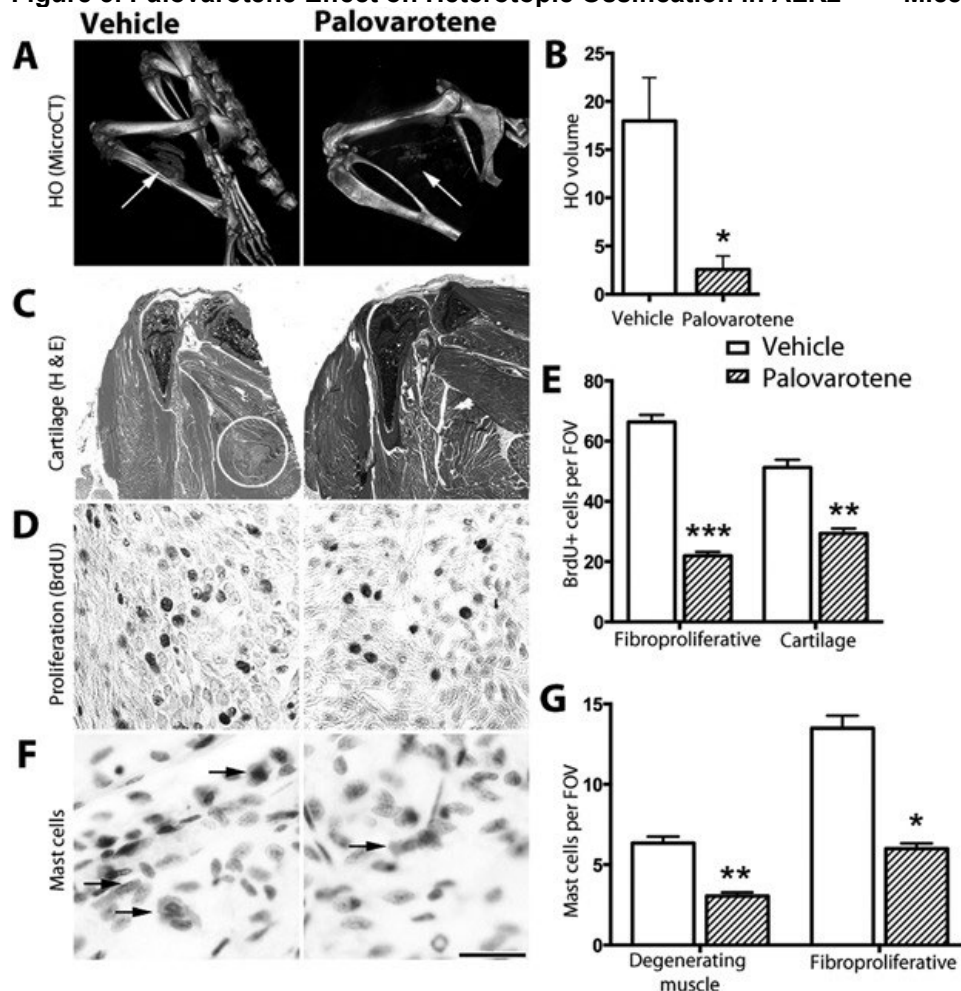
Source: Adopted from ; Study report CLM001-PD-002; and .

Abbreviations: BMP, bone morphogenetic protein; FOP, fibrodysplasia ossificans progressiva; HO, heterotopic ossification; HED, human equivalent dose; WT, wild type

ALK2^{R206H} mice (1 month old) were treated with doxycycline to induce global expression of the mutant allele ALK2^{R206H} and were then subjected to hindlimb muscle injury with cardiotoxin to induce local inflammation and HO.³ Treatment started from Day 1 to Day 3 postinjury (align with chondrogenic phase) with palovarotene at 4 mg/kg [HED =19 mg]), followed by 0.6 mg/kg (HED =3 mg) from Day 4 to Day 14, or with vehicle for 14 days. Analysis by microCT and 3D image reconstruction at Day 14 showed that large HO tissue masses formed in the targeted injured muscles of ALK2^{R206H} mice receiving vehicle. Vehicle-treated R206H mice also showed impaired movement of the HO-affected leg. In palovarotene-treated mice, HO was greatly diminished by more than 86% (to 14% of vehicle control) based on bone volume/total volume quantification; joint mobility of the HO-affected leg was also maintained ([Figure 3](#)).

Histochemical analysis confirmed that newly formed heterotopic cartilaginous tissue and endochondral bone were present in vehicle-treated but not in palovarotene-treated ALK2^{R206H} mice. Palovarotene treatment also reduced muscle damage-induced mast cell infiltration and fibroproliferative response.

Figure 3. Palovarotene Effect on Heterotopic Ossification in ALK2^{R206H} Mice



Source:
Abbreviations: ALK2, activin-like kinase 2; FOV, field of view; H&E, hematoxylin and eosin stain; HO, heterotopic ossification

In addition to the injury-based model, palovarotene was effective in inhibiting spontaneous HO formation in *Prrx1-R206H* mice (which contain tissue specific expression of R206H mutation in skeletal progenitor cells). These mutant mice recapitulate many of the defects (malformed great toes at birth, development of HO postnatally in hindlimbs and later also in forelimbs) noted in FOP patients. Palovarotene markedly blocked noninjury (spontaneously) induced HO formation in the fore and hind limbs of pups when nursing dams were dosed orally with palovarotene at 2 mg/kg (HED =10 mg) beginning from delivery and continuing for 15 days and treatment was continued by oral gavage (2 mg/kg~HED =7 mg) on alternate days until age 30 days. Furthermore, the severe movement impediment and difficulties noted in vehicle group was absent as drug-treated mutants were mobile and appeared to function well.

Treatment of control mice with palovarotene caused reduction in skeletal growth. This study suggests a potential for palovarotene to pass to the pups through breastfeeding, but it does not provide compelling evidence, as pups were also exposed to the drug via oral administration from postnatal Days 16 to 30. When palovarotene treatment was delayed until Day 14 and given only to the young mice, it was not as effective at inhibiting HO and maintaining mobility (not shown), suggesting importance of early treatment.

In conclusion, the Applicant's in vivo pharmacology studies provided a proof-of-principle that palovarotene is effective in blocking injury-induced HO formation in different mouse models of FOP (BMP-2 implant, ALK2Q207D, ALK2R206H and Prrx1-R206H). Window of intervention studies indicate that palovarotene prevents HO formation during the prechondrogenic and chondrogenic stages but has minimal effect during the ossification phase.

This purported MOA justifies the rationale for treating at the time of flare-up before new cartilage and bone formation have taken place. It is worth noting that the animal models have limitations, as they do not replicate the human disease (i.e., heterotrophic implantation models are artificial local systems created with unphysiologically high concentration of osteogenic factors, genetic models contain mutation (Q207D) that is not found naturally in FOP patients, conditional knock-in models only allow the study of one gene). Furthermore, the efficacy of palovarotene in reducing spontaneous HO was evaluated in one mouse model (Prrx1-R206H), and even though this model recapitulates many of the features of human FOP, the clinical translatability of the findings from this study is questionable because the animals were exposed to palovarotene via breast milk until weaning and treated orally until postnatal day 30. For these reasons, the completed nonclinical pharmacology studies may not provide substantial evidence of efficacy in the prevention of HO in humans.

The details of the nonclinical pharmacology studies are provided in Section [13](#).

Secondary (Off-Target) Pharmacology

Palovarotene does not possess clinically relevant pharmacodynamic activity on off-target receptors or enzymes when screened in vitro on a panel of 75 molecular receptors and 24 enzymes at 10 μ M.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

The development program for palovarotene for the treatment of FOP explored four different dosing regimens in the phase 2 Studies PVO-1A-201 ("Study 201") and PVO-1A-202A/B ("Study 202A/B"). The primary endpoint was the volume of new HO as assessed by low-dose CT scan at the flare-up site 12 weeks after flare-up initiation. The dosing regimens included the following:

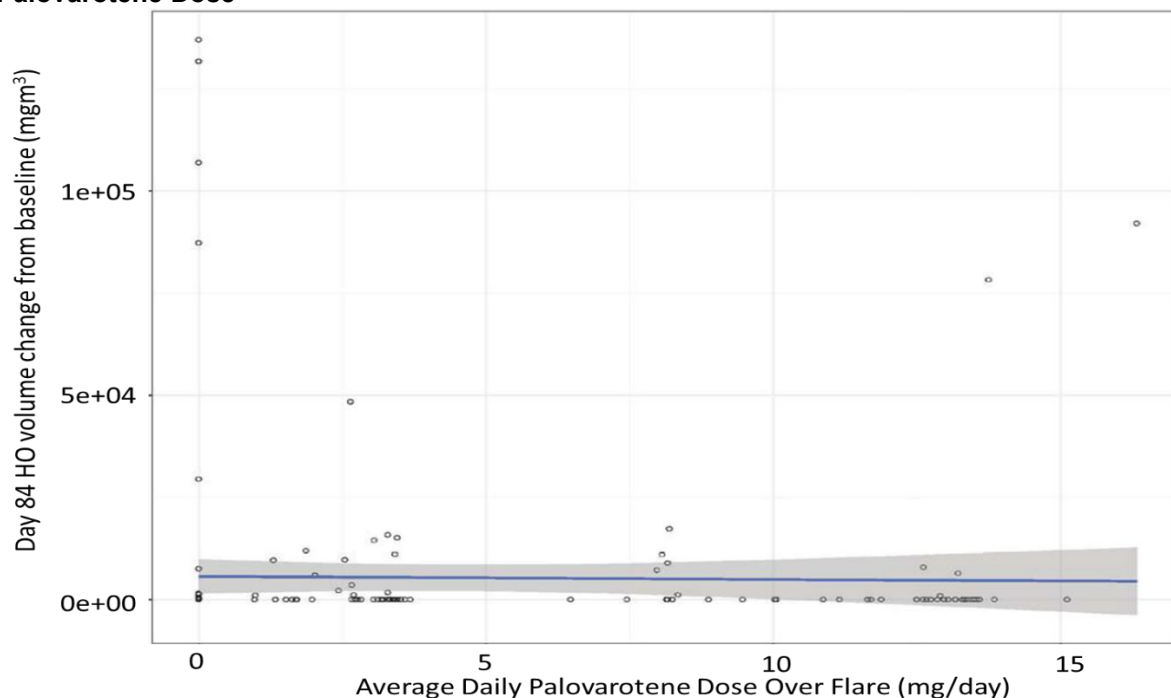
- Palovarotene 5 mg once daily for 2 weeks followed by 2.5 mg once daily for 4 weeks (5/2.5 mg flare-up only regimen) within 7 days of flare-up initiation.
- Palovarotene 10 mg once daily for 2 weeks followed by 5 mg once daily for 4 weeks (10/5 mg flare-up only regimen) within 7 days of flare-up initiation.
- Palovarotene 20 mg once daily for 4 weeks followed by 10 mg once daily for 8 weeks (20/10 mg) within 7 days of flare-up initiation, with treatment extension in 4 week increments for persistent symptoms.
- Palovarotene 5 mg daily with increased dosing at the time of a flare-up to palovarotene 20 mg once daily for 4 weeks followed by 10 mg once daily for 8 weeks (chronic/flare-up

regimen) within 7 days of flare-up initiation, with treatment extension in 4-week increments for persistent symptoms.

Skeletally immature pediatric patients enrolled in Studies 201 and 202A/B received weight-based flare-up dosing only according to four weight categories (10 to <20 kg, 20 to <40 kg, 40 to <60 kg, and ≥ 60 kg).

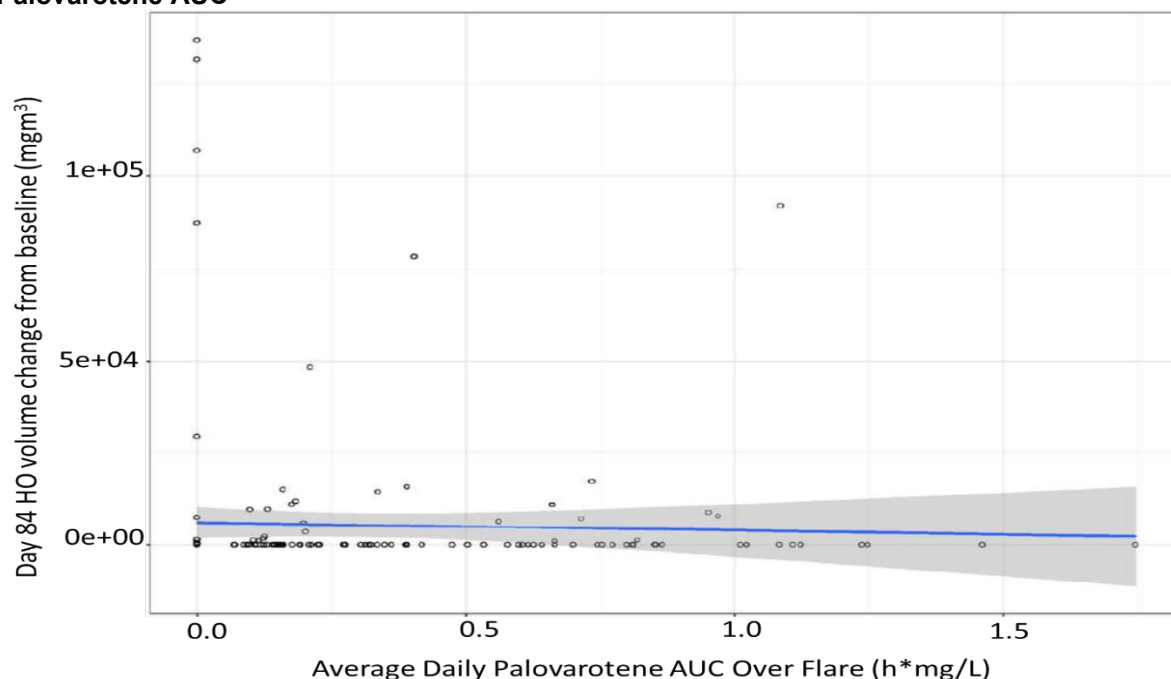
The Applicant explored the relationship between change in HO volume on Day 84 (the last timepoint with available HO data in this study) and mean daily palovarotene dose during flare-up treatment based on 165 flares in 82 FOP patients enrolled in Studies 201 and 202A/B ([Figure 4](#)). No dose-response relationship for change in HO volume was observed in the regression analysis. Similarly, the Applicant explored the relationship between change in HO volume on Day 84 and mean daily palovarotene area under the concentration-time curve (AUC) during flare-up treatment based on 162 flares in 81 FOP patients ([Figure 5](#)). No exposure-response relationship for change in HO volume was observed. In addition, the relationship between change in HO volume on Day 84 and cumulative palovarotene dose during flare-up treatment was explored but no trend was observed. This ER analysis was based on Phase 2 and NHS data, and additional ER analysis with Phase 3 data is presented in Figure 7.

Figure 4. Regression Analysis Between Change in HO Volume (mm³) on Day 84 and Mean Daily Palovarotene Dose



Source: Applicant's Exposure Response Exploration Report, Figure 5-1
Abbreviations: HO, heterotopic ossification

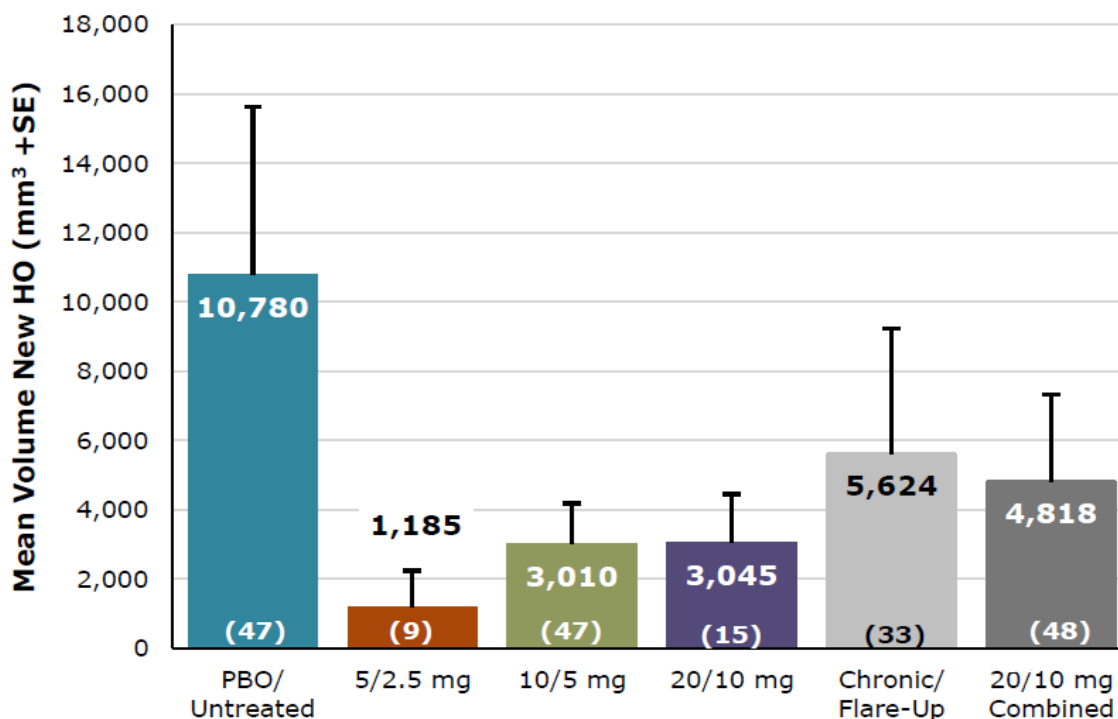
Figure 5. Regression Analysis Between Change in HO Volume (mm³) on Day 84 and Mean Daily Palovarotene AUC



Source: Applicant's Exposure Response Exploration Report, Figure 5-1
Abbreviations: AUC, area under the concentration versus time curve; HO, heterotopic ossification

Flare-up new HO data from the NHS, Study 201 and Study 202A/B were integrated and pooled according to the corresponding palovarotene dosing regimens. The pooled analysis was based on a total of 151 flare-ups with evaluable CT imaging data at Week 12, including 38 untreated flare-ups from the NHS, 9 flare-ups treated with placebo from Study 201, 9 flare-ups treated with the palovarotene 5/2.5 mg dose in Study 201, 47 flare-ups treated with the palovarotene 10/5 mg dose in Studies 201 and 202A, 15 flare-ups treated with the palovarotene 20/10 mg dose (no prior chronic dosing) in Study 202B, and 33 flare-ups treated with the palovarotene 20/10 mg dose (prior chronic dosing) from Study 202B. As shown in Figure 6, both 10/5 mg and 20/10 mg flare-up dosing inhibited new HO volume by approximate 72% relative to the placebo/untreated group. Although a dose-dependent suppression of new HO volume was not observed, given the cumulative and irreversible nature of HO, the Applicant believes that the highest dose tolerated should be selected to prevent as much new HO as possible. Also, nonclinical pharmacology data suggested that a dose of ~6 mg/kg or 20 mg human equivalent dose (HED) once daily may provide greater efficacy in inhibiting HO in a FOP mouse model. Therefore, the 20/10 mg dose was selected as the flare-up treatment dose.

Figure 6. Flare-up New HO at Week 12 for the Placebo/Untreated and Palovarotene-Treated Flare-ups in Pooled Studies PVO-1A-001 (NHS), PVO-1A-201 and PVO-1A-202A/B



Source: Applicant's Integrated Summary of Efficacy, Figure 44

Abbreviations: AUC, area under the concentration versus time curve; HO, heterotopic ossification; NHS, natural history study; PBO, placebo; PVO, palovarotene; SE, standard error

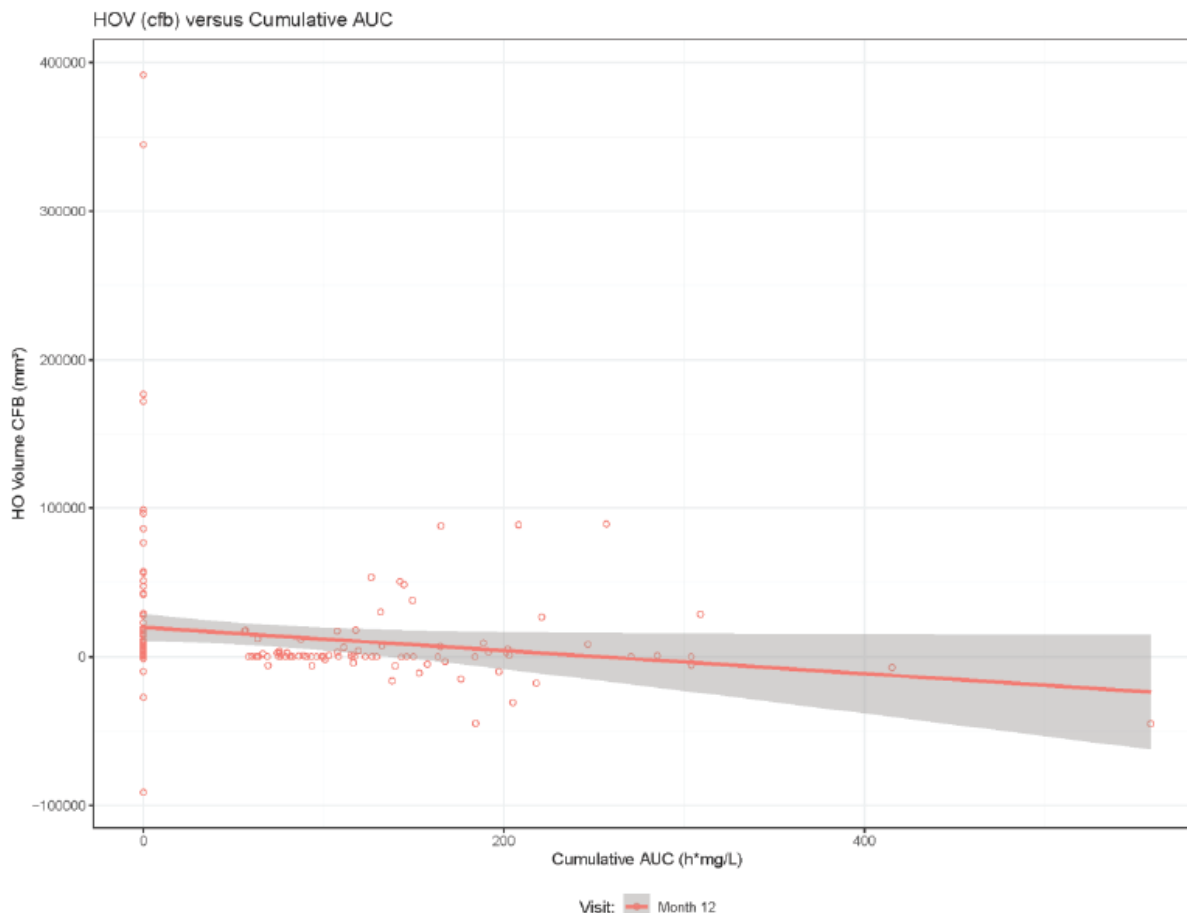
The 5-mg chronic dosing was selected based on the following nonclinical and clinical observations: (1) In the FOP mouse model, chronic daily treatment with palovarotene at an HED of approximately 5 mg reduced new HO volume and improved mobility; and (2) Substantial soft tissue edema, muscle necrosis, and immature HO were detected in FOP patients within 7 days of flare-up symptom onset, suggesting new HO formation starts before clinical symptoms of a flare-up. Therefore, the chronic/flare-up dosing regimen (chronic 5 mg QD, flare-up 20/10 mg QD) was selected for further investigation in pivotal Study PVO-1A-301 ("Study 301").

6.1.1. Phase 2/3: Studies PVO-1A-202B/C and PVO-1A-301

The annualized change in new HO volume as assessed by WBCT was used as one of the secondary efficacy endpoints in Study 202B and the primary efficacy endpoint in Study 202C and Study 301. The annualized changes in new HO volume in patients with and without flare-ups enrolled in Studies 202B/C, 301 and the NHS are summarized in Table 6. The criteria for initiating flare-up treatment in Study 202B (e.g., requiring at least two flare-up symptoms) were stricter than those in Study 301, which might result in undertreatment of flare-ups in Study 202B. An exposure-response analysis for annualized change in new HO volume at Month 12 and palovarotene exposure metrics (average daily dose, cumulative dose of palovarotene, average AUC and cumulative AUC of palovarotene) was conducted. Plots and regression analyses show a trend to decrease change from baseline or relative change from baseline in HO volume versus the assessed exposure metrics. Furthermore, a statistically significant relationship (linear

regression analysis) was observed between change from baseline in HO volume at Month 12 and cumulative AUC ($p=0.0497$), suggesting higher dose/exposure level might have better efficacy as measured by annualized change in new HO volume (Figure 7).

Figure 7. Plots of Change From Baseline in HO Volume (HO Volume CFB in mm^3) at Month 12



Source: Applicant's Exposure Response Exploration Report (Report PVO-FOP-ER-002), Figure 6-2.

Abbreviations: AUC, area under the concentration versus time curve; CFB, change from baseline; HO, heterotopic ossification

The results for ER analyses are different between phase 2 and phase 3 studies, possibly due to the longer duration of new HO volume measurement in the phase 3 study (12 months) as compared to the phase 2 study (84 days). However, we should also consider that this ER analyses based on the phase 3 study has some limitations due to the study design, as only one dosing regimen or placebo was tested in Study 301: (1) Patients with annualized change in new HO volume data were either treated with one dosing regimen (chronic 5 mg, flare-up 20/10 mg) or not treated with palovarotene; (2) patients with flare-ups were treated with high doses (20/10 mg QD) and patients without flare-ups were treated with the low dose (5 mg QD). In addition, we note that placebo response (mainly obtained from the NHS) has a large variability, in which HO volume change from baseline could range from -91300 mm^3 to 391730 mm^3 by Month 12 for the placebo group. This large variability limited the precision for interpreting the placebo response, and therefore we have less confidence in the detected ER relationship as shown in Figure 7. In general, we still consider that there is no obvious exposure-response relationship for

palovarotene and new HO volume up to 12 months, thus further change in the dose of palovarotene above the doses of chronic 5 mg and flare-up 20/10 mg is unlikely to further improve response for HO volume. Flare-up dosing controlling for new HO formation seemed to be appropriate.

Table 6. Annualized New HO Volume in Patients With and Without Flare-ups in Palovarotene-treated and Untreated Groups (Studies PVO-1A-202B/C and PVO-1A-301)

Study No.	PVO-1A-202 B/C			PVO-1A-301		PVO-1A-001 (NHS)	
Treatment	Chronic + flare-up dosing (N=9)	Chronic dosing (N=9)	Untreated/undertreated flare-ups ¹ (N=30)	Chronic + flare-up dosing (N=64)	Chronic dosing (N=33)	Untreated flare-ups (N=46)	Untreated no flare-ups (N=44)
Annualized Total WBCT	-3024 (23974)	33451 (63002)	25549 (42468)	10741 (4675)	3183 (1739)	38380 (12208)	6150 (3345)
New HO Volume ² (mm ³ /year)							

Source: Applicant's CSR

¹ Subjects who had at least one flare-up event that was not treated due to the different criteria for flare-up treatment and the treatment of intercurrent flareups in PVO-1A-202B and PVO-1A-301.

² No square root transformation; negative values included

Abbreviations: HO, heterotopic ossification; N, number of subjects; NHS, natural history study; PVO, palovarotene; WBCT, whole-body computed tomography

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Phase 3: Study PVO-1A-301

6.2.1.1. Design

Study Title: A Phase 3 Efficacy and Safety Study of Oral Palovarotene for the Treatment of Fibrodysplasia Ossificans Progressiva (FOP)

Study PVO-1A-301 (Study 301) was a phase 3 study with the primary objective of evaluating the efficacy of the chronic/flare-up dosing regimen of palovarotene to decrease new HO development in adult and pediatric patients with FOP, in comparison to untreated patients in the Applicant's prospective FOP natural history study (NHS; PVO-1A-001). The single-arm design of Study 301, with use of the NHS as an external control group, raises issues regarding the comparability of these studies/groups, which are discussed below (see Section 6.3.2). The protocol synopsis is included in Section 15 of this review.

Study 301 subjects received chronic treatment of 5 mg palovarotene once daily outside of acute FOP flare-up episodes. At the onset of any symptom of a flare-up (e.g., pain, swelling) in any location or after a high-risk trauma event, as confirmed by the investigator, subjects increased to flare-up dosing of 20 mg daily for 4 weeks, followed by 10 mg daily for 8 weeks. If flare-up symptoms persisted, treatment could be extended further with 10 mg daily in 4-week increments. If a subject experienced an intercurrent flare-up at a new location, or marked worsening of the initial flare-up, the treatment cycle was restarted at 20 mg. When acute symptoms had resolved and the flare-up treatment cycle was completed, chronic 5 mg daily treatment resumed.

Subjects <18 years old with <90% skeletal maturity received reduced equivalents of the above doses based on body weight. Skeletal maturity of $\geq 90\%$ was based on a bone age of ≥ 12 years 0 months for girls, and ≥ 14 years 0 months for boys, as determined by hand/wrist x-rays using the atlas of Greulich and Pyle and standards of Bayley-Pinneau. Subjects with bone age below these marks received body weight-adjusted doses according to [Table 7](#). If a subject (of any age) experienced intolerable side effects, the dose could be reduced to the next lower dose listed for their weight category.

Table 7. Study 301: Weight-Adjusted Palovarotene Doses for Skeletally Immature (<90%) Subjects and Dose De-escalation Dosing for All Subjects

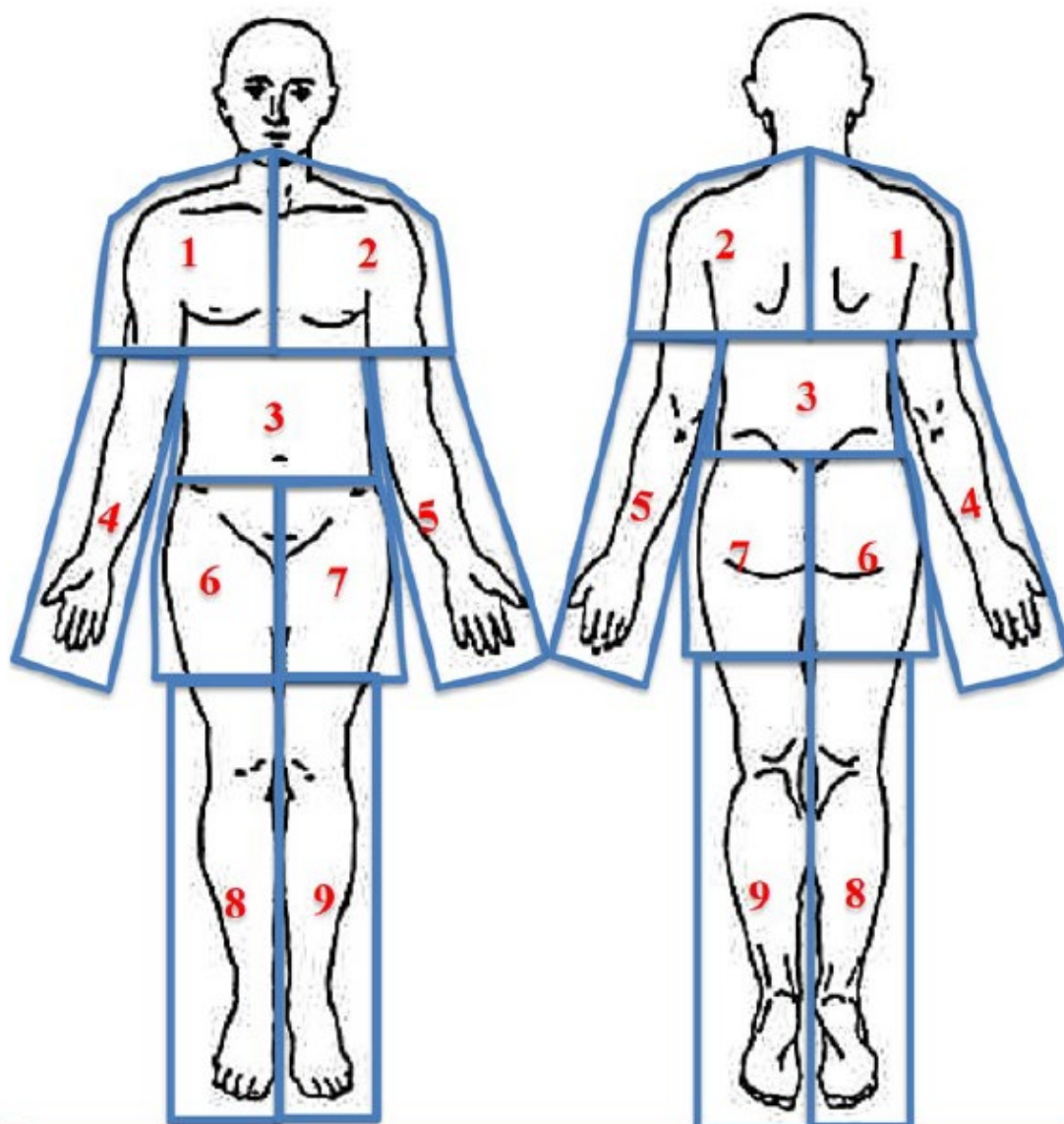
Weight Range Category	20 mg Equivalent	15 mg Equivalent*	10 mg Equivalent	7.5 mg Equivalent*	5 mg Equivalent	2.5 mg Equivalent*
<20 kg	10 mg	7.5 mg	5 mg	3 mg	2.5 mg	1 mg
20 to <40 kg	12.5 mg	10 mg	6 mg	4 mg	3 mg	1.5 mg
40 to <60 kg	15 mg	12.5 mg	7.5 mg	5 mg	4 mg	2 mg
≥ 60 kg	20 mg	15 mg	10 mg	7.5 mg	5 mg	2.5 mg

Source: Study 301 protocol Table 3

*In the event of dose de-escalation from 20 mg, 10 mg or 5 mg equivalents, respectively

HO was assessed by whole-body CT scan every 6 months in Study 301, and every 12 months in the NHS (or at the time of transfer into Study 301). The image acquisition methods in these studies were similar. At a central imaging facility, scans from the two studies were interspersed for readings that were blinded to the study/treatment group and other clinical data pertinent to the subject. In baseline scans from either study, each of 9 body regions (excluding the head, see Figure 8) was evaluated for the presence of HO by two radiologists. In each CT slice, regions of interest (ROIs) were delineated by reviewers around each area of HO; data from adjacent slices were integrated by image analysis software to yield volume of the ROI. Total volume of HO (cm^3) was calculated by consensus for each region, and summed to yield baseline total body HO.

Figure 8. WBCT Body Regions for Assessment of HO



Source: Study 301/NHS Independent Review Charter

Key: 1, 2: Chest, Neck, Shoulder (Right and Left); 3: Mid Torso; 4, 5: Arm (Right and Left); 6, 7: Hip (Right and Left); 8, 9: Lower Leg (Right and Left)

Abbreviations: HO, heterotopic ossification; WBCT, whole-body computed tomography

For postbaseline scans, HO volume was recalculated for any body region that appeared to contain, upon initial qualitative review, new HO in comparison to the previous scan (either a new area of HO, or enlargement of an existing lesion), with adjudication of any disagreements between reviewers. Any reduction in HO volume of other lesions in that region would also be captured as an offset to the total gains, and the change in volume from baseline could be positive or negative for any region and/or for total-body. HO volume was not remeasured postbaseline in regions where there was no apparent new HO compared to the previous scan. Intra- and inter-reader variability were evaluated via secondary rereads of a random subset of WBCT scans and considered to be acceptable.

Because HO volume measurements were reported by body region, and data pertaining to individual HO lesions were not recorded in the datasets, these studies were not designed to evaluate the extent to which palovarotene may inhibit the development of new lesions. When new HO was seen in a region, readers were instructed to classify the new HO as “new lesion” or “enlarged lesion” or “both new and enlarged lesion.” for the region as a whole. This information was entered in the comments section of the imaging raw data and was not analyzed in the submitted NDA. Pursuant to a U.S. Food and Drug Administration (FDA) request, the Applicant plans to tabulate this information for a future submission (not within the current review cycle).

A subset of subjects participated in both studies, having completed at least one post baseline assessment in the NHS and subsequently enrolling in Study 301. For most of these subjects, the NHS end-of-study WBCT scans also served as the baseline WBCT scan in Study 301. These scans were read twice (as NHS postbaseline, and as Study 301 baseline) because of the differing procedures involved.

6.2.1.2. Eligibility Criteria

Adult and pediatric patients age ≥ 4 years with a clinical diagnosis of FOP and no flare-up symptoms within the previous 4 weeks were eligible to enroll in Study 301. To facilitate comparisons with the NHS, most of the subjects (i.e., the Principal Analysis population) were required to have the classic R206H mutation and no prior exposure to palovarotene. There were exclusion criteria based on known retinoid safety issues, including pregnancy and increased suicide risk.

6.2.1.3. Statistical Analysis Plan

The primary endpoint was the annualized change in new HO volume. This endpoint was compared between treated subjects from Study 301 and untreated subjects from the NHS. Scheduled WBCT scans were performed at baseline, Month 12, Month 24 and Month 36 in the NHS, and at baseline, Month 6, Month 12, Month 18, and Month 24 in the Study 301. WBCT scans were also performed at the time of early study discontinuation. The key secondary endpoint was the proportion of subjects with any new HO. The other secondary endpoints were the number of body regions with new HO, the proportion of subjects reporting flare-ups, and the rate of flare-ups per subject-month.

Exploratory endpoints included change from baseline in range of motion (ROM) assessed by CAJIS (Cumulative Analogue Joint Involvement Scale for FOP), change from baseline in physical function using age-appropriate forms of the FOP-PFQ (FOP Physical Function Questionnaire), and change from baseline in physical and mental function for subjects ≥ 15 years old and mental function for subjects < 15 years old using age-appropriate forms of the PROMIS (Patient Reported Outcomes Measurement Information System) Global Health Scale.

Primary Analysis

The prespecified primary analysis for the primary endpoint was based on a Bayesian compound Poisson model. Under this model, the change in new HO since previous CT scan was modeled as a compound distribution of the number of body regions with new HO and the new HO volume per region where new HO occurred. The compound Bayesian model counted the occurrence of a positive new HO as an event. The treatment effect was expressed as the ratio of the annualized new HO between treated and untreated subjects, which was estimated by the ratio of annual

event rates multiplied by the ratio of the growth rates per event. This method is equivalent to estimating the mean annualized new HO by multiplication of the mean annual number of events and the mean growth per event. More details regarding the Bayesian analysis are included in the Part [III](#).

The Bayesian compound model was estimated based on the number of regions with positive new HO and the average growth per region where positive new HO occurred since the previous WBCT scan. Negative new HO values were set to 0 in the analyses. The prespecified analysis included a square root transformation of each change in HO since the previous scan by region. The Applicant chose this statistical model “to more appropriately accommodate the high degree of variability in the volume of new HO assessed by WBCT.” The square root transformation was included in the Bayesian compound Poisson analysis because simulations suggested that if palovarotene reduced the probability of new HO as much or more than it reduced the new HO volume given new HO, introducing a square root transformation could marginally increase power. Additionally, square root transformation would likely decrease the variance of the endpoint by shrinking any extremely large values of new HO volume.

Three early interim analyses and one final analysis were prespecified in the 2017 protocol. The first interim analysis was planned to occur when 35 subjects had completed at least one year of follow-up, and the second when all subjects enrolled in the Principal Enrolled Population had completed 12 months of follow-up. A Pocock alpha-spending function was prespecified for the interim analyses, with an overall Type I error rate of 0.025, one-sided. To preserve the overall Type I error rate, the alpha threshold for each interim and final analysis was set at 0.0091.

The trial crossed the futility boundary at the second interim analysis and the study was paused for dosing. However, additional post hoc analyses, including the Bayesian compound model without square root transformation, found evidence of potentially clinically meaningful benefit of palovarotene. Upon review of the additional post hoc analyses, the data monitoring committee (DMC) noted that the impact of the prespecified square root transformation was unexpectedly large and appeared to have moved the statistical conclusion from significant therapeutic benefit to showing futility of the treatment. The DMC concluded that “the dilemma created by these highly disparate results precludes a confident conclusion about futility.” Dosing in study 301 was allowed to resume. The DMC recommended that “palovarotene be continued in skeletally mature children ≥ 14 years.”

6.2.1.4. Results of Analyses

Demographic and Baseline Characteristics

Baseline demographic data in Table 8 pertain to the Principal Safety Set (PSS) of Study 301 and the NHS, consisting of subjects with FOP due to the classic R206H mutation and no previous treatment with palovarotene; and for Study 301, subjects who received at least one dose of palovarotene.

Table 8. Studies PVO-1A-301 and PVO-1A-001: Baseline Demographic and Clinical Characteristics, Principal Safety Set*

Characteristic	Study PVO-1A-301 Palovarotene (N=99)	Study PVO-1A-001 NHS control (N=111)
Sex, n (%)		
Male	53 (54%)	60 (54%)
Female	46 (47%)	51 (46%)
Age, years		
Mean (SD)	15.1 (9.6)	17.5 (9.8)
Median (min, max)	13 (4,61)	15 (4,56)
Age groups (years), n (%)		
4 to <11	34 (34%)	29 (26%)
11 to <18	41 (41%)	37 (33%)
≥18	24 (24%)	45 (41%)
Race, n (%)		
White	70 (71%)	81 (73%)
Asian	9 (9%)	9 (8%)
Black/African American	1 (1%)	0
Other/unknown**	19 (19%)	21 (19%)
Ethnicity, n (%)		
Hispanic	19 (19%)	23 (21%)
Non-Hispanic	69 (70%)	72 (65%)
Not reported**	11 (11%)	16 (14%)
Country of participation, n (%)		
United States	38 (39%)	38 (34%)
United Kingdom	9 (9%)	17 (15%)
France	10 (10%)	15 (14%)
Sweden	8 (8%)	0
Australia	6 (6%)	6 (5%)
Italy	5 (5%)	14 (13%)
Spain	6 (6%)	0
Canada	4 (4%)	1 (1%)
Brazil	5 (5%)	1 (1%)
Argentina	4 (4%)	19 (17%)
Japan	4 (4%)	0
Baseline characteristics		
Whole-body HO volume* (cm ³)		
Mean (SD)	231.2 (292.5)	312.5 (373.6)
Median (min, max)	127.2 (0, 1382.0)	195.4 (0, 1906.2)
Number of body regions with HO*, mean	6.1	6.5
Number of flare-ups within 12 months of enrollment, mean (SD)	1.4 (1.86)	2.5 (5.98)
Number of flare-ups within 12 months of enrollment, median (min, max)	1.0 (0,8)	1.0 (0, 40)
Mean CAJIS score	10.0	11.8
Mean FOP-PFQ score	44.3	47.0

Source: Study 301, ADSL and ADHOV, ISE ADNHS MOV and Tables S39A and S40.1

*HO data are based on Principal Full Analysis Set of study 301 (N=97) and NHS (N=101)

**Note: Large number of subjects with race/ethnicity data missing is partly due to French legal restrictions

Abbreviations: CAJIS, Cumulative Analogue Joint Involvement Scale for FOP; FOP-PFQ, fibrodysplasia ossificans progressiva Physical Function Questionnaire; HO, heterotopic ossification; N, number of subjects in treatment group; n, number of subjects with given characteristic; NHS, natural history study; PVO, palovarotene; SD, standard deviation

As shown in [Table 8](#), the two study populations were similar in demographics except that NHS subjects were somewhat older than Study 301 subjects (mean age 17.5 versus 15.1 years, respectively, at baseline). NHS subjects also tended to have worse measures of FOP disease severity (whole-body HO volume, number of body regions with HO, CAJIS and FOP-PFQ scores measuring impaired range of motion and physical function, respectively). These differences are likely age-related, as cross-sectional analyses of baseline data showed that increasing age correlates with greater HO accumulation and with worsening FOP-related functional impairments.

The mean number of flare-ups reported by the subject (or parents) within the 12 months prior to study enrollment was higher for NHS compared to Study 301 subjects (2.5 versus 1.4), but the median number was the same (1). The mean for the NHS was skewed by two subjects (b) (6), age 9 and 8 years) who, at NHS enrollment, reported 40 and 37 flare-ups in the previous year, respectively. During their participation in the NHS, the number of flare-ups reported by these two subjects was much lower (1 in 18 months, 4 in 30 months, respectively).

Study 301 and NHS subjects were generally similar with respect to other FOP-related history, including mean age at FOP diagnosis (6.6, 7.5 years); history of great toe malformations (99%, 100%); cervical spine malformations (44%, 51%); hearing loss (46%, 35%); and family history of FOP (1%, 5%).

Disposition

In Study 301, seven patients with FOP failed screening based on various enrollment criteria. In the NHS, three patients were not included in the Principal Enrolled Population because they did not have FOP or the required R206H mutation. In Study 301, there were eight patients with FOP who did not have this mutation and were allowed to enroll as a “Supplemental” population. The Principal Safety Set (PSS) used for many analyses was limited to patients with the R206H mutation and consisted of 99 patients in Study 301 who received at least one dose of palovarotene and 111 patients in the NHS with available comparison data. Within the PSS, the Principal Full Analysis Set (P-FAS) comprised subjects with evaluable whole-body HO data.

Table 9. Studies PVO-1A-301 and PVO-1A-001: Patient Disposition

Disposition Category	Study PVO-1A-301 Palovarotene	Study PVO-1A-001 NHS control
Patients enrolled	107	117
Principal enrolled population	99	114
Supplementary enrolled population	8	N/A
Principal safety set (PSS)	99	111
Principal full analysis set (P-FAS)	97	101
Ongoing in study	88	2
Completed study	0	31
Discontinued study	19	81
Enrolled in another interventional study	0	66
Adverse event	6	N/A**
Death	0	1
Worsening of clinical condition	0	1
Withdrawal by subject	11	9
Other*	2	4

Source: Study 301 CSR, Table 12

*Applicant request, noncompliance, lost to follow-up, or subject did not want to travel

**AEs were not recorded in the NHS

Abbreviations: NHS, natural history study; P-FAS, Principal Full Analysis Set; PSS, Principal Safety Set; PVO, palovarotene

As shown in [Table 9](#), over half of the NHS subjects left this study before completion in order to enroll in an interventional study, including eight subjects who enrolled in Study 201 at the onset of a flare-up, and others who enrolled in Study 202B (n=13), Study 301 (n=39), or studies of other potential FOP therapies under different sponsors (n=7).

Because of multiple reports of PPC among pediatric patients in Study 301 (see Section [7.7.1](#)), a partial clinical hold was imposed on December 3, 2019, for the dosing of all patients <14 years of age. This partial clinical hold remains in effect; some affected patients resumed treatment after reaching age 14. On January 15, 2020, dosing was also paused for other study participants (≥14 years of age) due to a finding of futility in an interim efficacy analysis (see below); many of these patients resumed treatment following approximately 3 to 19 months' hiatus. Because of the prolonged interruption and/or discontinuation of treatment in nearly all participants, the efficacy analyses in the original NDA, based on a cut-off date of February 28, 2020, have not been updated. Recently, the Applicant reported that new efficacy data (WBCT scans) have been collected on many participants following treatment restart through the study end in September 2022; these data will be submitted at a later date (not within this review cycle) to aid in the overall assessment of efficacy.

Primary Efficacy Endpoint Results

The primary efficacy endpoint of annualized new whole-body HO volume (cm³/year) by CT scan was analyzed in the Principal Full Analysis Set (P-FAS), consisting of 97 palovarotene-treated subjects in Study 301 and 101 untreated controls in the NHS with evaluable screening and postbaseline HO data. Table 10 below summarizes the number of subjects with evaluable CT data at each visit; note that scans were scheduled at 6-month intervals in Study 301, and 12-month intervals in the NHS.

Table 10. Studies 301 and NHS: Number of Subjects With Whole-Body HO Data by Visit (P-FAS)

Timepoint	Study PVO-1A-301 Palovarotene	Study PVO-1A-001 NHS control
Screening	97	101
Month 6	94	2
Month 12	93	90
Month 18	78	11
Month 24	12	63
Month 30	0	9
Month 36	0	33
Month 42	0	4

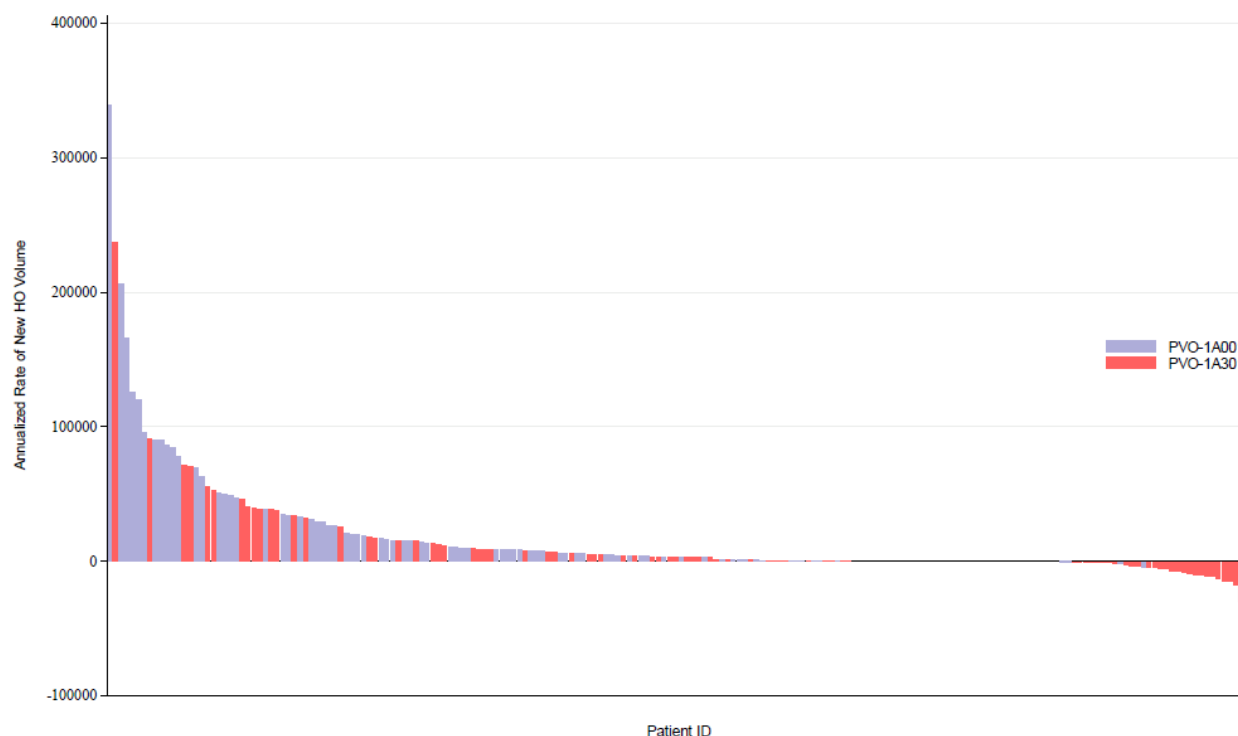
Source: FDA reviewer

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

Abbreviations: HO, heterotopic ossification; NHS, natural history study; P-FAS, principal full analysis set; PVO, palovarotene

The data for new HO in these studies are highly variable, as shown in the waterfall plot [below](#). On the left side of the plot, representing subjects with large HO increases, there is a preponderance of untreated subjects; 5 NHS subjects (in gray) developed new HO at rates >100 cm³/year versus one palovarotene recipient in Study 301 (in red). On the right side, numerous subjects, mostly in Study 301, had net negative new HO. The significance of negative new HO data is unclear and is discussed below (see Section [6.3.2](#)).

Figure 9. Study 301 and NHS: Individual Subject Annualized New HO Volume Distribution for Palovarotene-treated and Untreated Subjects (P-FAS)



Source: Study 301 Appendix 16.1.13.5 final IA3, Figure S14.1.1

Abbreviations: HO, heterotopic ossification; NHS, natural history study; P-FAS, principal full analysis set; PVO, palovarotene

The primary endpoint of annualized new HO failed to demonstrate efficacy of palovarotene with adequate posterior probability, using the Applicant's prespecified Bayesian analysis ([Table 11](#)). The posterior probability of a reduction in annualized new HO was 0.65. The 95% credible interval of the between study ratio of annualized new HO was (0.74, 1.22).

Table 11. Studies 301 and NHS: Ratio of Annualized Change in HO Volume per Year

PVO-1A-301 Palovarotene	PVO-1A-001 NHS control	Median Ratio (95% CI)	Pr(ratio <1)
N=97	N=101	0.95(0.74, 1.22)	0.65

Source: Table compiled by the primary Statistical reviewer.

Prespecified primary analysis method; values are square root transformed, and body region negative new HO volumes are set to 0. 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).

Abbreviations: CI, confidence interval; NHS, natural history study; Pr, probability; PVO, palovarotene

Applicant's Post hoc Bayesian Analyses

The Applicant's post hoc Bayesian analyses without square root transformation supported the efficacy of palovarotene with a high posterior probability of reduction (>0.99) in annualized new HO in study 301 subjects compared with NHS subjects. The Applicant's analyses with additional covariates yielded similar results.

Table 12. Studies 301 and NHS: Ratio of Annualized Change in HO Volume—post Hoc Bayesian Analyses

Analysis Method	Median Ratio (95% CI)	Pr(ratio <1)
No square root transformation	0.64(0.45, 0.90)	>0.99
No square root transformation, added covariates [#]	0.58(0.41, 0.82)	>0.999

Source: ISE

[#]covariates: baseline HO divided by baseline age, baseline age, sex, baseline CAJIS, time since last flare-up

Negative new HO set to zero.

The median ratio is the median of the posterior distribution of the ratio (annualized rate of new HO for subjects in study PVO-1A-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).

Abbreviations: CAJIS, Cumulative Analogue Joint Involvement Scale for FOP; CI, confidence interval; HO, heterotopic ossification; NHS, natural history study; Pr, probability

Applicant's Post Hoc Weighted Linear Mixed Effect Model Analysis

The Applicant's post hoc wLME analysis with baseline annualized HO (calculated as baseline total HO volume divided by baseline age) as the only covariate achieved nominal significance (Table 13). In this analysis, the annualized new HO for each subject was calculated using the new HO volume from baseline associated with the longest follow-up divided by the length of follow-up. The length of follow-up varied substantially among subjects and between studies. For example, annualized new HO was based on the Month 18 observation for 66% of subjects in study 301 and the Month 36 observation for 32% of subjects in the NHS. The wLME model accounted for the various follow-up lengths using a weighted approach. We note that the estimated treatment effect based on various lengths of follow-up could be difficult to interpret without the strong assumption of a constant rate of change in HO.

Table 13. Studies 301 and NHS: Applicant's wLME Analyses on Annualized New HO at Last Scan

Statistic	Study PVO-1A-301 Palovarotene N=97	Study PVO-1A-001 NHS control N=101
Annualized HO Mean at baseline, (SD)	13.4 (13.1)	15.7 (14.0)
Mean Annualized new HO, (SE)	9.4 (3.1)	23.7 (4.9)
Median (min, max)	0.4 (-30.2, 237)	6.1 (-37.9, 339)
Mean difference from NHS	-14.3	-
LS Mean difference (95% CI)	-10.9 (-21.2, -0.6)	-
p-value, comparison to NHS	0.039	-

Source: CSR.

Subject level random effect included to account for the correlation among repeated measures on the same subject, for those subjects who transitioned from NHS to Study 301; No square root, negative new HO included; Full Analysis Set; Covariates: annualized HO at baseline; Annualized HO at baseline calculated by dividing baseline HO by baseline age; response variable-annualized change in HO at last visit.

Abbreviations: CI, confidence interval; HO, heterotopic ossification; NHS, natural history study; PVO, palovarotene; SD, standard deviation; SE, standard error; wLME, Weighted Linear Mixed Effects Analyses

As the distribution of annualized new HO is skewed, the Applicant performed sensitivity analyses to investigate the influence of large values on the analyses conclusion. These analyses indicate that the conclusions are not driven by the few extremely large values seen in subjects in the NHS (see Section [16](#)).

Subgroup Summary by Sex and Age

Subgroup summaries indicate a smaller effect size among females and among subjects older than 18 years (Table 14). This finding may be explained by the smaller annualized growth of new HO in the control group (NHS) patients in these subgroups. However, it is not possible to rule out that the drug's effect is less in older patients for whom the disease stage is often more advanced. An explanation for the smaller effect in females is uncertain. Findings from these subgroup analyses should be interpreted with caution because with a smaller number of subjects in each subgroup, the influence of a few large values and imbalances in confounders in the absence of randomization could be greater on the mean difference, compared with analyses based on the overall population.

Table 14. Subgroup Summary on Annualized New HO (cm³) Based on the Last Scan

Subgroup	Statistics	Study 301 (N=97)	NHS (N=101)	Difference
Sex				
Male	n	51	56	
	Mean (SD)	8.4 (22.7)	31.3 (55.3)	-22.9
Female	n	46	45	
	Mean (SD)	10.6 (37.3)	14.3 (37.7)	-3.7
Age				
>=18	n	22	40	
	Mean (SD)	8.6 (19.4)	10.7 (22.2)	-2.1
<18	n	75	61	
	Mean (SD)	9.7 (33.0)	32.3 (58.8)	-22.5

Source: FDA Statistical reviewer's analysis

Abbreviations: HO, heterotopic ossification; N, number of subjects; NHS, natural history study; SD, standard deviation

Secondary Efficacy Endpoint Results

Proportion of subjects with any new HO

This endpoint was evaluated using HO data from month 12, which is the timepoint with the most consistent follow-up data across both Study 301 and the NHS (there were few subjects with data for Month 24 in Study 301, and for Month 18 in the NHS). In the Principal FAS, the proportion of subjects with any new HO (new volume >0 cm³ in any body region) at month 12 compared to baseline was essentially the same in palovarotene-treated subjects (59/92, 64%) and untreated subjects (56/90, 62%).

Number of body regions with new HO

This endpoint was also analyzed at month 12 based on the availability of HO data in most subjects at this point. The mean (SD) number of body regions with new HO per subject since baseline at month 12 was 1.3 (1.4) in Study 301 subjects and 1.5 (1.6) in untreated NHS subjects. The difference was not statistically significant according to the Applicant's prespecified analysis.

Proportion of subjects reporting flare-ups/ Flare-up rate per subject-month of exposure

Based on the hypothesis that chronic palovarotene dosing has the potential to interrupt initiation of a flare-up, the incidence and rate of new flare-ups were designated as secondary efficacy endpoints in Study 301. This hypothesis was not supported by the data: compared to the NHS, the proportion of palovarotene-treated subjects with reported flare-ups through Month 12 was slightly higher (67% versus 56%), and the rate of flare-ups per month was also higher (0.15 versus 0.07). Although this finding may be related to issues of study design, it is considered to represent a potential safety issue based on the known musculoskeletal effects of retinoids and is discussed as such in Section [7.7.3](#) of this review.

Exploratory Efficacy Endpoint Results

Range of motion assessed by CAJIS

Changes from baseline in CAJIS score were small and similar between treatment groups at Month 12. There was a mean (SD) increase of 0.5 (2.0) in Study 301 subjects and 0.6 (2.4) in untreated NHS subjects (based on 0 to 30 scale, with higher scores indicating more impaired ROM).

Physical function assessed by FOP-PFQ

At baseline, mean FOP-PFQ scores in Study 301 and NHS subjects were 44.3 and 47.0, respectively (scale of 0 to 100, with higher scores indicating worse physical function by patient report). Mean changes from baseline were 2.8 and 4.5, respectively, at month 12, a nonsignificant difference.

PROMIS Global Health Scale

Very small changes from baseline were seen in Study 301 subjects, similar to untreated NHS subjects.

6.2.2. Phase 2: Studies PVO-1A-201 and PVO-1A-202A/B/C

6.2.2.1. Design

The first study of palovarotene in patients with FOP was PVO-1A-201 (“Study 201”), a 12-week, randomized, double-blind, placebo-controlled study of 40 FOP patients who were experiencing an acute flare-up episode, with at least 2 of 6 prespecified symptoms. The primary objective was to evaluate the ability of palovarotene to prevent new HO at flare-up sites, as assessed by radiograph. Starting within 7 days of symptom onset, patients received one of three treatment regimens:

- Palovarotene 10 mg daily x 2 weeks, followed by 5 mg daily x 4 weeks (10/5 regimen) (n=21)
- Palovarotene 5 mg daily x 2 weeks, followed by 2.5 mg daily x 4 weeks (5/2.5 regimen) (n=9)
- Placebo capsules x 6 weeks (n=10)

The study used an adaptive design. For the first 16 patients enrolling in this study (Cohort 1), the randomization ratio was 3:1 (palovarotene 10/5: placebo). Subsequently, the 5/2.5 regimen was added, and the randomization ratio was changed to 3:3:2 (10/5 mg: 5/2.5 mg: placebo) for the last 24 patients (Cohort 2). Treatments could not be extended beyond 6 weeks for any ongoing or new symptoms.

Enrollment began in July 2014 and was initially limited to FOP patients at least 15 years of age who were at least 90% skeletally mature (based on bone age, derived from hand/wrist x-ray). During enrollment of Cohort 2 (protocol amendment 6), the minimum age was lowered to 6 years with reduced doses for skeletally immature patients according to the following table (this schedule is nearly identical to the dose adjustments used subsequently in Study 301).

Table 15. Study 201: Weight-Adjusted Palovarotene Doses for Skeletally Immature (<90%) Subjects

Weight Range Category	10 mg Equivalent	5 mg Equivalent	2.5 mg Equivalent*
20 to <40 kg	6 mg	3 mg	1.5 mg
40 to <60 kg	8 mg	4 mg	2 mg
≥60 kg	10 mg	5 mg	2.5 mg

Source: Study 201 CSR Table 1

*In the event of dose de-escalation

Prior to this study, plain radiographs were sometimes used in clinical practice to assess formation of new HO at FOP flare-up sites, but the sensitivity and optimal timing of this and other potential HO imaging modalities were largely unknown. In this study, imaging of the flare-up sites included assessments of HO by standard AP/lateral radiograph and CT scan, including measurements of HO area (mm²) and HO volume (mm³), respectively; and assessment of soft tissue edema at the site by MRI, or by ultrasound (US) if MRI was not feasible. This imaging was conducted at baseline, 6 weeks (end of treatment) and 12 weeks (end of post-treatment observation period).

All 40 subjects completed Study 201 and enrolled in the open-label extension study PVO-1A-202 (“Study 202”), which was conducted in 3 parts:

- Study 202 Part A

Subjects who experienced up to 2 additional flare-ups following Study 201 received the palovarotene 10/5 regimen (weight-adjusted) used in Study 201 for 6 weeks, with assessments at Week 12. New HO at flare-up sites was evaluated mainly by CT, which was found to be more sensitive than standard radiograph. Subjects without flare-up symptoms were not treated. In addition, follow-up evaluations of the original flare-up site in Study 201 were conducted at 12 months.

- Study 202 Part B (Protocol amendment 3; known as study PVO-1A-204 in France; implemented March 2016)

Based on new nonclinical data, the doses and duration of flare-up treatment were increased, and chronic dosing was introduced, with two new palovarotene regimens:

- Chronic/flare-up regimen (“Adult Cohort”): skeletally mature subjects received 5 mg daily, with increased dosing during a flare-up to 20 mg for 4 weeks followed by 10 mg for 8 weeks, with treatment extension in 4-week increments allowed for flare-ups with ongoing symptoms.
- Flare-up-only regimen (“pediatric cohort”): skeletally immature patients received the same regimen for flare-ups, with weight-adjusted dose equivalents of 20 mg for 4 weeks and 10 mg for 8 weeks and treatment extension as necessary, but with no chronic dosing between flare-ups (as a safety measure). Dose adjustments for body weight 40 to <60 kg, or 20 to <40 kg, followed the same schedule as Study 301 (see table in Section [6.2.1.1](#) of this review).

Enrollment in Part B included most of the subjects from Study 201/202A, as well as new subjects not previously treated. As in Studies 201/202A, two or more symptoms were required to initiate flare-up treatment. Flare-ups treated with the new 20/10 regimen (with or without prior 5 mg chronic treatment) were assessed by CT of the flare-up site through Week 12, and end of treatment (EOT) for subjects with treatment extended. In addition, subjects receiving the chronic regimen underwent annual evaluations that included measurement of new whole-body HO by CT scan. Flare-ups with only one reported symptom, or intercurrent flare-ups at other sites during treatment of an initial flare-up, were not treated as flare-ups and were instead reported as AEs of “condition aggravated,” which is the MedDRA preferred term for a FOP flare-up.

- Study 202 Part C (Protocol amendment 4; PVO-1A-204 in France; implemented Sept 2017)

The chronic/flare-up regimen was continued and expanded to all subjects, including skeletally immature children who received weight-adjusted equivalents of the 5 mg, 20 mg and 10 mg doses. Flare-up dosing was expanded to include flare-ups with any number of symptoms (≥ 1), intercurrent flare-ups at a new location, or substantial trauma “likely to lead to a flare-up”; any such events restarted the 12-week 20/10 mg treatment cycle. Thus, the 202C treatment protocol was essentially identical to the phase 3 study, 301. Flare-up site imaging was not included in Part C, as efficacy was assessed by the annual whole-body CT scans. All 202C subjects were drawn from 202B; no new subjects

were enrolled in Part C. This study was ongoing at the February 28, 2020, cutoff date for the interim study report.

6.2.2.2. Eligibility Criteria

In Study 201, the initial cohort consisted of subjects with clinically diagnosed classic FOP, at least 15 years of age and $\geq 90\%$ skeletal maturity, with symptomatic onset within 7 days of a distinct flare-up; with at least two out of 6 specified symptoms (pain, swelling, decreased ROM, stiffness, redness, warmth); and consistent with their previous flare-ups. Flare-ups qualifying for enrollment and treatment were in an appendicular area (upper or lower extremity), abdomen or chest. Excluded were flare-ups in the head, because imaging would involve radiation to the brain, and flare-ups in the upper back, which were considered by consulting experts to be unpredictable and relatively difficult to assess. After the initial cohort and with availability of juvenile toxicity data, enrollment in Study 201 was expanded to children age ≥ 6 years (Protocol amendment #6). In extension Study 202A and 202B, the criteria which qualified additional flare-up(s) for palovarotene treatment and evaluation/ imaging were the same as in Study 201, i.e., the presence of at least 2 symptoms, and onset within 7 days.

In the NHS, which began enrollment shortly after initiation of Study 201, any subject with a flare-up meeting the above criteria was eligible to transfer into Study 201 for treatment. Except for the requirement of ≥ 2 symptoms, severity of the flare-up was not intended to be a determining factor. Most subjects remained in the NHS during flare-ups, and a subset of these events (maximum one per year per subject) were evaluated in-clinic over 12 weeks and provided untreated control data, including imaging, for comparisons to palovarotene-treated flare-ups.

The additional group of subjects who had not participated in Studies 201 and 202A, and who began palovarotene treatment in Study 202 Part B, was restricted to subjects who were $\geq 90\%$ skeletally mature and who therefore joined the “Adult Cohort.” Additional enrollment criteria for these new subjects were a history of at least two flare-ups within the past 2 years, but no flare-up symptoms within the past 4 weeks; a confirmed R206H mutation; and a CAJIS score of 6 to 16. Most of these subjects whose initial Study 202 enrollment was in Part B transferred from the NHS. As in Study 301, the selection of specific NHS subjects for transfer into a treatment study among those eligible was apparently nonrandom, and any factors that may have been considered in these decisions are unknown.

6.2.2.3. Statistical Analysis Plan

Flare-up Site Outcomes

In Studies 201, 202A/B and the NHS, flare-up site images were evaluated by radiologists at a central facility with blinding for study and treatment assignment. In Study 201, the primary endpoint specified in the protocol and SAP was the proportion of “responders” as defined by no or minimal new HO at the site (a grade of ≤ 3 on a 0 to 6 scale on both AP and lateral views) by standard radiograph at Week 6 compared to baseline. Although it was predicted that about 80% of untreated FOP flare-ups would result in new HO, the observed incidence in this and other studies was substantially lower, especially by standard radiograph (see below). Secondary imaging endpoints included the proportion of responders at Week 12; volume of new HO by CT; and soft tissue swelling and/or cartilage by MRI or US.

The Study 201 protocol and Independent Review Charter documents specified the interpretation of each imaging modality independently, with double-read review and consensus adjudication (the “primary read” process). Based on emerging data showing the limitations of plain radiograph, and general uncertainty about optimal imaging of HO, the SAP described an additional “global read” process in which radiologists and investigators (blinded to treatment group) determined the presence/absence of new HO based on a comprehensive evaluation of all images, including radiographs and CT, as well as MRI or US assessments of soft tissue edema at the flare-up site, at all timepoints.

Other secondary endpoints in Study 201 included flare-up related pain and swelling assessed by NRS (Numeric Rating Scale) or FPS-R (Faces Pain Scale-Revised), and range of motion at the joint closest to the flare-up site by goniometry.

The limited number of flare-ups evaluated in Study 201 was supplemented by flare-up data from the extension study 202A/B (palovarotene-treated events) and the NHS (untreated events). The Integrated Summary of Efficacy (ISE) presents pooled analyses by treatment regimen and by flare-up event rather than by subject (tabulated as “M” rather than “N”), because many subjects were evaluated in multiple events, including in some cases different studies/regimens. The F-FAS (Flare-up Full Analysis Set) consists of all reported flare-ups in these studies, and within the F-FAS, the IF-FAS (Imaged Flare-up Full Analysis Set) consists of all events with CT imaging across studies. Flare-ups in the head or upper back in the NHS were excluded from the IF-FAS, because flares in these locations were not eligible for evaluation in palovarotene-treated subjects. Also excluded from the IF-FAS were NHS flare-ups that were followed remotely by Telephone Contact (TC), without in-clinic evaluation and imaging.

Key endpoints for the pooled ISE flare-up analyses were the proportion of flare-ups with new HO (the primary endpoint in 201 and 202A/B), volume of new HO (cm³), and new HO status/volume by baseline edema status. Other flare-up endpoints at Week 12 included range of motion at the flare-up site by goniometry; Global Assessment of Movement; local pain and swelling by NRS or FPS-R (<8 y/o); physical function (FOP-PFQ); and general health (PROMIS Global Health Scale or PROMIS Pediatric Global Health Scale).

Chronic/Flare-up Dosing Outcomes

Whole-body (excluding head) CT scan was performed prior to the initiation of chronic dosing in Study 202 Part B (Adult Cohort) or Part C (Pediatric Cohort) to assess baseline whole-body HO, and then repeated annually during chronic/flare-up treatment. The ISE did not pool these data with Study 301 HO data based on the following rationale: most of the Study 202B/C subjects (36/54) were originally enrolled in Study 201 to treat an acute flare-up, and therefore may not be comparable to subjects in Study 301 and the NHS, who enrolled during relative disease quiescence (defined as no symptoms within 4 weeks). In addition, qualifying criteria for treatment of flare-ups in Study 202B were more restrictive than in Studies 202C and 301; therefore, many subjects continued only chronic (5 mg) dosing during symptomatic episodes that would have been treated with flare-up (20/10 mg) dosing in the later studies.

Whole-body CT scans from Study 202 B/C were read by the same imaging contractor as in Study 301 and the NHS, with some differences in methodology. Study 202 B/C scans were read by a single radiologist, without concurrent comparison to any control group. Baseline WBCT for each subject at the initiation of chronic dosing was evaluated for presence, severity

(mild/moderate/severe) and volume of HO in each body region (using 15 rather than 9 regions). Postbaseline scans were evaluated for change from prior scan(s), and HO volume was remeasured if a change was apparent. It does not appear that there was any systematic evaluation of intrareader agreement, such as the random rereads conducted in Study 301/NHS.

The primary endpoint of Study 202B (protocol amendment 3), similar to Studies 201 and 202A, was the absence of new HO at flare-up sites. Secondary endpoints of 202B with respect to nonflare-up based treatment were the change from Part B baseline in whole-body HO at months 12 and 24; change in CAJIS scores; and number of flare-ups per subject-month.

Since the implementation of Part C (protocol amendment 4), the primary efficacy endpoint of Study 202 has been the annualized change in new whole-body (less head) HO volume, with comparison of the annualized change in Parts B and C to data collected from the NHS. Secondary endpoints in Part C include percent of subjects with new HO at months 12, 24, 36 and overall; and changes in CAJIS, FOP-PFQ, and PROMIS Global Health Scale.

6.2.2.4. Results of Analyses

Study 201: Flare-up Outcomes

In this randomized, placebo-controlled study, there were 40 patients with FOP with an acute flare-up who met eligibility criteria and were enrolled at one of four centers: UPenn (n=15), UCSF (n=14), one center in France (n=9) and one in UK (n=2). Among these were eight patients who enrolled initially in the NHS and subsequently transferred into Study 201 at the onset of a qualifying flare-up event. There were four other patients who failed Study 201 screening and were not enrolled or randomized; one of these patients enrolled in the NHS 17 months later.

All 40 enrolled subjects completed Study 201 and are included in the Full Analysis Set (FAS) population. One subject (# (b) (6)) in the 10/5 dosing arm was <80% compliant with study medication; the other 39 subjects constitute the Per-Protocol (PP) population.

Demographics for the 40 randomized patients in Study 201 are summarized in Table 16.

Table 16. Study 201: Demographics (FAS)

Characteristic	Placebo (N=10)	PVO 5/2.5 mg (N=9)	PVO 10/5 mg (N=21)
Sex, n (%)			
Male	3 (30%)	3 (33%)	12 (57%)
Female	7 (70%)	6 (67%)	9 (43%)
Age, years			
Mean (SD)	21.2 (13.7)	17.9 (8.6)	22.8 (10.3)
Median (min, max)	16 (9, 53)	21 (7, 29)	21 (9, 44)
Race, n (%)			
White	6 (60%)	7 (78%)	12 (57%)
Asian	1 (10%)	0	0
Black/African American	0	1 (11%)	1 (5%)
Multiple	0	1 (11%)	2 (10%)
Not available	3 (30%)	0	6 (29%)

Characteristic	Placebo (N=10)	PVO 5/2.5 mg (N=9)	PVO 10/5 mg (N=21)
Ethnicity, n (%)			
Hispanic	1 (10%)	1 (11%)	2 (10%)
Non-Hispanic	6 (60%)	8 (89%)	13 (62%)
Not available	3 (30%)	0	6 (29%)

Source: 201 CSR Table 10

Abbreviations: FAS, full analysis set; N, number of subjects; n, percentage of subjects with given characteristics; PVO, palovarotene; SD, standard deviation

The treatment groups were generally similar with respect to the subjects' FOP history and disease characteristics, including the number and location of regions with HO present by physical exam at baseline. The mean number of flare-ups per year reported at baseline was somewhat higher in the 10/5 group (4.6) than in the placebo group (2.3) or the 5/2.5 group (2.0).

Clinical characteristics of the flare-up events treated in Study 201 are summarized in Table 17. Flare-ups of the hip, knee, and shoulder, which may be associated with large volumes of new HO, accounted for most of the qualifying flare-ups in each treatment group. All subjects had at least 2 symptoms at baseline (per protocol) and the average number was four to five symptoms, the most common being pain, swelling and stiffness.

Table 17. Study 201: Flare-up Characteristics (FAS)

Flare-up Characteristic	Placebo N=10	PVO 5/2.5 mg N=9	PVO 10/5 mg N=21
Primary location, n (%)			
Hip	5 (50%)	2 (22%)	9 (43%)
Knee	2 (20%)	3 (33%)	4 (19%)
Shoulder	0	3 (33%)	1 (5%)
Elbow	1 (10%)	0	3 (14%)
Abdomen/chest	1 (10%)	1 (11%)	1 (5%)
Distal extremities	1 (10%)	0	3 (14%)
Subject-reported symptoms, n (%)			
Pain	8 (80%)	9 (100%)	21 (100%)
Stiffness	6 (60%)	6 (67%)	18 (86%)
Soft tissue swelling	8 (80%)	6 (67%)	14 (67%)
Decreased ROM	6 (60%)	6 (67%)	13 (62%)
Warmth	3 (30%)	5 (56%)	13 (62%)
Redness	3 (30%)	4 (44%)	5 (24%)
Baseline flare-up pain (NRS or FPS-R)*			
Mean	4.6	3.1	4.8
Min, max	0, 10	0, 9	1, 10
Number of flare-up symptoms			
Mean	4.1	5.1	4.5
Min, max	2, 7	2, 8	2, 8

Source: 201 CSR Table 14

*Pain scores are based on numeric rating scale (NRS) or, for children <8 years of age, the Faces Pain Scale-Revised (FPS-R); each scale is from 0 (no pain) to 10 (worst pain, or very much pain)

Abbreviations: FAS, full analysis set; FPS-R, Faces Pain Scale-Revised; N, number of subjects; n, number of subjects with given characteristics; NRS, numeric rating scale; PVO, palovarotene; ROM, range of motion; SD, standard deviation

In the overall study, 15% of subjects attributed their flare-up to blunt muscle trauma and 8% cited muscle fatigue, while in most cases the cause was considered unknown. The mean time from onset of flare-up symptoms to first dose was 5.8 days; treatment was begun within 7 days in all cases except one subject in the 10/5 group who began treatment on day 8. Glucocorticoids were used to treat the flare-up in 78 to 95% of subjects. HO was present at the flare-up site at baseline by CT in 61% of cases.

Primary Endpoint: Incidence of New HO at Flare-up Sites

In Study 201, when compared to baseline, standard radiographs of the flare-up site at week 6 showed more than minimal new HO (grade >3 on 0 to 6 scale) in only two subjects (one each in placebo and palovarotene 5/2.5 mg groups, none in 10/5 mg group) out of the total of 40 subjects. Therefore, 89%, 89% and 100% of subjects in these respective groups were classified as “responders,” yet because there was no difference between groups, the study did not demonstrate efficacy based on the prespecified primary endpoint. At Week 12, standard radiographs showed more than minimal new HO in 4/40 subjects compared to baseline (n=2, 1 and 1 subjects in the placebo, 5/2.5 and 10/5 groups, respectively). CT was more sensitive than radiographs, showing new HO in these four subjects and six additional subjects at Week 12.

The primary read data at Week 12 in Table 18 indicate a numerically higher incidence of new HO (by either radiograph or CT, or both) in placebo subjects (40%) compared to the two palovarotene groups (incidence 20 to 24%). However, one of the placebo subjects (# (b) (6)) with new HO exhibited only a small area of grade 3 (“minimal”) new HO by radiograph, and none by CT, and thereby met the protocol definition of “responder.” Therefore, only 3/10 (30%) of placebo recipients were “nonresponders” because the minimal HO by radiograph in subject # (b) (6) was considered to likely represent artifact.

The Global Read process also gave a numerically higher incidence of new HO at Week 12 in the placebo group compared to the 10/5 group (40% versus 19% in FAS). Subject # (b) (6) (placebo group) and one subject in the 10/5 group were considered to have new HO by primary read, but no new HO by Global Read. Three other subjects (one in placebo group, two in 5/2.5 group) were considered to have no new HO by primary read, but new HO by Global Read (Table 18).

Table 18. Study 201: Incidence of New HO at Flare-up Location, by CT or Radiograph at Week 12

	Placebo (N=10)	PVO 5/2.5 mg (N=9)	PVO 10/5 mg (N=21)
Primary read: new HO at Week 12 (FAS)	4/10 (40%)	2/9 (22%)	5/21 (24%)
Primary read: new HO at Week 12 (PP*)	4/10 (40%)	2/9 (22%)	4/20 (20%)
Primary read: nonresponder at Week 12 (FAS)	3/10 (30%)	2/9 (22%)	5/21 (24%)
Primary read: nonresponder at Week 12 (PP*)	3/10 (30%)	2/9 (22%)	4/20 (20%)
Global read: new HO at Week 12 (FAS)	4/10 (40%)	4/9 (44%)	4/21 (19%)
Global read: new HO at Week 12 (PP*)	4/10 (40%)	4/9 (44%)	3/20 (15%)

Source: CSR Tables 14.2.2.22, 14.2.2.22a, 14.2.2.33, 14.2.2.34; Listings 16.2.6.2.3 and 16.2.6.3.3

*PP = Per-protocol excludes one subject (# (b) (6)) in the PVO 10/5 group who developed new HO at Week 12 (volume 15.9 cm³) but who was only 60% compliant with study medication (≥80% was required for per-protocol)

FAS = Full Analysis Set = all randomized subjects

Abbreviations: CT, computed tomography; FAS, full analysis set; HO, heterotopic ossification; N, number of subjects; PP, per protocol; PVO, palovarotene

Study 201 Secondary Endpoints: Volume of New HO at Flare-up Sites

In Study 201, about half of subjects had HO present at baseline at the flare-up site by CT (Table 19). At Week 12, the mean volume of new HO in the placebo group (averaged across all subjects, including those with new HO volume =0) was 16.2 cm³, which was numerically higher than in the two palovarotene groups. This was mainly attributable to one placebo recipient (subject # (b) (6)) with a left hip flare-up that resulted in a large volume of new HO at Week 12 (131.7 cm³). The other flare-ups resulting in new HO >10 cm³ also involved the hip: a placebo subject with new hip HO of 29.5 cm³; and three subjects in the palovarotene 10/5 group with new hip HO of 48.4 cm³, 15.9 cm³ and 11.1 cm³, respectively. The lower mean volume of new HO in the palovarotene 5/2.5 group (and lack of dose-response overall) may be in part related to the lack of flare-ups at the hip with new HO in this 5/2.5 group, and lower proportion of hip flare-ups overall in this group (22%, versus 43% and 50% in the other groups).

Table 19. Study 201: Volume of New HO at Flare-up Location by CT

	Placebo (N=10)	PVO 5/2.5 mg (N=9)	PVO 10/5 mg (N=21)
Baseline, n	9	8	19
Subjects with baseline HO at flare-up site, n	4	5	12
Baseline volume at flare-up site, mean (SD), cm ³	21.9 (44.2)	17.0 (20.8)	27.7 (58.3)
Week 12, n (FAS)	10	9	18*
Subjects with new HO, n	3	2	5
New HO volume, mean (SD), cm ³	16.2 (41.6)	1.2 (3.2)	4.5 (11.8)
Min, max, cm ³	0, 131.7	0, 9.6	0, 48.4
Week 12, n (PP*)	10	9	17*
Subjects with new HO, n	3	2	4
New HO volume, mean (SD), cm ³	16.2 (41.6)	1.2 (3.2)	3.9 (11.9)
Min, max, cm ³	0, 131.7	0, 9.6	0, 48.4

Source: 201 CSR Tables 14.2.2.4.1, 14.2.2.4.4

FAS = Full Analysis Set = all randomized subjects

*PP = Per-protocol excludes one subject (# (b) (6)) in PVO 10/5 group who developed new HO at Week 12 (volume 15.9 cm³) but who was only 60% compliant with study medication (≥80% was required for per-protocol)

*Does not include three subjects in the 10/5 group (# (b) (6)) with no CT data at Week 12 (not performed, or data not evaluable)

Abbreviations: CT, computed tomography; FAS, full analysis set; HO, heterotopic ossification; N, number of subjects; n, number of subjects with specific HO; PP, per protocol; PVO, palovarotene; SD, standard deviation

Other Study 201 Secondary Endpoints

Among eight subjects with no edema at the flare-up site at baseline by MRI, none developed new HO at Week 12. Among 20 subjects with baseline edema, nine developed new HO, including 3/6 in the placebo group, 4/6 in the 5/2.5 mg group and 2/8 in the 10/5 mg group.

Among subjects who maintained diary entries, the mean number of days to resolution of flare-up symptoms was 64, 46 and 36 days for the placebo, 5/2.5, and 10/5 groups, respectively.

Flare-up pain, as assessed by the NRS (or FPS-R for age <8 years), tended to decline from baseline to Week 12 in each group. Mean changes were -2.2, -1.9 and -3.6 in the placebo, 5/2.5 and 10/5 groups, respectively. The mean changes in NRS score for flare-up swelling were -2.3, -2.5 and -2.1 in these groups.

The range of motion at the joint nearest the flare-up site, as measured by goniometry, showed minimal changes from baseline to Week 12; mean percent change was -2.3, -4.2 and +0.6 in the

placebo, 5/2.5 and 10/5 groups, respectively. There were no significant differences between subjects with or without new HO, regardless of treatment group.

Patient reported scores for physical function (FOP-PFQ) and global health (PROMIS Global Physical and Global Mental Health scales) showed small changes which were not significantly different between treatment groups.

Flare-up Site Outcomes Across Studies (201, 202A/B, NHS)

All 40 subjects enrolled in Study 201 completed the 12-week study and enrolled in the initial Part A of the extension study (Study 202A). During Study 202A (mean duration of participation =11.3 months), 20/40 subjects did not experience a qualifying flare-up and received no treatment, while the other 20 subjects underwent evaluation and treatment (with 10/5 regimen) of a total of 28 new flare-ups. Subjects who had received the 10/5 regimen in Study 201 were more likely to have another flare-up treated in Study 202A (14/21 subjects, 67%), compared to subjects who had received the 5/2.5 regimen (3/9 subjects, 33%) or placebo (3/10 subjects, 30%).

When the Study 202 Part B protocol was implemented with revised treatment regimens, 36/40 subjects from Part A enrolled and 18 new subjects (including 13 from the NHS) entered the study, for a total of 54 subjects. During Study 202B (mean duration of participation =19 months), 33 of these subjects were treated and evaluated for a total of 52 new qualifying flare-ups. Among 10 subjects who withdrew from either Part A (n=4) or Part B (n=6), none were attributed to adverse effects (Table 20).

Table 20. Studies 201, 202 Parts A/B: Disposition

Treatment Group	Flare-up Placebo	Flare-up PVO 5/2.5 mg	Flare- up PVO 10/5 mg	Flare-up PVO 20/10 mg	Chronic + Flare-up PVO 20/10	Chronic PVO 5 mg	Untreated	Total
Enrolled/treated in study 201, n	10	9	21	-	-	-	-	40
Completed 201 and enrolled in 202A, n	10	9	21	-	-	-	-	40
Treatment in 202A, n	-	-	20	-	-	-	20	40
Withdrew from part A, n*	-	-	1	-	-	-	3	4
Enrolled in 202B, n	-	-	19	-	-	-	17	36
New subjects added in 202B, n	-	-	-	-	-	-	-	18
Treatment in 202B, n**	-	-	-	12	25	44	2	54
Withdrew from part B, n*	-	-	-	1	2	4	1	6
Duration of participation in part B, months (mean)	-	-	-	19	20	19	13	19

Sources: CSRs study 201 Table 7; study 202 Tables 18,19

*Withdrawals from 202A and B were due to physician decision, noncompliance, withdrew consent and miscellaneous

**Two subjects attained skeletal maturity during Part B and received both 20/10-only and chronic + flare-up 20/10 treatment

Abbreviations: n, number of subjects; PVO, palovarotene

Across these phase 2 studies and the NHS, a total of 160 flare-ups with imaging data at baseline and Week 12 comprised the IF-FAS. These events were pooled by treatment group as follows:

- Placebo/untreated (total N=42 subjects, M =50 flare-ups): 10 flare-ups treated with placebo in Study 201, combined with 40 untreated flare-ups in the NHS
- Palovarotene 5/2.5 mg (N=9, M =9): 9 flare-ups treated with 5/2.5 regimen in Study 201
- Palovarotene 10/5 mg (N=27, M =49): 21 flare-ups in Study 201, and 28 flare-ups in Study 202A, treated with 10/5 regimen
- Palovarotene 20/10 mg (N=12, M =18): 18 flare-ups in Study 202B treated with 20/10 flare-up-only regimen (no prior chronic dosing) in skeletally immature subjects
- Palovarotene chronic/flare-up 20/10 (N=23, M =34): 34 flare-ups in Study 202B treated with 20/10 mg regimen (with prior chronic 5 mg dosing) in skeletally mature subjects

Because treatment compliance was <80% in only 2/160 flare-ups, the ISE presents analyses of the IF-FAS (all imaged flare-ups), without analyses of a “per-protocol” population. The maximum number of imaged flare-ups in any individual subject/treatment group was 4. In addition to the flare-ups imaged in Study 202B (18 without prior chronic dosing, 34 with prior chronic dosing), there were 14 others (5 without/9 with chronic dosing) that were treated but not imaged; in most cases this was related to the pending transition to Study 202C in which flare-up site imaging was not conducted.

Demographic data for the groups contributing these data are presented in Table 21. As expected, the group receiving only 20/10 mg flare-up dosing was younger (mean age 13.6 years) than the other treated groups (mean 18 to 25 years). Untreated/imaged subjects in the NHS were also somewhat younger (mean 16.7 years) and had a higher proportion of males (56%) than the other groups. Demographic data for the F-FAS, i.e., including subjects with flare-ups that were not imaged (mostly in the NHS), were similar to the IF-FAS data.

Table 21. Demographics of Phase 2 and NHS Subjects Treated With Flare-up Dosing (IF-FAS)

Characteristic	NHS (N=32)	Placebo (N=10)	PVO 5/2.5 mg (N=9)	PVO 10/5 mg (N=27)	Flare-up	
					PVO 20/10 mg (N=12)	Chronic/flare- up 20/10 mg (N=23)
Sex, n (%)						
Male	18 (56%)	3 (30%)	3 (33%)	14 (52%)	4 (33%)	8 (35%)
Female	14 (44%)	7 (70%)	6 (67%)	13 (48%)	8 (67%)	15 (65%)
Age, years						
Mean (SD)	16.7 (9.2)	21.2 (13.7)	17.9 (8.7)	23.3 (9.5)	13.6 (7.3)	25.0 (8.4)
Median (min, max)	15 (4, 39)	16 (9, 53)	21 (7, 29)	22 (9, 44)	11 (7, 34)	25 (12, 46)
Race, n (%)						
White	25 (78%)	6 (60%)	7 (78%)	17 (63%)	6 (50%)	18 (78%)
Asian	2 (6%)	1 (10%)	0	0	1 (8%)	0
Black/African American	0	0	1 (11%)	1 (4%)	0	0
Other or not available	5 (16%)	3 (30%)	1 (11%)	9 (33%)	5 (42%)	5 (22%)

Characteristic	NHS (N=32)	Placebo (N=10)	PVO 5/2.5 mg (N=9)	PVO 10/5 mg (N=27)	Flare-up	Chronic/flare- up 20/10 mg (N=23)
					PVO 20/10 mg (N=12)	
Ethnicity, n (%)						
Hispanic	8 (25%)	1 (10%)	1 (11%)	2 (7%)	2 (17%)	0
Non-Hispanic	23 (72%)	6 (60%)	8 (89%)	18 (67%)	6 (50%)	20 (87%)
Not available	1 (3%)	3 (30%)	0	7 (26%)	4 (33%)	3 (13%)

Source: ISE Tables 75, 76

Abbreviations: IF-FAS, Imaged Flare-up Full Analysis Set; N, number of subjects in treatment group; n, number of subjects with given characteristic; PVO, palovarotene; SD, standard deviation

FOP history (e.g., age at diagnosis, associated findings such as great toe, thumb or cervical spine malformations) of subjects with evaluated flare-ups in the IF-FAS are summarized in [ISE Tables 77 and 78](#) (not shown). The mean time since the subject's last previous flare-up was shorter in the 20/10 mg flare-up-only group (4.9 months) and Study 201 placebo group (5.5 months) relative to the other treatment groups (11.0 to 18.7 months).

Clinical features of the 160 flare-ups evaluated in the IF-FAS are summarized by treatment group in Table 22. The most common flare-up locations were hip (21 to 33% of events) and knee (18 to 33%). The combined proportion of flare-ups involving one of the locations where large quantities of HO tend to form (hip, knee, and shoulder) was slightly lower for the placebo/untreated group (54%) compared to the various palovarotene groups (62 to 89%). The mean number of symptoms per subject was four to five in each group; the most common symptoms were pain, stiffness and swelling.

Table 22. Flare-up Characteristics, by Pooled Treatment Groups (IF-FAS)

Flare-up Characteristics	Placebo/ untreated M =50	PVO 5/2.5 mg M =9	PVO 10/5 mg M =49	PVO Flare-up 20/10 mg M =18	PVO Chronic/ Flare-up 20/10 mg M =34
Primary location, m (%)					
Hip	11 (22%)	2 (22%)	14 (29%)	6 (33%)	7 (21%)
Knee	10 (20%)	3 (33%)	14 (29%)	6 (33%)	6 (18%)
Shoulder	6 (12%)	3 (33%)	3 (6%)	3 (17%)	8 (24%)
Elbow	3 (6%)	0	6 (12%)	0	2 (6%)
Lower spine/abdomen	6 (12%)	0	2 (4%)	1 (6%)	4 (12%)
Distal extremities	6 (12%)	0	6 (12%)	2 (11%)	3 (9%)
Upper spine/chest	2 (4%)	1 (11%)	0	0	1 (3%)
Subject-reported symptoms, m (%)					
Pain	45 (90%)	9 (100%)	34 (69%)	18 (100%)	32 (94%)
Stiffness	22 (44%)	6 (67%)	27 (55%)	12 (67%)	18 (53%)
Soft tissue swelling	38 (76%)	6 (67%)	26 (53%)	12 (67%)	26 (77%)
Decreased ROM	25 (50%)	6 (67%)	19 (39%)	8 (44%)	12 (35%)
Warmth	17 (34%)	5 (56%)	18 (37%)	10 (56%)	20 (59%)
Redness	12 (24%)	4 (44%)	9 (18%)	5 (28%)	11 (32%)

Flare-up Characteristics	Placebo/ untreated M =50	PVO 5/2.5 mg M =9	PVO 10/5 mg M =49	PVO Flare-up 20/10 mg M =18	PVO Chronic/ Flare-up 20/10 mg M =34
Baseline flare-up pain score (NRS or FPS-R)*					
Mean	3.7	3.3	4.3	3.6	3.2
Min, max	0, 10	0, 9	0, 10	0, 7	0, 8
Number of flare-up symptoms					
Mean	3.9	5.1	4.0	4.5	4.0
Min, max	1, 8	2, 8	2, 8	2, 9	2, 8

Source: ISE Tables 80 and 93

Data are by flare-up episodes and not by subject. PVO = palovarotene

*Pain scores are based on numeric rating scale (NRS) or, for children <8 years of age, the Faces Pain Scale-Revised (FPS-R); each scale is from 0 (no pain) to 10 (worst pain, or very much pain)

Abbreviations: IF-FAS, Imaged Flare-up Full Analysis Set; M, number of flare-ups in treatment group; m, number of flare-ups with given characteristic, PVO, palovarotene; ROM, range of motion; SD, standard deviation

The use of glucocorticoids to treat the flare-up was similar among the treatment groups (78 to 90%). In the flare-up-only 20/10 and chronic/flare-up 20/10 treatment groups, palovarotene doses were reduced based on tolerability in 23% of subjects at the higher flare-up dose of 20 mg, and in 11% of subjects at the lower flare-up dose of 10 mg, and three subjects (9%) discontinued the drug during flare-up dosing. (Note that all doses were reduced by weight in skeletally immature subjects, prior to any reductions based on tolerability.) In the 10/5 mg and 5/2.5 mg groups, no subjects required dose reduction or discontinuation related to tolerability.

Flare-ups in the NHS that are included in the IF-FAS (m =40) represent only a small fraction of all reported NHS flare-ups (m =228 in the F-FAS). Most of the other NHS events (m =174) were followed by Telephone Contact (TC) and were not imaged. Flare-ups of the upper back, which comprised 18% of this NHS TC group, were excluded from treatment by protocol from phase 2 studies and from the IF-FAS. Of the remaining flare-up locations, the most frequent among NHS TC flare-ups were hip (18%), lower spine/abdomen (13%), shoulder (13%), distal extremities (12%), upper spine/chest (9%) and knee (8%). The mean number of symptoms was slightly lower in the TC group compared to imaged (IF-FAS) NHS flare-ups (2.7 versus 3.9), and the proportion with only one symptom was higher (15% versus 5%).

Flare-ups Across Phase 2/NHS Studies: Incidence and Volume of New HO at Flare-up Sites

At Week 12, the ISE states that new HO had developed at the flare-up location in 13/40 (33%) NHS (untreated) flare-ups, and 4/10 (40%) placebo recipients in Study 201, or 17/50 (34%) overall for placebo plus untreated flare-ups. The mean volume of new HO (including all subjects, with or without new HO) was higher with placebo versus NHS (18.0 versus 9.1 cm³); this may be related to a greater proportion of hip flare-ups (50% versus 15%). The mean new HO volume was 10.8 cm³ for the combined placebo/untreated group.

Data for new HO at Week 12 in the 160 imaged (IF-FAS) flare-ups by pooled treatment group are summarized in Table 23. The proportion of palovarotene-treated subjects with new HO (21 to 41%) was in general not markedly different from placebo/untreated subjects (34%), but the mean volume of new HO was lower at each palovarotene dose level (1.2-5.6 cm³ treated, compared to 10.8 cm³ untreated), albeit with no apparent dose-response effect.

Table 23. New HO at Flare-up Location at Week 12, by Pooled Treatment Groups (IF-FAS)

Variable	Placebo/ untreated M =50	PVO 5/2.5 mg M =9	PVO 10/5 mg M =49	PVO Flare-up 20/10 mg M =18	PVO Chronic/ Flare-up 20/10 mg M =34
New HO present	17/50 (34%)	2/9 (22%)	15/49 (31%)	7/17 (41%)	7/34 (21%)
Volume of new HO at Week 12* (cm ³), m	47	9	47	15	33
Mean (SD)	10.8 (33.2)	1.2 (3.2)	3.0 (8.1)	3.0 (5.5)	5.6 (20.7)
Min, max	0, 137.0	0, 9.6	0, 48.4	0, 17.4	-7, 92.0

Source: ISE Table 14.1.11.2.1

HO data are by flare-up episode, not by subject.

HO status at Week 12 could not be determined in 1 flare-up (Flare-up 20/10 group) because of different anatomical coverage of baseline and postbaseline scans.

New HO volume at Week 12 could not be measured in 8 flare-up events.

*HO volume data includes all imaged flare-ups, with or without new HO

Abbreviations: HO, heterotopic ossification; IF-FAS, Imaged Flare-up Full Analysis Set; PVO, palovarotene; SD, standard deviation

Table 24 shows that hip flare-ups accounted for large mean volumes of new HO in the placebo/untreated and chronic/flare-up 20/10 treatment groups. Shoulder flare-ups also were associated with large HO volumes in the placebo/untreated group.

Table 24. New HO at Specific Flare-up Locations at Week 12 (IF-FAS)

Variable	Placebo/ untreated M =50	PVO 5/2.5 mg M =9	PVO 10/5 mg M =49	PVO Flare-up 20/10 mg M =18	PVO Chronic/ Flare-up 20/10 mg M =34
Hip					
New HO present	3/10	0/2	6/17	3/5	3/7
Volume of new HO at Week 12* (cm ³), mean	29.8	0.0	5.6	5.4	24.5
Knee					
New HO present	2/10	1/3	5/13	0/4	0/6
Volume of new HO at Week 12* (cm ³), mean	0.8	0.3	3.2	0.0	0.0
Shoulder					
New HO present	4/6	1/3	1/3	1/3	2/8
Volume of new HO at Week 12* (cm ³), mean	32.6	3.2	1.2	0.4	1.0

Source: ISE Tables 14.1.11.2.1.1, 14.1.11.2.1.2 and 14.1.11.2.1.3

Data for New HO present indicates number of flare-ups (m) with new HO out of all events with HO volume evaluable

*HO volume data includes all imaged flare-ups, with or without new HO

Data are by flare-up episodes and not by subject.

Abbreviations: HO, heterotopic ossification; IF-FAS, Imaged Flare-up Full Analysis Set; PVO, palovarotene

The following list of subjects with “catastrophic” large volumes of new HO (defined as >30 cm³ per flare-up event) at Week 12 shows that the IF-FAS data are largely driven by a few individuals with flare-ups mainly involving the hip, and to a lesser extent the shoulder (Table 25). Flare-ups of the knee appeared to be less consequential; the largest HO volume at a knee was 15.1 cm³ in a subject treated with the 10/5 regimen. However, it should be noted that the clinical impact of new HO is also dependent on factors other than HO volume, including the exact location of HO lesions around the adjacent joint.

Table 25. Subjects With Large Volume of New HO at Flare-up Site (IF-FAS)

Subject	Study	Treatment Group	Age Sex	Flare-up Site	Volume of new HO (cm ³)	
					Week 12	EOT
(b) (6)	NHS	Placebo/Untreated	16 F	Hip	137.0	129.3 (Week 19)
	201	Placebo/Untreated	14 F	Hip	131.7	
	202B	Chronic/Flare up 20/10	24 M	Hip	92.0	
	NHS	Placebo/Untreated	15 F	Shoulder	107.0	
	NHS	Placebo/Untreated	24 F	Shoulder	87.3	
	202B	Chronic/Flare up 20/10	17 M	Hip	78.3	
	201	10/5 mg	16 F	Hip	48.4	

Source: ISE, ADHO

Abbreviations: EOT, End of extended treatment cycle; F, female; HO, heterotopic ossification; IF-FAS, Imaged Flare-up Full Analysis Set; M, male; NHS, natural history study

Regarding the lack of dose-response in new HO, the Applicant notes that flare-ups treated with 20/10 mg (with or without prior chronic dosing) had a greater prevalence of baseline edema by MRI or ultrasound (69 to 73%), compared to flare-ups treated with 10/5 mg (49%) or 5/2.5 mg (56%) or placebo/untreated (62%). As shown in Table 26, flare-ups with baseline edema were more likely to result in new HO, within each treatment group.

Table 26. New HO at Flare-up Location at Week 12, by Baseline Edema Status (IF-FAS)

	Placebo/ untreated M =50	PVO 5/2.5 mg M =9	PVO 10/5 mg M =49	PVO Flare-up 20/10 mg M =18	PVO Chronic/ Flare-up 20/10 mg M =34
Baseline edema present	26/42 (62%)	5/9 (56%)	16/33 (49%)	11/15 (73%)	22/32 (69%)
New HO at Week 12, with baseline edema	11/27 (41%)	2/5 (40%)	10/16 (63%)	6/12 (50%)	6/23 (26%)
New HO at Week 12, without baseline edema	3/16 (19%)	0/4 (0%)	2/17 (12%)	0/3 (0%)	1/10 (10%)

Source: ISE Tables 80, 87

Data are by flare-up episodes and not by subject.

Abbreviations: HO, heterotopic ossification; IF-FAS, Imaged Flare-up Full Analysis Set; PVO, palovarotene

Flare-ups treated with 20/10 mg (with or without prior chronic dosing) also had a greater prevalence of baseline HO at the flare-up site (78 to 82%), compared to flare-ups treated with 10/5 mg, 5/2.5 mg or placebo/untreated (59 to 67%). Based on the data in [Table 27](#), it is unclear whether flare-up sites with pre-existing HO may be more likely to develop new HO, or whether the baseline imbalance may have impacted the outcomes.

Table 27. New HO at Flare-up Location at Week 12, by Baseline HO Status (IF-FAS)

	Placebo/ untreated M =50	PVO 5/2.5 mg M =9	PVO 10/5 mg M =49	PVO Flare- up 20/10 mg M =18	PVO Chronic/ Flare-up 20/10 mg M =34
Baseline HO present	29/49 (59%)	6/9 (67%)	32/49 (65%)	14/18 (78%)	27/33 (82%)
New HO at Week 12, with baseline HO	13/29 (45%)	0/6 (0%)	11/32 (34%)	6/13 (46%)	5/27 (19%)
New HO at Week 12, without baseline HO	4/20 (20%)	2/3 (67%)	4/17 (24%)	1/4 (25%)	1/6 (17%)

Source: ISE Tables 80, 87

Data are by flare-up episodes and not by subject.

Abbreviations: HO, heterotopic ossification; IF-FAS, Imaged Flare-up Full Analysis Set; PVO, palovarotene

Efficacy of Flare-up Dosing in “Target” Population (≥ 8 Years for Females/ ≥ 10 Years for Males)

Based on the safety issue of PPC and risk/benefit considerations (see Section 7.7.1), the Applicant seeks approval only for this “ $\geq 8F/\geq 10M$ ” population of FOP patients. Among the flare-ups evaluated in the NHS and phase 2 studies, only 10 occurred in younger subjects (i.e., <8 -year-old girls, <10 -year-old boys): four events in the NHS; and two, three, and one events, respectively, in the palovarotene 5/2.5, 10/5 and 20/10 flare-up groups. Because the majority of flare-ups (150 of total 160 IF-FAS events, 94%) occurred in this “target” population, the baseline data are similar to the overall F-FAS and IF-FAS except for slightly older mean ages, and the efficacy data are also similar (see ISE Table 14.2.11.2.1).

Efficacy of Flare-up Dosing by Age Group

Because of the variability of new HO volume data and small size of subgroups, evaluation of subgroups is challenging. Table 28 summarizes integrated flare-up HO volume data in two prespecified age subgroups. In the ≥ 12 - to <17 -year-old subgroup, mean volume of new HO in untreated flare-ups was high (mean 25.6 cm³), due in part to three events with new HO volume >100 cm³ at Week 12 (representing all such events in the overall IF-FAS); mean volume was substantially lower in each palovarotene treatment group. In adults (≥ 18 years), who contributed more than half of the overall flare-up data, the volume of new HO in untreated flare-ups was much lower (mean 4.5 cm³), therefore the relative reductions in palovarotene groups were smaller.

Table 28. New HO at Flare-up Location at Week 12 in Selected Age Subgroups (IF-FAS)

	Placebo/ Untreated	PVO 5/2.5 mg	PVO 10/5 mg	PVO Flare-up 20/10 mg	PVO Chronic/ Flare-up 20/10 mg
Age ≥ 12 to <17 years					
New HO present at Week 12	7/17 (41%)	0/0	5/8 (63%)	1/2 (50%)	1/5 (20%)
Mean volume of new HO*, cm ³	25.6	-	8.4	5.5	1.6
Age ≥ 18 years					
New HO present at Week 12	4/20 (20%)	1/5 (20%)	7/35 (20%)	0/4 (0%)	5/28 (18%)
Mean volume of new HO*, cm ³	4.5	1.9	1.7	0	3.7

Source: ISE Tables 14.6.11.2.1 and 14.8.11.2.1

HO data are by flare-up episode, not by subject.

*HO volume data includes all imaged flare-ups, with or without new HO

Abbreviations: HO, heterotopic ossification; IF-FAS, Imaged Flare-up Full Analysis Set; PVO, palovarotene

Efficacy of Flare-up Dosing by Sex

Among subjects with imaged flare-ups (IF-FAS), males and females were generally balanced with respect to demographic characteristics, prior FOP history, flare-up symptoms and distribution of flare-up locations. However, new HO data were strikingly different between the sexes. Mean volume of new HO at Week 12 was higher (20.2 cm³) in females with untreated flare-ups, due in large part to two hip flare-ups with new HO of 137.0 and 131.7 cm³ and two shoulder flare-ups with new HO of 107.0 and 87.3 cm³. Mean new HO volumes in palovarotene

treated females were much lower (0.3 to 3.5 cm³). In males, mean new HO volume was very low in untreated flare-ups (mean 0.1 cm³), and was also low with palovarotene treatment except for the chronic/flare-up 20/10 group (mean 19.8 cm³), which was influenced by two hip flare-ups with new HO of 92.0 and 78.3 cm³ (Table 29).

Table 29. New HO at Flare-up Location at Week 12 by Sex (IF-FAS)

	Placebo/ Untreated	PVO 5/2.5 mg	PVO 10/5 mg	PVO Flare-up 20/10 mg	PVO Chronic/ Flare- up 20/10 mg
Females					
New HO present at Week 12	9/25 (36%)	2/6 (33%)	7/22 (32%)	4/9 (44%)	4/25 (16%)
Mean volume of new HO*, cm ³	20.2	1.8	3.5	2.8	0.3
Males					
New HO present at Week 12	8/25 (32%)	0/3 (0%)	8/27 (30%)	3/8 (38%)	3/9 (33%)
Mean volume of new HO*, cm ³	0.1	0.0	2.5	3.2	19.8

Source: ISE Table 14.1.11.2.3

HO data are by flare-up episode, not by subject.

*HO volume data includes all imaged flare-ups, with or without new HO

Abbreviations: HO, heterotopic ossification; IF-FAS, Imaged Flare-up Full Analysis Set; PVO, palovarotene

Efficacy of Flare-up Dosing by Race

Most subjects with IF-FAS flare-up data were White. The remainder were described by race as Asian (n=2), Black or African American (n=2), “multiple” (n=4), “other” (n=1), and “not available” (n=9). The latter nine subjects were enrolled in France where regulations prohibit collection of race data (at least some of these subjects were probably White). In the ISE, all these groups not designated as White were pooled for analysis and the data were widely variable. Therefore, the evidence does not support any conclusions regarding flare-up efficacy in non-White groups.

Other Flare-up-Based Endpoints

Flare-up pain by NRS was assessed in all FOP studies, though it should be noted that subjects were unblinded to treatment except in Study 201. Mean pain scores ranged from 3.2 to 4.3 (on 0 to 10 scale) among the various treatment groups at baseline and declined in each group with mean changes at Week 12 ranging from -1.9 to -3.0. NRS scores for flare-up swelling also declined over 12 weeks, with similar changes between treatment groups. There were no consistent trends of change in range of motion at the joint nearest the flare-up site or in FOP-PFQ scores.

A variety of biomarkers were assessed during flare-ups, including markers of bone formation (P1NP, BSAP, osteocalcin) and bone resorption (CTX); angiogenesis (FGF); and inflammation/muscle degeneration (ESR, IL-6, TNF, LDH, CRP, IL-1 beta, CPK). No notable changes were seen in any of these markers through flare-up Week 12.

Summary of Efficacy of Flare-up Dosing with Respect to the Flare-up Site

A total of 160 flare-ups were evaluated across studies, including 110 events treated with palovarotene in Studies 201 and 202A/B, 10 events treated with placebo in Study 201 and 40 events untreated in the NHS. There was no evidence that the incidence of new HO at the flare-up site (the prespecified primary endpoint in Study 201) was reduced by palovarotene treatment. There were trends of reduced volume of new HO at the flare-up site with each regimen (5/2.5 mg, 10/5 mg, 20/10 mg) compared to untreated flare-ups. However, this finding is not conclusive because of several factors, including insufficient quantity of placebo-controlled data in Study 201; lack of control and randomization in Study 202; differences in design and population across studies; and lack of positive dose response across treatment regimens.

Among secondary and other clinical endpoints (not based on HO assessments) in these studies, there was no clear evidence of improved outcomes in treated versus untreated flare-ups. In the randomized, blinded Study 201, subjects receiving the 10/5 mg regimen exhibited trends of greater reduction in flare-up pain severity and improved ROM at the flare-up site, compared to 5/2.5 mg and placebo. However, the differences were not statistically significant and appear unlikely to be clinically meaningful.

Non-Flare-up-Based Outcomes of Chronic/Flare-up Dosing (Studies 202B/C)

There were 48 phase two subjects who received the chronic/flare-up treatment regimen and who participated in Study 202 Parts B and/or C for a mean of 19 and 20 months, respectively, prior to the February 28, 2020, cutoff date (Table 30). Like Study 301, Study 202C has been on partial clinical hold since December 2019 for treatment of pediatric subjects <14 years old due to risk of PPC, and treatment was paused in older subjects in January 2020; restart data will be available on some of these subjects at a later date (see Section [6.2.1.4](#)).

Table 30. Study 202 Part B/C: Disposition

Treatment Group	Flare-up PVO	Chronic + Flare-up PVO	Chronic PVO	PVO Total	Untreated
	20/10 mg	20/10 mg	5 mg		
Enrolled in 202B*, n	12	25	44	54	2
Withdrew from Part B, n	1	2	4	6	1
Duration of participation in Part B in months, mean	19	20	19	19	13
Enrolled in Part C, n	-	36	43	46	2
Withdrew from Part C, n	-	5	7	7	0
Adverse event, n	-	1	2	2	0
Noncompliance, n	-	0	1	1	0
Other, n	-	4	4	4	0
Duration of participation in Part C in months, mean	-	21	19	20	22

Source: Study 202 CSR Tables 19, 20

*Two subjects attained skeletal maturity during Part B and received both 20/10-only and chronic 20/10 treatment. Subjects who received chronic 5 mg treatment are also included in chronic 20/10 and PVO total columns.

Abbreviations: PVO, palovarotene

Demographics of Study 202B/C subjects were similar to subjects in Study 301 and the NHS, except that age was somewhat older (mean age 20.3 years, versus 15.1 and 17.5, respectively, at enrollment), based on the differences in study design. The median duration of dosing as of the cutoff date was 100.2 weeks (Table 31).

Table 31. Study 202 Part B/C: Demographics (FAS)

Demographic	Study 202 Part B/C (N=48)
Age (years)	
Mean (SD)	20.3 (8.0)
Median (min, max)	19 (7, 46)
Sex, n (%)	
Female	25 (52%)
Male	23 (48%)
Race, n (%)	
White	36 (75%)
Asian	1 (2%)
Other/multiple	14 (29%)
Not available	9 (19%)
Ethnicity, n (%)	
Hispanic	4 (8%)
Not Hispanic	35 (73%)
Not available	9 (19%)

Source: ISE Table 60

Abbreviations: FAS, full analysis set; N, number of subjects, n, number of subjects within specific demographic; SD, standard deviation

Study 202B/C: Whole-Body HO results With Chronic/Flare-up Dosing

Whole-body CT was conducted to assess baseline whole-body HO at the initiation of chronic palovarotene dosing, which occurred either in 202 Part B (Adult Cohort) or in Part C (Pediatric Cohort). The Adult Cohort subjects followed the Part B protocol through the first postbaseline whole-body CT at Month 12 (n=36) and then transitioned to the Part C protocol prior to the Month 24 and 36 WBCT scans, except for one subject who remained in Part B through Month 24. Compared to Part C, flare-up dosing was used less extensively in Part B (18% versus 32% of total number of days dosed) because of the more restrictive qualifying criteria for flare-up treatment, including requirement for $\geq$ two symptoms and lack of treatment of intercurrent flare-ups.

As indicated above, the primary endpoint of Study 202, as per protocol amendment 4 (initiation of Part C), was the annualized change in whole-body HO volume in Parts B and C, as compared to the NHS; and secondary endpoints included percent of subjects with new HO at months 12, 24, 36 and overall. The NDA did not include these analyses with the rationale that 202C was ongoing as of the February 28, 2020, efficacy cut-off date.

In lieu of these analyses, the ISE only reported WBCT new HO data for the overall Study 202B/C FAS (N=48), and for the following three subgroups based on clinical review of flare-up symptoms and treatments received (including palovarotene and corticosteroids) in Part B:

- All treated flare-ups (n=9): subjects with all reported flare-ups and flare-up symptoms treated

- Untreated/undertreated flare-ups (n=30): subjects with at least one event in Part B with symptoms consistent with a flare-up that did not meet the criteria to initiate flare-up dosing (reported as adverse event (AE) of “condition aggravated”)
- No flare-ups or flare-up symptoms (n=9)

Annualized new whole-body HO volumes for these subgroups are listed in Table 32. There were large increases in new HO (mean 33.5 cm³/year) in the second subgroup, which the Applicant attributes to undertreatment of flare-up symptoms per the Part B protocol. The subgroup of nine subjects with no flare-up symptoms also experienced a substantial increase in HO (mean 25.6 cm³/year) despite receiving continuous palovarotene 5 mg.

Table 32. Study 202B/C: WBCT Annualized New HO Volume (cm³/Year) (FAS)

Statistic	All Treated Flare-ups N=9	Untreated/ undertreated Flare-ups N=30	No Flare-ups N=9	Overall Combined N=48
Mean (SD)	-3.0 (24.0)	33.5 (63.0)	25.6 (42.5)	25.1 (55.2)
Median	-0.8	5.7	5.0	3.1
Min, max	-54.3, 40.0	-32.0, 236.0	-8.4, 112.7	-54.3, 236.0

Source: ISE Table 14.1.26.1

Abbreviations: FAS, full analysis set; HO, heterotopic ossification; SD, standard deviation; WBCT, whole-body computed tomography

Because of the difference in criteria for flare-up dosing between Parts B and C, Table 33 summarizes new HO volume accrued during each part separately, based on each subject's first and last WBCT scans within that part. As shown, mean annual new HO volume declined slightly in Part C compared to Part B, but remained at high levels in comparison to palovarotene-treated subjects in Study 301.

Table 33. Study 202B/C: WBCT Annualized New HO Volume (cm³/Year) for Parts B/C (FAS)

Statistic	Part B N=37	Part C N=32
Mean (SD)	28.0 (82.4)	24.3 (63.3)
Median	0	7.0
Min, max	-51.2, 349.7	-103.2, 227.5

Source: IR ISE Supplemental Table 2 and Response to IR, submitted on 07/20/21

Data are based on each subject's baseline and last WBCT scans within each part of study 202. For Part C, this could be the subject's first WBCT scan (for skeletally immature subjects, who began chronic/flare up treatment in Part C).

Abbreviations: FAS, full analysis set; HO, heterotopic ossification; SD, standard deviation; WBCT, whole-body computed tomography

Subjects who had previously participated in Studies 201/202A tended to develop larger volumes of new whole-body HO in 202B/C compared to new subjects who entered the study in Part B (mean new HO of 121.3 versus 57.8 cm³ at Week 36, in 16 and 13 subjects, respectively). It should be noted that the latter group began chronic treatment in Part B following at least 4 weeks without flare-up symptoms (per protocol); this was not necessarily the case for subjects transitioning from Studies 201/202A. Potentially, subjects with a recent flare-up could have had continued accrual of new HO at the site following the baseline WBCT and start of chronic treatment.

There were 13 subjects who transferred from the NHS to Study 202 Part B/C for chronic/flare-up treatment, including nine subjects with baseline and at least one post baseline WBCT scan in the NHS prior to transfer. In these nine subjects, mean annualized new HO in the NHS was 61.9 cm³ (range 0-338.4), which is high relative to the overall NHS. (Note that this differs from subjects who transferred from NHS to Study 301, in whom mean new WBHO during the NHS was lower than in subjects who remained in the NHS.) There were six subjects with WBHO data in the NHS and in 202 Parts B and C. As shown in Table 34, mean new HO for this group declined during Study 202, primarily due to two subjects with large volumes of new HO during the NHS.

Table 34. WBCT Annualized New HO volume (cm³/year) for Subjects Who Transferred From NHS to Study 202B/C*

Statistic	NHS	202 Part B	202 Part C
n	6	6	6
Mean (SD)	79.1 (136.1)	21.4 (40.4)	17.3 (24.1)
Min, max	0, 338.4	-21.2, 73.7	-3.2, 49.0

Source: Table 1 in Response to IR, submitted on 08/25/22
*Table represents only the six subjects who had at least one postbaseline WBCT scan in each study (NHS, 202B, 202C)
Abbreviations: HO, heterotopic ossification; NHS, natural history study; SD, standard deviation; WBCT, whole-body computed tomography

The lack of consistency of the Study 202B/C whole-body HO data as compared to Study 301, which followed a similar treatment protocol, is not easily explained and was not addressed by the Applicant in the NDA. Additional analyses of these data are needed, as discussed in Section [6.3.4](#).

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Phase 3: Appropriateness of Reliance on Post Hoc Analyses To Support Efficacy

Issue

Phase 3 study: appropriateness of reliance on post hoc analyses to support efficacy

Background

The prespecified primary analysis for the primary endpoint was based on a Bayesian compound Poisson model. Three early interim analyses and one final analysis were prespecified in the protocol of Study 301. The trial crossed the futility boundary at the second interim analysis and the study was paused for dosing. However, additional post hoc analyses, including the Bayesian compound model without square root transformation, found evidence of clinically meaningful benefit of palovarotene.

Therefore, the submission relies on post hoc analyses to support the efficacy of palovarotene.

Assessment

Post hoc analyses are generally considered to be hypotheses generating, as they may inflate type-I error and raise concerns for potential bias caused by selection of analyses toward an intended favorable outcome. However, in this specific context, we recognize that the prespecified primary analysis may not have been appropriate for analyzing the primary endpoint, making the results challenging to interpret. Acknowledging the limitations of the prespecified analyses, we think it is reasonable to consider whether alternative, more appropriate analyses may provide evidence of efficacy.

Assessment of the Impact of Square Root Transformation

The primary endpoint was annualized new HO. However, the rate of growth in HO volume was estimated based on the square root transformation of each incremental change in HO by region between scans. Since WBCT scans were not performed at the same interval in the two studies (scheduled every 6 months in study 301 and every 12 months in the NHS), the prespecified analysis involves summing the square root of each incremental change to compare the square root of the sum of each change, which is problematic as they are not equivalent. This could have resulted in a bias against palovarotene due to the differential schedule of new HO assessments between study 301 and the NHS, which thus might have contributed to the failure of the primary analysis.

Table 35 illustrates how more frequent assessment could lead to a bias against palovarotene under the prespecified Bayesian analysis using the square root transformation. Assuming a new HO volume of 200 occurs in a body region before Month 6 and subsequently the region grows 200 more in HO volume during Month 6 to Month 12, the annual new HO will be 400. With the prespecified statistical model, it will be counted as two events with growth rate of $\sqrt{200}$ per event under the square root transformation in study 301 and one event with growth rate of $\sqrt{400}$ in the NHS. Therefore, the estimated annual new HO will be $2 \times \sqrt{200} = 28.3$ in study 301 and $\sqrt{400} = 20$ in the NHS, respectively. This example illustrates that the prespecified approach may lead to a nonsensible difference in the estimated annualized new HO and a bias against more frequent assessment.

Table 35. An Illustrative Example of Impact of Square Root Transformation on Annualized New HO

					Estimated Annual New HO#
Study	Month 6 Change	Month 12 Change	From Month 6	Total Change	
301	200		200	400	$2 \times \sqrt{200} = 28.3$
NHS	Not assessed		400	400	$\sqrt{400} = 20$

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.
Abbreviations: HO, heterotopic ossification

FDA’s Assessment of Post Hoc Bayesian Analysis Without Square Root Transformation

The Applicant’s post hoc Bayesian analysis without square root transformation resulted in a high posterior probability in support of efficacy. We note that inference from the Bayesian model could be affected by different specification of prior distributions of the multiple parameters in the model and the results could differ if influential priors are specified. FDA’s analyses will focus on

frequentist methods that directly analyze the annualized new HO of each subject with minimal assumptions.

FDA's Assessment of Applicant's Post Hoc wLME Analyses

As noted in the previous section, the Applicant's post hoc wLME analysis, based on the CT scan associated with the longest follow-up and without square root transformation, achieved nominal statistical significance. However, results from the Applicant's wLME could be difficult to interpret as the annualized new HO for each subject was based on various length of follow-up. As most subjects had WBCT assessments on Month 12 (Table 10), we compared the changes in HO volume between study 301 and NHS subjects during a 12-month observation period as a landmark analysis, which does not rely on assumptions on a constant rate of change. Some subjects did not have changes in HO through a 12-month period (four subjects in study 301 and 11 subjects in NHS). Depending on how subjects with no 12-month HO change could be handled, there are different ways for performing the landmark analysis.

We performed the landmark analyses using different methods for subjects who did not have 12-month data to investigate the consistency of findings. For all these analyses, a robust sandwich variance estimator was used to account for heteroscedasticity in variance. Results from these landmark analyses with different ways of handling subjects without 12-month data and including different covariates were consistently in favor of palovarotene (Table 36). In addition, our analyses did not transform negative new HO values to zero.

Table 36. FDA's Landmark Analyses Without Square Root Transformation

Analysis Method#/Least Square Mean (SE)	Study 301 (N=97)	NHS (N=101)	Difference (95% CI)	P-Value
Include only subjects who provided Month 12 HO	93	90		
Covariates 1*	6.7(2.4)	22.0 (6.4)	-15.3 (-28.5, -2.1)	0.0229
Covariates 2*	6.2 (2.4)	21.8 (6.1)	-15.5 (-28.8, -2.3)	0.0212
Covariates 3*	6.6 (2.5)	22.0 (6.2)	-15.4 (-28.8, -2.0)	0.0243
Include only subjects with HO data up to Month 12	97	92		
Covariates 1	8.1 (2.8)	22.5 (6.3)	-14.3 (-27.8, -0.9)	0.0368
Covariates 2	7.6 (2.8)	22.3 (6.1)	-14.7 (-28.2, -1.3)	0.0321
Covariates 3	8.1 (2.9)	22.7 (6.2)	-14.6 (-28.2, -1.0)	0.0354
Include all subjects using Month 12 data if available [§]	97	101		
Covariates 1	8.1(2.8)	20.7 (5.3)	-12.5 (-24.0, -1.1)	0.0317
Covariates 2	7.5 (2.9)	21.0 (5.2)	-13.5 (-25.3, -1.7)	0.0249
Covariates 3	7.8 (2.9)	21.7 (5.5)	-13.9 (-26.3, -1.5)	0.0275
Include all subjects with Month 12 and multiple imputation for missing Month 12; with Covariates 3	8.3 (3.0)	22.7 (6.3)	-14.4 (-28.1, -0.7)	0.0395

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

* 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

Generalized estimating equation, no square root transformation, negative new HO included

[§] 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 cm³ is added to the imputed values in treated subjects.

Abbreviations: CAJIS, Cumulative Analogue Joint Involvement Scale for FOP; CI, confidence interval; HO, heterotopic ossification; N, number of subjects; SE, standard error

Compared with the treatment effect based on observations associated with the longest follow-up ([Table 13](#)), the estimated effects from these landmark analyses are generally larger but also have greater variability.

Conclusion

The prespecified Bayesian compound Poisson model incorporating square root transformation appears to have a bias against palovarotene due to the more frequent assessment in study 301. FDA identified more appropriate methods to compare the annualized new HO between study 301 and NHS subjects and conducted them post hoc.

Although these post hoc analyses support that the annualized new HO of study 301 subjects was lower than that of NHS subjects, post hoc analyses should be interpreted with caution.

6.3.2. Phase 3: Use of an External Control Group (NHS) for Evaluation of Efficacy of the Chronic/Flare-up Regimen

Issue

Phase 3 study: Use of an external control group (NHS) for evaluation of chronic/flare-up regimen

Background

Because of a paucity of published data regarding FOP disease characteristics and progression over time, the Applicant initiated the natural history study (NHS, Study PVO-1A-001) in 2014 and enrolled 117 subjects, a relatively large proportion of the known global population of approximately 800 FOP patients. During the subsequent planning of the phase 3 study, 301, the Applicant considered that the NHS study population and assessments were suitable to serve as an external control group, as the two studies would be conducted at the same centers, with generally consistent standards of care and associated background treatment, such as use of prednisone for flare-ups. The relative objectivity and blinded assessment of the primary outcome measure, change in HO volume, was considered to minimize the potential for bias. Based on these considerations and the small number of FOP patients available for recruitment, Study 301 was designed as an open-label, single arm study. The Applicant also anticipated that about 40% of NHS subjects would go on to participate in Study 301, adding further consistency between the respective study populations.

Assessment

General Consideration

Despite the limitations associated with using an external control rather than a randomized concurrent control, FDA recognizes that support for effectiveness can emerge using an externally controlled trial when the following are met:

- Natural history of the disease is well defined
- 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
- Results provide compelling evidence of a change in the established progression of disease (December 2019)

The concomitant treatments in this population are not expected to affect the outcome of interest. The NHS study was performed to characterize the disease process and outcome. The focus here is whether the difference between the study populations in the NHS and study 301 impacted the conclusion regarding efficacy and whether the results are compelling enough to overcome the general concerns of potential confounding factors.

FDA's Assessment of Comparability of Study Populations

The enrollment criteria for the NHS and Study 301 were generally similar. Because NHS was restricted to subjects with the classic R206H mutation, which represents ~97% of FOP patients, the principal analysis population of Study 301 excluded a small number of participants with other mutations.

Allocation of subjects into these studies was sequential, as NHS enrollment was complete before Study 301 was initiated. All NHS sites also participated in Study 301, and a total of 39 subjects transferred from the NHS into Study 301 and contributed efficacy data to both studies. Any NHS subject who met enrollment criteria (e.g., without retinoid-safety-related exclusions) was eligible for this transition. According to the Applicant, Study 301 enrollment occurred rapidly, exceeding original projections, which resulted in the capping of enrollment at one site (1001, UCSF) which enrolled nine subjects from the NHS. Although the selection process for transition was not random, the Applicant did not assess reasons for not enrolling in 301 among those who were eligible but did not transition. In addition to NHS-to-301 transitions, eight subjects left the NHS to enroll in phase 2 study, 201, at the onset of a flare-up, and many other subjects left the NHS to enroll in other interventional studies. These transfers out of NHS were likely driven at least in part by clinical factors, which are largely unknown.

Table 37 presents baseline data for three cohorts within the Principal FAS: the 39 transition subjects who contributed efficacy data to both the NHS and Study 301; 62 NHS subjects who did not enroll in Study 301; and 58 subjects in Study 301 who had not participated in the NHS. Transition subjects' data at both NHS baseline and Study 301 baseline (at an average of 2.2 years later) are presented.

As shown, NHS subjects who remained in the NHS were older (mean age 20.0 year) than subjects who transitioned to Study 301 (mean 13.1 year) and other Study 301 subjects (mean 14.2 year). Consistent with older age, the NHS-only subjects tended to have more advanced disease, with generally higher whole-body HO volumes, greater number of body regions with HO, and higher scores on CAJIS and FOP-PFQ, indicating more severely impaired range of motion and physical function. Transition subjects reported a higher number of flare-ups prior to NHS enrollment (mean 3.8 within 12 months) than the other groups; this was driven by two outliers as discussed above (Section [6.2.1.4](#)).

Table 37. NHS, Study 301 and Transition Subjects: Baseline Data (Principal FAS)

Characteristic	NHS Only N=62	Transition Subjects*		Study 301 Only N=58
		NHS Data N=39	Study 301 Data N=39	
Mean age, year	19.9	13.1	15.3	14.1
Sex, male/female (%)	52/48	61/39		47/53
Race, White/Asian/Other (%)	78/7/15	66/11/24		73/8/19
Country, US/Europe/Other (%)	25/47/28	45/32/24		36/42/22
WBHO volume, cm ³ , mean	389.4	213.3	266.0	208.0
Number of body regions with HO, mean	6.8	6.1	6.4	6.0
Number of flare-ups within 12 months of enrollment, mean	1.6	3.8	1.1	1.6
CAJIS score, mean	13.1	9.6	10.4	9.4
FOP-PFQ score, mean	49.5	42.7	44.4	42.7

Source: Response to IR, submitted 5/27/21

*Note: there were 39 transition subjects with both NHS data and Study 301 data

Abbreviations: CAJIS, Cumulative Analogue Joint Involvement Scale for FOP; FAS, full analysis set; FOP-PFQ, fibrodysplasia ossificans progressiva Physical Function Questionnaire; NHS, natural history study; WBHO, whole-body heterotopic ossification

Postbaseline data on these cohorts are shown in Table 38. Untreated NHS-only subjects accumulated new HO at a higher rate than Study 301-only subjects (27.5 versus 10.3 cm³/year). In comparison, the 38 transition subjects accumulated somewhat less new HO during each study (16.7 cm³/year in NHS, 6.5 cm³/year in Study 301). The rate of flare-ups was higher during Study 301, overall and within the transition cohort (0.09/month in NHS, 0.15/month in Study 301); this may be related to possible under-reporting of flare-ups in the NHS (see Section 6.3.4).

Table 38. NHS, Study 301 and Transition Subjects: Postbaseline Data (Principal FAS)

Variable	NHS Only N=62	Transition Subjects*		Study 301 Only N=58
		NHS Data N=39	Study 301 Data N=39	
Duration of chronic dosing, days, mean	-	-	361	378
Duration of flare-up dosing, days, mean	-	-	218	192
Months in study, mean	30.8	27.8	20.4	20.5
Annualized new WBHO volume, cm ³ /year, mean	29.1	15.2	7.0	11.1
Flare-up rate per month in study, mean	0.06	0.08	0.14	0.13

Source: Responses to IR, submitted 5/7/21 and 7/26/21

*Note: there were 39 transition subjects with both NHS data and Study 301 data

Abbreviations: FAS, full analysis set; NHS, natural history study; WBHO, whole-body heterotopic ossification

Assessment of Impact of Subject Difference at Baseline

To assess the impact of subject differences between Study 301 and the NHS, the Applicant conducted sensitivity analyses by adjusting for additional baseline covariates, including the propensity score quartile, performing matching and weighting based on propensity score among subjects who did not enroll in both the NHS and Study 301 (i.e., non-transition subjects) (Table 39). Results from these analyses were consistent with those from the post hoc wLME method without square root transformation.

Table 39. Analyses After Propensity Score Matching and Weighting – Non-Transition Subjects

Analysis Method/mean	Study 301 (N=58)	NHS (N=61)	Difference	P-value
Propensity score matching* (39 matched)	5.6	24.1	-18.5	<0.05
Unstabilized propensity score weighting	9.5	28.9	-19.4	<0.05
Stabilized propensity weighting	9.5	28.9	-19.4	<0.05

Source: Applicant's matched analysis report.

Endpoint: annualized new HO, calculated as change in total HO from baseline divided by actual length of follow-up; *nearest neighbor, caliper =0.2, covariates (specified by Agency): age-adjusted baseline HO volume, baseline age, sex, months since last flare up, and baseline CAJIS.

Abbreviations: N, number of subjects; NHS, natural history study

The FDA review team performed landmark analyses on the P-FAS population using propensity score weighting, matching, and targeted maximum likelihood estimation methods that are commonly used for causal inference for nonrandomized studies. Results from these analyses are also consistent (Table 40). Balance assessments showed the covariates were well balanced after weighting and matching (Section 16).

Results from the propensity score-based weighting and matching did not consider that some NHS subjects crossed over to Study 301 in the weighting or matching process, although the within-subject correlation was accounted for in the analysis after matching. The application of a propensity score based matching method needs to consider a bias-variance tradeoff and whether the matched subset is still representative of the target population. When tighter matching on more covariates is requested, the number of matched subjects is much smaller. The targeted maximum likelihood estimation method is generally believed to be robust for inferring the treatment effect for nonrandomized studies, with results that are consistent with results from analyses based on the propensity score weighting and matching. However, validity of conclusions on treatment effects from these analyses relies on the unverifiable assumption that there are no unknown or unmeasured confounding factors that could impact the difference between study 301 and NHS subjects.

Although loss to follow-up may remain an issue, the majority of subjects in these analyses completed the 12-month follow-up, so results may not be substantially changed. However, because the pattern of losses to follow-up may vary at different follow-up intervals between the two studies, the impact of differential loss to follow-up on results beyond 12 months is unknown.

Table 40. FDA's Landmark Analyses Without Square Root Transformation Based on Methods for Causal Inference

Analysis Method	Study 301 (N=97)	NHS (N=101)	Difference (95% CI)	P-Value
Propensity score weighting/ mean (SE)				
Include all subjects using 12-month data if available	97	101		
Covariates 1*	8.9 (3.1)	22.8 (5.9)	-14.0 (-27.0, -0.8)	0.0364
Covariates 2**	8.7 (3.0)	22.9 (5.9)	-14.2 (-27.2, -1.2)	0.0321
Covariates 3*** (excluded 4 subjects missing covariates)	9.1 (3.2)	23.0 (6.1)	-13.9 (-27.4, -0.5)	0.0422
Propensity score Matching#				
Exact match on sex and age group, nearest neighbor with caliper 0.2 for covariates 3	Matched N=61	Matched N=61	-16.2 (-25.7, -6.6)	0.0022
Targeted maximum likelihood estimation				
Covariates 1	N=97	N=101	-14.3 (-27.3, -1.3)	0.0309
Covariates 3 (excluded 4 subjects missing covariates)	N=97	N=97	-15.2 (-30.7, 0.03) ^s	0.0551
Covariates 3; including all 12-month changes	N=97	N=101	-11.6 (-21.8, -1.2)	0.0281

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; \$bootstrap 95% CI: (-31.2, -0.5)

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

Abbreviations: CI, confidence interval; N, number of subjects; SE, standard error

Assessment of Analyses Based on Subjects Transitioned from NHS to Study 301

The Applicant performed analyses limited to subjects who transitioned from the NHS to study 301 (i.e., baseline control). One of the Applicant's analyses compared the observations associated with the longest follow-up between studies. The other analysis compared the last 12-month change of HO in the NHS with the first 12-month change in study 301. Results from the two analyses favored palovarotene (Table 41).

Table 41. Applicant's Analyses on Annualized New HO (cm³) in Subjects Transitioned to Study 301

Analysis Method/Least Square Mean (SE)	Study 301 (N=39)	NHS (N=39)	Difference (95% CI)	P-Value
wLME using the observation associated with the longest follow-up	8.1 (4.0)	16.7 (3.3)	-8.6 (-17.7, 0.5)	0.0634
wLME using last 12-month change in NHS and first 12-Month change in study 301*	4.9 (4.9)	18.2 (5.2)	-13.2 (-25.7, -0.8)	0.0377

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.

Abbreviations: CI, confidence interval; HO, heterotopic ossification; N, number of subjects; NHS, natural history study; SE, standard error; wLME, Weighted Linear Mixed Effects Analyses

Interpretation of results from this analysis should consider to what extent the disease is expected to progress similarly to what was observed in the NHS after these subjects transitioned to study 301. However, the impact of disease progression when enrolled into study 301 could not be fully assessed without a concurrent control.

Conclusion

When an external control is used, there will be a lack of assurance of comparability between treated and untreated subjects given the lack of randomization. To address the potential impact of measured confounding factors, various analyses using methods that are commonly used for nonrandomized studies were performed and these analyses provided consistent results. However, there is a residual uncertainty on the impact of unknown confounding factors and potential bias (e.g., differential loss to follow-up) on the study conclusion.

An issue related to differential loss to follow-up is the nonrandom enrollment of NHS subjects into study 301, which may have a potential selection bias if the enrollment was due to clinical outcome observed in NHS. Study 301 subjects were enrolled after NHS enrollment was complete at the same centers. Thus, there was no period of overlap in enrollment, during which clinical factors might have influenced the choice of studies in which to enroll. The enrollment of 39 NHS subjects to transition to Study 301 was non-random and yielded a cohort of subjects who were younger and with less severe disease than other NHS subjects, and who developed somewhat less new HO both off- and on-treatment compared to other subjects. This process could create bias, although the consistency of new HO data (palovarotene versus untreated) among both transition and non-transition subjects tends to support efficacy of the chronic/flare-up treatment regimen, and the transition subjects' data provide some "baseline-controlled" data within a specific group. Ultimately, however, the Applicant did adequately address the concern regarding potential bias caused by non-random enrollment of NHS subjects into Study 301. A randomized control group would have provided more reliable phase 3 results.

6.3.3. Phase 3: Uncertain Clinical Implications of Negative New HO Volume Data

Issue

Negative new HO volume data: clinical significance, and implications for primary phase 3 efficacy analysis

Background

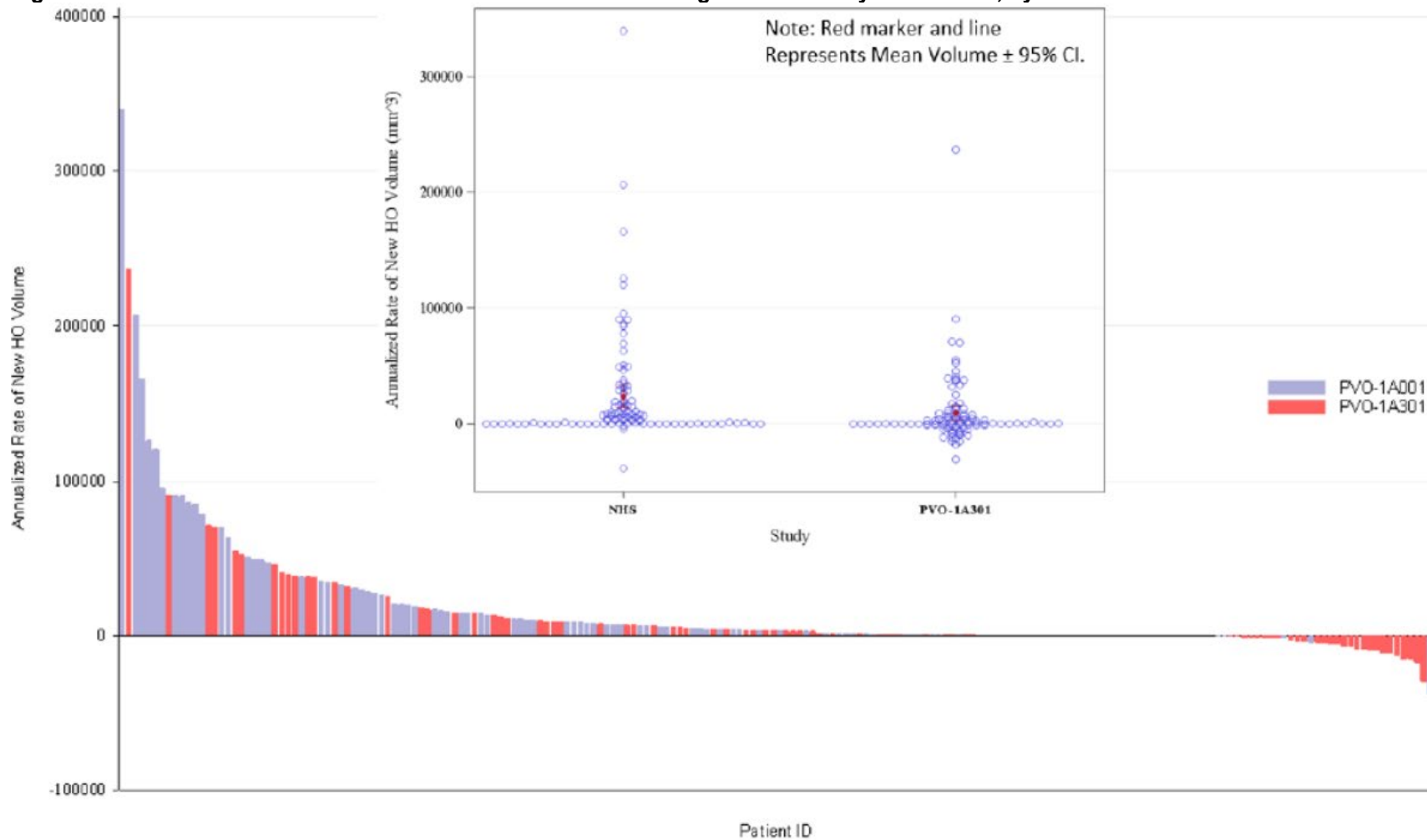
FOP is characterized by accumulation of HO, which is considered to be irreversible. As noted above (Section [6.2.1.3](#)), the prespecified analysis of the phase 3 primary endpoint (volume of new HO per year in Study 301 versus NHS) used a Bayesian compound Poisson model that required any negative new HO data by region to be reset to 0. It was anticipated that the extent of negative HO data would be limited. However, results of these studies showed substantial declines in HO volume in some instances, raising questions about the clinical significance of such changes.

The negative changes in HO volume had substantial impact on the reduction in annualized new HO in treated subjects. Most post hoc analyses, which were performed by retaining negative HO volumes and produced nominally significant results, would lose nominal significance should negative changes be set to 0.

Assessment

In Studies 301 and the NHS, postbaseline WBCT scans were compared to the previous scan. If any new HO was qualitatively present in a certain body region, all HO in that region was remeasured. In many cases, the net change in HO was negative ($<0 \text{ cm}^3/\text{year}$) for a specific body region. There were more palovarotene-treated versus untreated subjects (47% and 24% in Study 301 and the NHS, respectively) with negative changes in new HO volume in at least one body region at the last measured timepoint. Net negative changes for total body HO also occurred more frequently in Study 301 (29% in Study 301 versus 5% in the NHS); Figure 10 shows a preponderance of palovarotene-treated patients (in red) with negative new total body HO compared to NHS patients (in gray).

Figure 10. Studies 301 and NHS: Distribution of Annualized Change in Total Body HO Volume, by Individual Patient

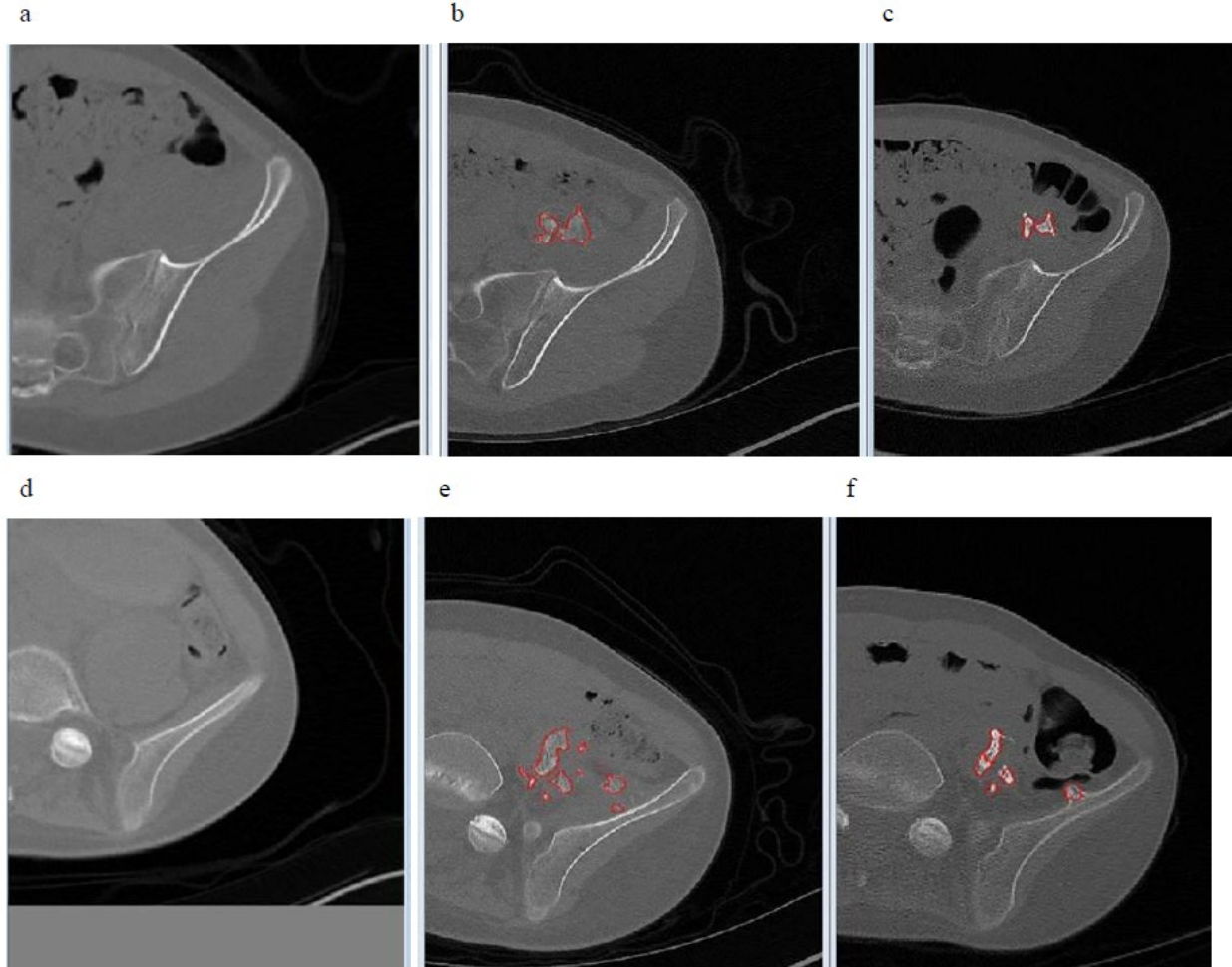


Source: Study 301 CSR Figure 5

Abbreviations: CI, confidence interval; HO, heterotopic ossification; NHS, natural history study; PVO, palovarotene

This phenomenon is illustrated in the following WBCT images from a 14-year-old female. The patient received placebo treatment in Study 201 for a left hip flare-up, resulting in new HO at Week 12 (frames b,e) that was not present at baseline (a, d). Subsequently, she received palovarotene 10/5 mg treatment for a knee flare-up, and a 1-year follow-up scan of the left hip (c,f) appeared to show the areas of new HO at Week 12 becoming smaller over time while increasing in radiodensity. The measured difference in volume for the left hip region over this interval was substantial (-46 cm^3).

Figure 11. Images of Heterotopic Ossification in Hip Over Time



Source: Study 301 CSR, Figure 2

Literature reports indicate that shrinkage of HO lesions may occur in untreated FOP patients, as well as in nongenetic forms of HO. While the mechanism is unknown, it is plausible that this may be related to resolution of edema in newer lesions with progressive calcification and consolidation to mature cortical bone, analogous to the remodeling of callus around a fracture. (per the Applicant's response to IR submission to the NDA on August 5, 2021).

Because negative HO volume changes were reported more frequently in Study 301 than in the NHS, the Applicant contends that palovarotene treatment may cause HO regression. However, it is important to note that all HO volume measurements in these studies were by body region,

therefore shrinkage in individual lesion(s) could be offset or masked by increasing size of other lesions within the same region. NHS subjects generally had more HO lesions that were growing in size; therefore, negative changes would tend to be underestimated in these untreated patients to a greater extent than in palovarotene recipients. Because of the lack of data on individual HO lesions in these studies, there is insufficient evidence to conclude that the negative new HO data resulted from palovarotene-related regression of existing lesions as seen radiographically (perhaps due to consolidation of the lesion or decreased inflammation), in addition to inhibition of new HO formation.

The most plausible rationale for excluding negative HO changes from the primary analyses (i.e., resetting to zero as was done in the prespecified analyses) would be that such changes may represent artifact due to measurement variation. The HO volume calculations were in part dependent on subjective assessments and varying orientation of axial slices on different CT scans, however, given the processes of double read and adjudication, measurement error is unlikely to explain some of the larger HO volume declines observed, as described above. Moreover, measurement error would apply equally to scans from treated and untreated subjects, therefore this mechanism alone cannot explain the disproportionate number of treated subjects with net negative HO.

Thus in at least some instances, negative new HO volume changes are likely to reflect actual shrinkage of lesions, possibly as a natural process of lesion maturation or due to a decrease in inflammation, rather than a decrease in HO itself. The data are insufficient to conclude that palovarotene promotes this process. However, regardless of the exact mechanism, there does not appear to be a plausible rationale for excluding negative HO changes from analyses. On the other hand, if the reduction in volume was due to consolidation or a decrease in the underlying inflammatory process rather than inhibition of the growth of new HO, it is unclear whether the occurrence of negative new HO should be viewed as a treatment benefit, given that neither lesion consolidation nor decrease in inflammation have been associated with improvement in functional status in patients with FOP.

Conclusion

More frequent occurrence of negative new HO was observed in treated subjects and contributed substantially to the reduction of annualized new HO. However, it remains unclear what could physiologically account for negative HO volume changes or whether the occurrence of negative new HO volume is beneficial to a patient. If negative HO volume is not beneficial (i.e., does not improve functional outcomes), the clinical meaningfulness of the difference in annualized new HO as measured by regional WBCT scan is questionable. Together, these uncertainties regarding how to handle negative changes in HO volume when assessing drug effect bring into question that reliability of the Applicant's pre-specified and post hoc analyses, and thus render any interpretation of a potential benefit of palovarotene on total HO volume problematic.

6.3.4. Phase 2 Studies: Efficacy of Flare-up-Only Dosing Was Not Established; Efficacy Data Pertaining to Chronic/Flare-up Dosing Were Generally Not Consistent With Phase 3 Data

Issue

Phase 2 studies: Efficacy of flare-up-only dosing was not established; efficacy data pertaining to chronic/flare-up dosing were generally not consistent with phase 3 data.

Background

The initial phase 2 studies were designed to demonstrate the potential of palovarotene to prevent formation of new HO at flare-up sites (Studies 201, 202A, 202B). The primary endpoint in this phase was the proportion of flare-ups resulting in significant new HO; this endpoint was not met with palovarotene treatment, although there were trends of reduced volume of new HO at the flare-up sites, a secondary endpoint. These findings are discussed in Section [6.2.2.4](#) above.

Subsequently (Studies 202B, 202C), chronic daily dosing was introduced, and the goal of treatment was changed to the reduction of new whole-body HO (annualized volume) as compared to untreated patients in the NHS, similar to the primary endpoint of Study 301. Unlike Study 301, Study 202 had no prespecified interim analyses, and because Study 202C was ongoing at the cutoff date for the NDA, few analyses of the 202B/C data were presented, and none involved the primary endpoint comparison to NHS data.

Assessment

Overall, the annualized rate of new whole-body HO was relatively high in Study 202B (mean 28.0 cm³/year) and Study 202C (mean 24.3 cm³/year), compared to Study 301 (mean 9.4 cm³/year) and the NHS (23.7 cm³/year) (raw data, negatives included, no square root transformation).

The palovarotene chronic/flare-up regimen was the same in Studies 202B/C and 301: daily 5 mg with increase to 20/10 mg for flare-ups for 12 weeks, extended in 4-week increments for persistent symptoms, with weight-based dose reductions for skeletally immature patients. However, as described in Section [Error! Reference source not found.](#), flare-up dosing was used less extensively in Study 202B compared to Studies 202C and 301 based on different flare-up qualifying criteria specified in the protocols. An analysis of subgroups in the ISE suggests that this resulted in undertreatment (i.e., only the 5 mg chronic daily dose) of at least some flare-up symptoms in a large proportion of subjects (30/48) in Study 202B and an especially high mean volume of new HO (33.5 cm³/year) in this subgroup, compared to the 9/48 subjects in whom all flare-up symptoms were treated with flare-up dosing (mean new HO -3.0 cm³/year). However, this observation is inconsistent with the data specific to Part C, in which all flare-up symptoms were treated but rates of new HO remained high.

Another issue is that the data from the “undertreatment of flare-up symptoms” subgroup of 30 subjects in Study 202B does not tend to support the effectiveness of the chronic 5 mg dose. In addition, the 9/48 subjects who had no reported flare-up symptoms in Study 202B/C experienced high levels of new HO (mean 25.1 cm³/year) despite continuous 5 mg dosing. This finding is not

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consistent with data from other studies indicating that subjects without any flare-up symptoms generally develop relatively smaller quantities of new HO: among such patients, mean new HO volumes were 2.9 cm³/year in Study 301 and 6.7 cm³/year in the NHS.

Comparisons across these studies are confounded by known and unknown differences in the respective study populations. Subjects in Study 202B/C were approximately 3 to 5 years older on average than Study 301 or the NHS because skeletally immature patients began chronic treatment later (in Study 202C rather than 202B) and were excluded from the group of additional patients who enrolled in the study at Part B.

Per protocol, subjects who enrolled de novo in Study 202B, and all subjects in Study 301 and the NHS, had not had any flare-up symptoms within 4 weeks of enrollment, and were therefore unlikely to develop substantial quantities of new HO at the site of any recent flare-up following the baseline whole-body CT. This did not apply to the other group of 202B/C subjects, who had participated in Studies 201 and 202A and may have begun chronic treatment in 202B immediately following a flare-up. In addition, the Applicant believes that this cohort may not be comparable to the other groups/studies because their initial enrollment (in Study 201) was prompted by an acute flare-up. Indeed, this cohort did exhibit larger quantities of new whole-body HO in 202B/C compared to the “de novo” cohort (mean new HO, 121.3 versus 57.8 cm³ at month 36 by clinical reviewer calculation).

Conclusion

Because of the apparent inconsistency of the Study 202B/C versus Study 301 data and these complicating factors of protocol changes and differences in study populations, a more complete assessment of palovarotene efficacy in FOP will require further analysis of the 202B/C data, including comparisons to untreated NHS subjects and control of covariates; analysis of subjects who transferred from the NHS to Studies 202B/C or 301; and discussion of differences in WBCT interpretation procedures that were used in these studies. A detailed request for additional data and analyses was communicated by DGE to the Applicant on October 28, 2022, and discussed in a teleconference on November 18, 2022. The Applicant now has access to all WBCT scans collected up to the last-patient-last-visit for Studies 202 and 301, with a cut-off date of September 2022. The requested additional data and analyses, which will include post restart data from subjects who resumed palovarotene following the treatment pause in 2020, will not be available during this review cycle and will be submitted at a later date.

Recognizing that whole-body HO data from Study 202 Part C is most comparable to Study 301 based on use of the same treatment protocol, the Applicant will conduct separate analyses for Part C, using as baseline the first WBCT scan in Part C that was not obtained during or within 1 month after the end of a flare-up, for consistency with the Study 301 and NHS data to be compared. Combined Part B/C data will also be analyzed, using each subject’s baseline WBCT scan at the time of initiating chronic therapy (either in Part B or Part C). Although there was less extensive use of flare-up dosing in Part B, analysis of the combined 202B/C HO data (as prespecified in the primary study endpoint) is important because the chronic 5 mg dose remained the same throughout, and because the combined data represent the longest duration of treatment (WBCT data are available through month 36 for most subjects in 202B/C versus month 18 for most subjects in 301).

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Toxicological characterization of palovarotene was conducted in a battery of studies consistent with the International Conference on Harmonization (ICH)-M3(R2) guidance for industry (January 2010). A series of pharmacology, pharmacokinetics (PK)/absorption, distribution, metabolism, excretion (ADME), repeat dose general toxicology studies of up to 26- and 39-week duration in rats and dogs, respectively, as well as reproductive toxicology (male and female fertility and early embryonic development (FEED), single species (rat) embryofetal development (EFD) and juvenile animal toxicity studies were conducted. Additional subchronic studies were completed in rabbits, rat, and dogs. As palovarotene adversely affected fetal development in pregnant rats, and retinoids as a class are known to carry a risk of affecting fetal development, neither an EFD study in pregnant animals of a second species nor a pre-/postnatal developmental toxicity study were warranted. A complete battery of genotoxicity studies was conducted. The Applicant provided a “weight-of-evidence”-based assessment of the carcinogenic potential of palovarotene. Nonclinical toxicity studies were also performed separately to qualify metabolites (M2, M3, M4a and M4b) for genetic toxicity and in vivo toxicity in rats and dogs.

Notable toxicities with potential clinical relevance will be discussed in more detail below.

Skeletal Toxicity

Palovarotene adversely affected the skeletal system in rats but not dogs. In juvenile rats (aged 3 weeks at initiation), changes were noted in the growth plates, cartilage/joints, and bones at doses ≥ 0.5 mg/kg/day (below clinical exposure, based on AUC). In long bones and vertebrae, physes were either widened due to an expanded zone of hypertrophy/maturation (accompanied by chondrodystrophy), narrowed, or partially/completely closed. Effects of palovarotene were also extended to hyaline and articular cartilages. Additional changes included avascular necrosis, sometimes with microfracture of trabeculae and severe malformation of the head and/or neck of the femur at 1.2 mg/kg/day (below clinical exposure). The skeletal effects occurred with correlative decreases in biochemical bone formation markers (OC and PINP), and impacted bone size, shape, mass, geometry, and growth in general. Recovery was not attained for the majority of the skeletal and growth plate effects. Premature physeal closure is also a risk noted in the palovarotene clinical program. In adult rats, skeletal effects were limited to chondrodystrophy in the epiphyseal growth plate of knee/stifle joint, which remains active throughout life in this species, with fractures near the long bone growth plates in a few rats at the highest dose level of 5 mg/kg/day (~ 1 -fold MRHD by AUC) but not at ≤ 1 mg/kg/day (below clinical exposure). Chondrodystrophy was partly reversed when mild or minimal but persisted when severe, which is expected based on the biology and time-dependence of the endochondral bone formation process.

Mucocutaneous Effects

Mucocutaneous toxicity occurred in a dose and time-related manner in adult rats, rabbits, and dogs that involved mainly the skin. The skin changes were characterized by hair coat changes,

skin erythema, edema, scaling, epithelial hyperplasia (acanthosis), acute/chronic inflammation, hyperkeratosis, and/or hypergranulosis in the epidermis. In juvenile rats, skin lesions were limited to dry skin, thin fur cover, and/or scab. Squamous epithelium effects in other tissues, such as nonglandular mucosa of the stomach (forestomach), esophagus (rabbits only), and conjunctivae of the eye and surface of inner ear (dogs only), were also noted and thought to be related to skin toxicity. Mucocutaneous effects were reversible when dosing stopped. Skin effects have long been known to occur in response to retinoids and similar mucocutaneous changes are the most reported adverse reactions across all palovarotene clinical programs.

Reproductive Toxicity

Teratogenicity

Administration of daily oral doses of palovarotene to pregnant rats during the period of organogenesis resulted in multiple fetal external, visceral, and skeletal malformations at ≥ 0.25 mg/kg/day (below clinical exposures), consistent with the pattern of retinoid-mediated embryopathy. While maternal toxicity was evident by reductions in body weight gains at ≥ 0.25 mg/kg/day and lower food consumption at 1.25 mg/kg/day, the teratogenic findings with palovarotene are consistent with malformations noted with the retinoid class and were considered unrelated to maternal toxicity.

The Applicant measured palovarotene levels in human semen samples as an indirect measure of male-mediated embryo and fetal development risk. The data showed that the maximal estimated level of palovarotene in single ejaculate (33 ng or $\sim 0.00017\%$ of the daily dose 20 mg administered) at 3 hours postdose resulted in a very low (2.7%) semen to plasma ratio. The maximum potential fetal exposure to palovarotene through semen is estimated to be 0.0066 ng/mL, which is 100-fold lower than exposure at the NOAEL (0.7 ng/mL) for effects on fetal malformations. Based on the absence of genotoxicity, testicular toxicity upon chronic exposure, and low transfer of the drug to human serum, palovarotene is considered unlikely to affect the development of an embryo or fetus carried by a pregnant female partner exposed to palovarotene via the patient's semen.

Testicular Toxicity

In the 4-week rat toxicity study, evidence of testicular toxicity including testicular degeneration, hypospermia, cellular debris in the epididymides and reduced sperm motility were seen in male rats given palovarotene at daily oral doses that exceeded maximum tolerated dose (MTD) of 5 mg/kg/day (~ 1 -fold MRHD by AUC). Though testicular changes were previously reported with retinoids, similar effects were not recapitulated in the pivotal 26-week repeat dose rat toxicity or male fertility studies and palovarotene had no effect on male rat fertility.

Genotoxicity and Carcinogenicity

Palovarotene was not genotoxic when tested in a battery of genotoxicity studies. Dedicated rodent carcinogenicity studies to assess the carcinogenic potential of palovarotene have not been conducted; instead, the Applicant assessed the carcinogenic potential of palovarotene using a WoE approach using data from the completed nonclinical studies, published literature and the intended patient population. The nonclinical reviewer concluded that the human carcinogenicity potential of palovarotene is uncertain based on the target signaling pathway, preneoplastic

changes observed in chronic rat and monkey studies, and tumor findings noted in rodent carcinogenicity studies with other retinoids. Carcinogenicity assessment in two rodent species is considered necessary as a post marketing requirement. Late in the review cycle, the Applicant submitted an amendment with additional nonclinical information requesting reconsideration of the postmarketing requirement for carcinogenicity studies. The nonclinical team will fully review the information amendment and request consultation from the Executive Carcinogenicity Assessment Committee upon NDA resubmission. Details are included in Sections [13](#) and [22](#).

Impurities

The Applicant proposed a high acceptance criterion (originally (b) (4) and current plan (b) (4) %) for a drug substance impurity, (b) (4), which was present at very low levels (up to (b) (4) %) in palovarotene batches used for pivotal nonclinical toxicity studies. In order to qualify the drug substance impurity (b) (4), the Applicant conducted genotoxicity assessments (QSAR, in vitro Ames and chromosomal aberration) and a 4-week oral repeat dose general toxicity study in rats. (b) (4) was not genotoxic and no safety issue was identified in the rat toxicity study (see detailed discussions in Sections [7.7](#) and [13](#)).

Conclusion

The safety issues identified in the nonclinical studies, including skin lesions, growth suppression, and premature closure of physis in juveniles, have been observed in humans treated with palovarotene. The skeletal findings are consistent with the retinoid class and are consistent with the desired pharmacological effect of palovarotene i.e., inhibition of chondrogenesis in the indicated FOP population. Risk of fetal malformations are based on the palovarotene rat EFD study and the class. Because of the exaggerated pharmacology in healthy animal models, no safety margins were established at the palovarotene NOAEL doses of <0.03 mg/kg/day and <12 mg/kg/day in the 26-week rat and 39-week dog toxicity studies, respectively ([Table 42](#)). The human risks might be manageable through various clinical interventions, including use of skin ointment for skin changes, growth monitoring in pediatric patients, labelling (e.g., contraindication and pregnancy testing before/during/after treatment) and other risk mitigation strategies, as appropriate. The available nonclinical database addressed all identified nonclinical safety issues. The nonclinical Pharmacology/Toxicology team identified no issues precluding approval of palovarotene in the indicated FOP population and considers postmarket studies necessary to characterize the long-term carcinogenicity risk with chronic palovarotene exposure.

Table 42. Palovarotene Nonclinical Safety Margins

Study	NOAEL ¹	Nonclinical Exposure (ng.h/mL)	Safety Margins ²	Basis for NOAEL
26-week rat	<0.03 mg/kg/day	<168	<0.2	Palovarotene-related partially recoverable growth plate chondrodystrophy of the stifle joint and persistent forestomach degeneration/dyskeratosis observed at all doses.
39-week dog	<12 mg/kg/day	<103	<0.1	Drug-related clinical and histological skin lesions (hypergranulosis) noted at all doses.

Source: Reviewer derived from data from Study # 1013603 and 1013980

¹NOAEL not established in chronic rat or dog repeat dose toxicity studies

²The maximum recommend human dose is 20 mg; Safety margins calculated based on AUC_{0-t}=1060 ng.h/mL at steady state in phase 3 study PVO-1A-301

Abbreviation: NOAEL, no observed adverse effect level

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Retinoids are associated with numerous class-related adverse effects. For palovarotene, the two most serious concerns are PPC and embryo-fetal toxicity, which have been reported with other retinoids and are discussed below (Sections [7.7.1](#) and [Error! Reference source not found.](#), respectively). By June 25, 2020, a total of 24 events of PPC were reported in 96 pediatric subjects aged <17 years at enrollment, which was approximately 30% in patients ≥8/10 to 11 years of age (4 of 12 (33%) boys aged 10 to 11 years and 5 of 17 (29%) girls aged 8 to 11 years). Reduced bone mineral density appears to be associated with palovarotene and other retinoids and is discussed in Section [7.7.4](#). Other potential retinoid class effects include neuropsychiatric effects including depression, suicidality, seizures and pseudotumor cerebri; mucocutaneous adverse effects; serious skin reactions such as Stevens-Johnson syndrome; musculoskeletal effects including arthralgia and back pain; hypersensitivity reactions; acute pancreatitis; hepatotoxicity; elevated triglycerides; inflammatory bowel disease; hearing impairment; and eye abnormalities including decreased night vision.

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7.3. Potential Safety Concerns Identified Through Postmarket Experience

Not applicable; palovarotene has not been marketed in any country.

7.4. FDA Approach to the Safety Review

The bulk of the FOP/palovarotene safety data involves the 5 mg chronic nonflare dose or the 20/10 mg flare-up regimen (all doses weight adjusted) in Studies 202B, 202C and 301. For this review, Clinical Data Scientist staff analyzed the pooled safety data from these studies for each of these regimens (chronic and 20/10 flare-up) in the Applicant's intended target population (females ≥ 8 years of age, males ≥ 10 years of age). These data are presented in this section alongside a Palovarotene (PVO) Total group consisting of all PVO-exposed subjects age ≥ 8 F/10M from all interventional FOP studies (201, 202A/B/C, 301), including the lower-dose flare-up regimens (10/5 mg, 5/2.5 mg) for which total exposure (including treatment duration) was relatively limited.

The safety data cutoff dates were February 28, 2020, for the initial NDA submission; July 30, 2021, for the NDA resubmission; and January 31, 2022, for the 90-day Safety Update. Although no subjects < 14 years of age have received palovarotene since the partial clinical hold issued on December 4, 2019, some off-treatment data pertaining to bone safety have been collected in these subjects. Subjects ≥ 14 years of age also interrupted treatment starting on January 24, 2020, because of findings of the Study 301 interim analysis #2. Many of these subjects have since resumed treatment following treatment interruptions lasting 3 to 19 months, and some younger subjects also resumed treatment after reaching age 14.

The FOP full analysis set (FOP-FAS) includes all subjects enrolled or dosed in FOP clinical studies, including the NHS. The FOP flare-up (F) full analysis set (FOP-F-FAS) includes all subjects with at least one flare-up in the NHS (monitored either by phone contacts, or by in-clinic evaluation), or at least one palovarotene- or placebo-treated flare-up while on-study in a FOP interventional study.

Safety data are also included in the NDA for pediatric patients with multiple osteochondromas (MO) in study PVO-2A-201 (MO-FAS); six phase 1 and 2 studies in adults with COPD (COPD-FAS); and 12 single- and multiple-dose studies in healthy volunteers (HV-FAS). These datasets were not pooled with the FOP data based on differences in study designs and populations.

In addition to routine safety assessments (AEs, concomitant medications, vital signs, ECG, physical exam, safety labs), the FOP palovarotene studies included frequent pregnancy testing, the Columbia-Suicide Severity Rating Scale (C-SSRS), and assessments related to bone safety and growth; the latter are discussed in Section [7.7.1](#). Because patients in the NHS were not treated, AE collection was limited to events resulting from study procedures.

No major data quality or integrity issues were identified that would preclude performing a safety review for this NDA. There were no major identified issues with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to MedDRA preferred terms for the events reported in Studies 201, 202A/B/C and 301 were reviewed and found to be acceptable. Treatment-emergent AEs (TEAEs) were protocol-defined as AEs that developed or worsened after administration of the first dose to 7 days after the last dose of study drug. All AEs in the reviewed trials were coded using MedDRA version 22.0 and reported according to standard criteria for mild, moderate or severe. These methods were found to be acceptable.

7.5. Adequacy of Clinical Safety Database

The NDA 215559 safety database for palovarotene is adequate for the proposed FOP indication and dosage regimens. The FOP phase 2 and 3 studies enrolled a relatively large proportion of the known patients with this disease globally. Although comparison safety data in untreated FOP patients is very limited, there is substantial placebo-controlled data available for palovarotene in prior COPD studies (adults) and a multiple osteochondromas study (pediatric), and the safety profile of retinoids as a drug class is well known from extensive experience with other retinoids.

A total of 164 patients with FOP received at least one dose of palovarotene, including 139 patients in the Applicant's intended target population (age $\geq 8/10$ years). The following table summarizes demographic characteristics for subjects in this target population who received, in any phase 2 or phase 3 study, the chronic palovarotene (PVO) 5 mg regimen (N=131), the PVO 20/10 flare-up regimen (N=105), or any PVO regimen (N=139).

Table 43. Baseline Demographic and Clinical Characteristics, Age at First Entry $\geq 8/10$ Years (FAS), Trial ISS

Characteristic	Chronic PVO 5 mg (Nonflare Dosing) N=131	PVO 20/10 mg (Flare-up Dosing) N=105	*PVO Total (All Exposed Subjects) N=139
Sex, n (%)			
Female	64 (49)	50 (48)	69 (50)
Male	67 (51)	55 (52)	70 (50)
Age, years			
Mean (SD)	18.9 (9.3)	18.6 (8.9)	19.1 (9.4)
Median (min, max)	16 (8, 61)	16 (9, 61)	16 (8, 61)
Age group, years, n (%)			
<14	40 (31)	33 (31)	42 (30)
≥ 14	91 (70)	72 (69)	97 (70)
Race, n (%)			
Asian	6 (5)	5 (5)	7 (5)
Black or African American	0	0	2 (1)
Multiple	5 (4)	3 (3)	6 (4)
Not Available	0	0	6 (4)
Other	1 (1)	0	1 (1)
Unknown	9 (7)	7 (7)	9 (7)
White	102 (78)	83 (79)	106 (76)
Missing	8 (6)	7 (7)	8 (6)
Ethnicity, n (%)			
Hispanic or Latino	19 (15)	15 (14)	22 (16)
Not Hispanic or Latino	94 (72)	75 (71)	99 (71)
Not Reported	18 (14)	15 (14)	20 (14)

Characteristic	Chronic PVO 5 mg (Nonflare Dosing) N=131	PVO 20/10 mg (Flare-up Dosing) N=105	*PVO Total (All Exposed Subjects) N=139
Country of participation, n (%)			
Argentina	5 (4)	3 (3)	5 (4)
Australia	8 (6)	4 (4)	8 (6)
Brazil	5 (4)	4 (4)	5 (4)
Canada	4 (3)	4 (4)	4 (3)
Spain	4 (3)	3 (3)	4 (3)
France	17 (13)	14 (13)	19 (14)
Great Britain	12 (9)	12 (11)	12 (9)
Italy	6 (5)	4 (4)	6 (4)
Japan	2 (2)	2 (2)	2 (1)
Sweden	6 (5)	5 (5)	6 (4)
United States	63 (48)	51 (49)	71 (51)

Source: adsl.xpt; Software: R

*Includes all exposed subjects 201, 202A, 202B, 202C, 301

Subjects may overlap between study arms.

All doses reduced by weight in subjects who were <90% skeletally mature by x-ray

Abbreviations: N, number of patients in treatment group; n, number of patients with given characteristic; PVO, Palovarotene; SD, standard deviation

The following table summarizes disposition for the target population.

Table 44. Patient Disposition, Trial ISS

Disposition Outcome	Chronic PVO 5 mg (Nonflare Dosing) N=131	PVO 20/10 mg (Flare- up Dosing) N=105	*PVO Total (All Exposed Subjects) N=139
Full Analysis Set population	131	105	139
Subjects randomized/enrolled	131	105	139
End of treatment, n (%)	41 (31)	31 (30)	41 (30)
Adverse event	5 (4)	3 (3)	5 (4)
Missing	17 (13)	13 (12)	17 (12)
Noncompliance	1 (1)	0	1 (1)
Other	4 (3)	2 (2)	4 (3)
Withdrawal by subject	14 (11)	13 (12)	14 (10)
End of study†, n (%)	60 (46)	48 (46)	65 (47)
Adverse event	9 (7)	6 (6)	9 (7)
Lost to follow-up	1 (1)	1 (1)	1 (1)
Noncompliance	1 (1)	0	1 (1)
Other	14 (11)	12 (11)	15 (11)
Applicant request	24 (18)	19 (18)	29 (21)
Withdrawal by subject	23 (18)	18 (17)	23 (17)

Source: adsl.xpt; Software: R

Median study duration is 12 weeks for Placebo/Untreated, 165.7 weeks for Chronic PVO 5 mg, 12.1 weeks for Flare-up PVO 5/2.5 mg, 50.4 weeks for Flare-up PVO 10/5 mg, 164.4 weeks for Flare-up PVO 20/10 mg, and 316.3 weeks for PVO Total.

Two subjects were untreated in 202B.

†Some subjects may have more than one reason for study discontinuation.

*Includes all exposed subjects 201, 202A, 202B, 202C, 301

Subjects may overlap between study arms.

All doses reduced by weight in subjects who were <90% skeletally mature by x-ray

Abbreviations: n, number of patients in specified population or group; N, number of patients in treatment arm; NA, not applicable; PVO, Palovarotene

The following table summarizes the duration of each of the 3 categories of exposure among target-population subjects, as of the July 30, 2021, ISS data cutoff. Mean duration of exposure per subject was 79 weeks and 35 weeks for the chronic 5 mg and 20/10 Flare-up regimens, respectively.

Table 45. Duration of Exposure, On-Study, Age at First Entry $\geq$ 8/10 Years (FAS), Trial ISS

Parameter	Chronic PVO 5 mg PVO 20/10 mg (Flare-up Dosing) (Nonflare Dosing) N=131	N=105	*PVO Total (All Exposed Subjects) N=139
Duration of treatment, weeks			
Mean (SD)	78.9 (50.4)	35.1 (25.8)	102.4 (59.4)
Median (Q1, Q3)	71.3 (44.9, 92.9)	28.1 (14.5, 46.7)	82.6 (72.9, 130.7)
Min, Max	0.9, 224.7	0.3, 134.1	4.1, 242.3
Total exposure (person years)	198.1	68.6	272.7
Patients treated, by duration, n (%)			
>0 to 3 months	9 (7)	24 (23)	8 (6)
>3 to 6 months	6 (5)	24 (23)	4 (3)
>6 to 9 months	11 (8)	19 (18)	3 (2)
>9 to 12 months	12 (9)	15 (14)	2 (1)
>12 to 18 months	38 (29)	13 (12)	38 (27)
>18 to 24 months	29 (22)	5 (5)	45 (32)
>24 to 30 months	8 (6)	1 (1)	4 (3)
>30 to 42 months	9 (7)	1 (1)	13 (9)
>42 to 54 months	9 (7)	0	21 (15)
>54 to 66 months	0	0	1 (1)
Missing	0	3 (3)	0

Source: adsl.xpt, adex.xpt; Software: R

Median study duration is 12 weeks for Placebo/Untreated, 165.7 weeks for Chronic PVO 5 mg, 12.1 weeks for Flare-up PVO 5/2.5 mg, 50.4 weeks for Flare-up PVO 10/5 mg, 164.4 weeks for Flare-up PVO 20/10 mg, and 316.3 weeks for PVO Total.

*Includes all exposed subjects 201, 202A, 202B, 202C, 301

Subjects may overlap between study arms. All doses reduced by weight in subjects who were <90% skeletally mature by x-ray
Abbreviations: FAS, full analysis set; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; PVO, Palovarotene; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Safety Findings and Concerns

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary

The following table presents an overview of treatment-emergent adverse events for the $\geq$ 8- to 10-year-old study population. There were no deaths during treatment or related to a TEAE. Serious AEs were reported in 36% of subjects overall, including in 24% of subjects receiving the chronic 5 mg regimen, and in 23% of subjects receiving the 20/10 mg flare-up regimen. These two regimens were also similar with regard to overall AEs (97% versus 94%) and AEs leading to drug interruption or discontinuation. However, AEs leading to dose reduction were more frequent among subjects receiving the higher 20/10 mg doses compared to chronic 5 mg dose (43% versus 8%).

Table 46. Overview of Adverse Events¹, Age at First Entry ≥8/10 Years (FAS), Trial ISS

Event Category	Chronic PVO 5 mg (Nonflare Dosing) N=131 n (%)	PVO 20/10 mg (Flare- up Dosing) N=105 n (%)	*PVO Total (All Exposed Subjects) N=139 n (%)
SAE	31 (23.7)	24 (22.9)	50 (36.0)
SAEs with fatal outcome	0	0	0
Life-threatening SAEs	0	0	0
AE leading to permanent discontinuation of study drug	6 (4.6)	5 (4.8)	11 (7.9)
AE leading to dose modification of study drug	29 (22.1)	52 (49.5)	69 (49.6)
AE leading to interruption of study drug	22 (16.8)	20 (19.0)	37 (26.6)
AE leading to reduction of study drug	10 (7.6)	45 (42.9)	50 (36.0)
Any AE	127 (96.9)	99 (94.3)	139 (100)
Severe and worse	22 (16.8)	20 (19.0)	33 (23.7)
Moderate	59 (45.0)	53 (50.5)	79 (56.8)
Mild	46 (35.1)	26 (24.8)	27 (19.4)

Source: adae.xpt; Software: R

¹Treatment-emergent adverse events defined as AEs that developed or worsened after administration of the first dose of study drug to the end of dosing as follows: (first dose date) ≤ (AE start date) ≤ (last dose date) + 7 days. For the FOP-FAS, TEAEs also included AEs after enrollment for subjects in Study PVO-1A-202/Part A who were not dosed due to the absence of a flare-up.

Median study duration is 12 weeks for Placebo/Untreated, 165.7 weeks for Chronic PVO 5 mg, 12.1 weeks for Flare-up PVO 5/2.5 mg, 50.4 weeks for Flare-up PVO 10/5 mg, 164.4 weeks for Flare-up PVO 20/10 mg, and 316.3 weeks for PVO Total.

Severity as assessed by the investigator.

*Includes all exposed subjects 201, 202A, 202B, 202C, 301

Subjects may overlap between study arms.

Abbreviations: AE, adverse event; FAS, full analysis set; FOP-FAS, fibrodysplasia ossificans progressiva full analysis set; N, number of patients in treatment arm; n, number of patients with at least one event; PVO, Palovarotene; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.1.2. Deaths

No deaths were reported during palovarotene treatment or for 30 days post-treatment in the FOP-FAS. In Study 301, a 13-year-old subject with a history of restrictive lung disease died 2.5 months after discontinuing palovarotene treatment because of disease progression and difficulty traveling. A postmortem exam determined the cause of death as restrictive lung disease from complications of FOP.

A 38-year-old female in the FOP NHS, with substantial disease burden based on high CAJIS score, died of a cardiac arrest. This subject never received palovarotene.

There were no deaths reported in the MO-FAS or HV-FAS.

In the COPD-FAS, most deaths were from cardiovascular or respiratory events and were related to the subjects' age and underlying disease. None of the deaths in the COPD-FAS were assessed as related to study treatment by the Investigator.

7.6.1.3. Serious Adverse Events

Serious adverse events (SAEs) occurred in 36% of palovarotene-treated FOP subjects age $\geq 8/10$ years. This high incidence is not unexpected given the severe morbidity related to the underlying disease. The most common SOC classes of serious adverse events were musculoskeletal and connective tissue disorders (13.7% of subjects) and infections and infestations (10.1%). These included musculoskeletal events associated with FOP and/or retinoid use including premature physeal closure (PT: epiphyses premature fusion, which is discussed in Section 7.7.1), arthralgia, back pain and pain in extremity. SAEs of “condition aggravated” represent FOP flare-ups that did not meet protocol criteria for treatment; this issue is discussed in Section 7.7.3.

Table 47. Patients With Serious Adverse Events by System Organ Class and Preferred Term, Age at First Entry $\geq 8/10$ Years (FAS), Trial ISS

System Organ Class Preferred Term	Chronic PVO 5 mg (Nonflare Dosing) N=131 n (%)	PVO 20/10 mg (Flare-up Dosing) N=105 n (%)	*PVO Total (All Exposed Subjects) N=139 n (%)
Any SAE	31 (23.7)	24 (22.9)	50 (36.0)
Blood and lymphatic system disorders (SOC)	0	1 (1.0)	1 (0.7)
Anemia	0	1 (1.0)	1 (0.7)
Gastrointestinal disorders (SOC)	6 (4.6)	3 (2.9)	9 (6.5)
Abdominal pain	1 (0.8)	1 (1.0)	2 (1.4)
Dysphagia	1 (0.8)	0	1 (0.7)
Incarcerated inguinal hernia	1 (0.8)	0	1 (0.7)
Esophageal stenosis	1 (0.8)	0	1 (0.7)
Small intestinal obstruction	1 (0.8)	0	1 (0.7)
Tooth disorder	1 (0.8)	0	1 (0.7)
Tooth impacted	1 (0.8)	1 (1.0)	2 (1.4)
Diarrhea	0	1 (1.0)	1 (0.7)
Mallory-Weiss syndrome	0	1 (1.0)	1 (0.7)
Vomiting	0	1 (1.0)	1 (0.7)
General disorders and administration site conditions (SOC)	2 (1.5)	7 (6.7)	9 (6.5)
Condition aggravated	1 (0.8)	3 (2.9)	3 (2.2)
Pain	1 (0.8)	1 (1.0)	2 (1.4)
Oedema peripheral	0	1 (1.0)	1 (0.7)
Peripheral swelling	0	2 (1.9)	2 (1.4)
Vessel puncture site pain	0	0	1 (0.7)
Infections and infestations (SOC)	7 (5.3)	8 (7.6)	14 (10.1)
Corona virus infection	4 (3.1)	0	4 (2.9)
Appendicitis	1 (0.8)	0	1 (0.7)
Bacterial sepsis	1 (0.8)	0	1 (0.7)
Influenza	1 (0.8)	0	1 (0.7)
Klebsiella bacteremia	1 (0.8)	0	1 (0.7)
Pneumonia	1 (0.8)	3 (2.9)	4 (2.9)
Cellulitis	0	3 (2.9)	3 (2.2)
Escherichia sepsis	0	1 (1.0)	1 (0.7)
Gastroenteritis	0	1 (1.0)	1 (0.7)
Hemophilus infection	0	1 (1.0)	1 (0.7)
Mycoplasma infection	0	1 (1.0)	1 (0.7)
Staphylococcal sepsis	0	1 (1.0)	1 (0.7)
Urosepsis	0	1 (1.0)	1 (0.7)

System Organ Class Preferred Term	Chronic PVO 5 mg (Nonflare Dosing) N=131 n (%)	PVO 20/10 mg (Flare-up Dosing) N=105 n (%)	*PVO Total (All Exposed Subjects) N=139 n (%)
Injury, poisoning and procedural complications (SOC)	6 (4.6)	4 (3.8)	9 (6.5)
Exposure to communicable disease	3 (2.3)	0	3 (2.2)
Extraskkeletal ossification	1 (0.8)	0	1 (0.7)
Femur fracture	1 (0.8)	1 (1.0)	1 (0.7)
Post procedural hematoma	1 (0.8)	0	1 (0.7)
Radius fracture	1 (0.8)	0	1 (0.7)
Ankle fracture	0	1 (1.0)	1 (0.7)
Fracture	0	1 (1.0)	1 (0.7)
Humerus fracture	0	1 (1.0)	1 (0.7)
Skull fracture	0	1 (1.0)	1 (0.7)
Subdural hemorrhage	0	1 (1.0)	1 (0.7)
Traumatic fracture	0	1 (1.0)	1 (0.7)
Metabolism and nutrition disorders (SOC)	0	1 (1.0)	1 (0.7)
Malnutrition	0	1 (1.0)	1 (0.7)
Musculoskeletal and connective tissue disorders (SOC)	9 (6.9)	11 (10.5)	19 (13.7)
Epiphyses premature fusion	5 (3.8)	4 (3.8)	9 (6.5)
Aneurysmal bone cyst	1 (0.8)	0	1 (0.7)
Arthralgia	1 (0.8)	3 (2.9)	3 (2.2)
Back pain	1 (0.8)	1 (1.0)	2 (1.4)
Epiphyseal disorder	1 (0.8)	0	1 (0.7)
Pain in extremity	1 (0.8)	2 (1.9)	3 (2.2)
Mobility decreased	0	1 (1.0)	1 (0.7)
Muscle tightness	0	1 (1.0)	1 (0.7)
Neck pain	0	0	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.8)	0	1 (0.7)
Uterine leiomyoma	1 (0.8)	0	1 (0.7)
Nervous system disorders (SOC)	1 (0.8)	4 (3.8)	5 (3.6)
Syncope	1 (0.8)	1 (1.0)	2 (1.4)
Epilepsy	0	1 (1.0)	1 (0.7)
Generalized tonic-clonic seizure	0	1 (1.0)	1 (0.7)
Myoclonus	0	1 (1.0)	1 (0.7)
Seizure	0	1 (1.0)	1 (0.7)
Psychiatric disorders (SOC)	0	0	1 (0.7)
Drug dependence	0	0	1 (0.7)
Renal and urinary disorders (SOC)	0	3 (2.9)	3 (2.2)
Hematuria	0	1 (1.0)	1 (0.7)
Renal failure	0	1 (1.0)	1 (0.7)
Urinary retention	0	1 (1.0)	1 (0.7)

System Organ Class Preferred Term	Chronic PVO 5 mg (Nonflare Dosing) N=131 n (%)	PVO 20/10 mg (Flare-up Dosing) N=105 n (%)	*PVO Total (All Exposed Subjects) N=139 n (%)
Respiratory, thoracic and mediastinal disorders (SOC)	3 (2.3)	1 (1.0)	4 (2.9)
Asthma	1 (0.8)	0	1 (0.7)
Dyspnea	1 (0.8)	0	1 (0.7)
Respiratory distress	1 (0.8)	1 (1.0)	2 (1.4)
Hypoxia	0	1 (1.0)	1 (0.7)
Vascular disorders (SOC)	1 (0.8)	0	1 (0.7)
Lymphedema	1 (0.8)	0	1 (0.7)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that developed or worsened after administration of the first dose of study drug to the end of dosing as follows: (first dose date) ≤ (AE start date) ≤ (last dose date) + 7 days. For the FOP-FAS, TEAEs also included AEs after enrollment for subjects in Study PVO-1A-202/Part A who were not dosed due to the absence of a flare-up.

Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Median study duration is 12 weeks for Placebo/Untreated, 165.7 weeks for Chronic PVO 5 mg, 12.1 weeks for Flare-up PVO 5/2.5 mg, 50.4 weeks for Flare-up PVO 10/5 mg, 164.4 weeks for Flare-up PVO 20/10 mg, and 316.3 weeks for PVO Total.

*Includes all exposed subjects 201, 202A, 202B, 202C, 301

Subjects may overlap between study arms.

Abbreviations: AE, adverse event; FAS, full analysis set; FOP-FAS, fibrodysplasia ossificans progressiva full analysis set; N, number of patients in treatment arm; n, number of patients with adverse event; PVO, Palovarotene; SAE, severe adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event

Retinoids, and hypervitaminosis A, have been associated with CNS adverse events including headache, benign intracranial hypertension/ pseudotumor cerebri and seizures/convulsions. In the FOP-FAS, two subjects (16 y/o female and 32 y/o male) experienced SAEs of tonic-clonic seizure or epilepsy during treatment with 20/10 mg flare-up dosing in Study 202B/C. In both cases, the subject had no prior history of a seizure and was begun on anticonvulsant treatment. In Study 301, a 15-year-old female with prior history of febrile convulsions experienced an SAE of syncope and later a nonserious syncopal seizure during flare-up treatment. In the MO study, a 7-year-old male with a history of febrile seizures experienced an SAE of status epilepticus on Day 199 of treatment with palovarotene 5 mg. Each of these subjects continued palovarotene treatment. A prior history of seizures was reported by 11% of subjects in the FOP NHS, and by 4% of Study 301 subjects at enrollment. In COPD studies, one subject (out of 458) treated with palovarotene 5 mg experienced an SAE of epilepsy, considered not related to treatment by the investigator. Based on a high background incidence of seizure in patients with FOP, these data do not support an association of palovarotene with seizures. One subject in Study 202, a 24-year-old female with a long history of myoclonus, discontinued the study due to an SAE of myoclonus, which appears to be associated with FOP.

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events

Among FOP subjects age $\geq 8/10$ years, treatment was discontinued due to an AE in 11 subjects (8%) and the incidence was similar between chronic and flare-up regimens (5% each). Infections and infestations were most common (4 discontinuations, 3% of subjects). Mucocutaneous AEs, such as dry skin, generally responded to dose reduction and resulted in only 2 discontinuations.

Table 48. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Age at First Entry $\geq 8/10$ Years (FAS), Trial ISS

System Organ Class Preferred Term	Chronic PVO 5 mg (Nonflare Dosing) N=131 n (%)	PVO 20/10 mg (Flare-up Dosing) N=105 n (%)	*PVO Total (All Exposed Subjects) N=139 n (%)
Any AE leading to Discontinuation	6 (4.6)	5 (4.8)	11 (7.9)
Infections and infestations (SOC)	1 (0.8)	3 (2.9)	4 (2.9)
Furuncle	1 (0.8)	0	1 (0.7)
Cellulitis	0	1 (1.0)	1 (0.7)
Hemophilus infection	0	1 (1.0)	1 (0.7)
Localized infection	0	1 (1.0)	1 (0.7)
Investigations (SOC)	1 (0.8)	0	1 (0.7)
Amylase increased	1 (0.8)	0	1 (0.7)
Lipase increased	1 (0.8)	0	1 (0.7)
Metabolism and nutrition disorders (SOC)	0	1 (1.0)	1 (0.7)
Malnutrition	0	1 (1.0)	1 (0.7)
Musculoskeletal and connective tissue disorders (SOC)	1 (0.8)	1 (1.0)	2 (1.4)
Epiphyses premature fusion	1 (0.8)	0	1 (0.7)
Mobility decreased	0	1 (1.0)	1 (0.7)
Nervous system disorders (SOC)	1 (0.8)	0	1 (0.7)
Myoclonus	1 (0.8)	0	1 (0.7)
Psychiatric disorders (SOC)	1 (0.8)	0	1 (0.7)
Intentional self-injury	1 (0.8)	0	1 (0.7)
Skin and subcutaneous tissue disorders (SOC)	1 (0.8)	1 (1.0)	2 (1.4)
Dry skin	1 (0.8)	1 (1.0)	2 (1.4)
Erythema	1 (0.8)	0	1 (0.7)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that developed or worsened after administration of the first dose of study drug to the end of dosing as follows: (first dose date) $\leq$ (AE start date) $\leq$ (last dose date) + 7 days. For the FOP-FAS, TEAEs also included AEs after enrollment for subjects in Study PVO-1A-202/Part A who were not dosed due to the absence of a flare-up.

Median study system duration is 12 weeks for Placebo/Untreated, 165.7 weeks for Chronic PVO 5 mg, 12.1 weeks for Flare-up PVO 5/2.5 mg, 50.4 weeks for Flare-up PVO 10/5 mg, 164.4 weeks for Flare-up PVO 20/10 mg, and 316.3 weeks for PVO Total.

*Includes all exposed subjects 201, 202A, 202B, 202C, 301

Subjects may overlap between study arms.

Abbreviations: AE, adverse event; FAS, full analysis set; FOP-FAS, fibrodysplasia ossificans progressiva full analysis set; N, number of patients in treatment arm; n, number of patients with adverse event; PVO, Palovarotene; SOC, system organ class; TEAE, treatment-emergent adverse event

7.6.1.5. Treatment-Emergent Adverse Events

Mucocutaneous adverse effects are characteristic of retinoids and hypervitaminosis A and were reported by most subjects. The most frequent AEs by the FDA Medical Dictionary for Regulatory Activities query (FMQ) were rash (62%), dry mouth (59%), pruritis (57%), arthralgia (49%), bacterial infection (46%), alopecia (42%) and hemorrhage (40%). In general, the pattern of AEs was similar between chronic and flare-up dosing, with no evidence of dose dependence.

Table 49. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Age at First Entry ≥8/10 Years (FAS), Trial ISS

System Organ Class FMQ (Narrow)	Chronic PVO 5 mg (Nonflare Dosing) N=131 n (%)	PVO 20/10 mg (Flare-up Dosing) N=105 n (%)	*PVO Total (All Exposed Subjects) N=139 n (%)
Blood and lymphatic system disorders (SOC)			
Anemia	1 (0.8)	3 (2.9)	6 (4.3)
Thrombocytopenia	1 (0.8)	2 (1.9)	2 (1.4)
Cardiac disorders (SOC)			
Arrhythmia	8 (6.1)	5 (4.8)	13 (9.4)
Tachycardia	7 (5.3)	5 (4.8)	12 (8.6)
Palpitations	0	3 (2.9)	4 (2.9)
Systemic Hypertension	0	2 (1.9)	2 (1.4)
Ear and labyrinth disorders (SOC)			
Vertigo	2 (1.5)	1 (1.0)	3 (2.2)
Endocrine disorders (SOC)			
Hyperglycemia	2 (1.5)	5 (4.8)	8 (5.8)
Gastrointestinal disorders (SOC)			
Dry Mouth	52 (39.7)	35 (33.3)	82 (59.0)
Abdominal Pain	21 (16.0)	16 (15.2)	34 (24.5)
Nausea	20 (15.3)	14 (13.3)	34 (24.5)
Vomiting	19 (14.5)	14 (13.3)	33 (23.7)
Diarrhea	17 (13.0)	8 (7.6)	21 (15.1)
Dyspepsia	9 (6.9)	7 (6.7)	14 (10.1)
Constipation	4 (3.1)	8 (7.6)	13 (9.4)
General disorders and administration site conditions (SOC)			
Fall	13 (9.9)	9 (8.6)	21 (15.1)
Dizziness	12 (9.2)	13 (12.4)	24 (17.3)
Peripheral Edema	12 (9.2)	20 (19.0)	31 (22.3)
Pyrexia	12 (9.2)	12 (11.4)	22 (15.8)
Decreased Appetite	7 (5.3)	9 (8.6)	17 (12.2)
Fatigue	7 (5.3)	12 (11.4)	19 (13.7)
Local Administration Reaction	3 (2.3)	2 (1.9)	7 (5.0)
Volume Depletion	2 (1.5)	1 (1.0)	3 (2.2)
Hepatobiliary disorders (SOC)			
Hepatic Injury	2 (1.5)	7 (6.7)	8 (5.8)
Immune system disorders (SOC)			
Hypersensitivity	13 (9.9)	21 (20.0)	28 (20.1)
Angioedema	1 (0.8)	0	1 (0.7)

System Organ Class	Chronic PVO 5 mg (Nonflare Dosing) N=131 n (%)	PVO 20/10 mg (Flare-up Dosing) N=105 n (%)	*PVO Total (All Exposed Subjects) N=139 n (%)
FMQ (Narrow)			
Infections and infestations (SOC)			
Bacterial Infection	42 (32.1)	31 (29.5)	64 (46.0)
Nasopharyngitis	35 (26.7)	14 (13.3)	48 (34.5)
Viral Infection	19 (14.5)	10 (9.5)	31 (22.3)
Fungal Infection	13 (9.9)	10 (9.5)	21 (15.1)
Purulent Material	6 (4.6)	2 (1.9)	7 (5.0)
Pneumonia	4 (3.1)	5 (4.8)	8 (5.8)
Metabolism and nutrition disorders (SOC)			
Lipid Disorder	3 (2.3)	4 (3.8)	8 (5.8)
Cachexia	2 (1.5)	2 (1.9)	4 (2.9)
Musculoskeletal and connective tissue disorders (SOC)			
Arthralgia	47 (35.9)	32 (30.5)	68 (48.9)
Back Pain	22 (16.8)	12 (11.4)	30 (21.6)
Myalgia	15 (11.5)	9 (8.6)	26 (18.7)
Fracture	7 (5.3)	6 (5.7)	11 (7.9)
Tendinopathy	3 (2.3)	1 (1.0)	4 (2.9)
Osteoporosis	0	1 (1.0)	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)			
Malignancy	1 (0.8)	0	1 (0.7)
Nervous system disorders (SOC)			
Headache	25 (19.1)	20 (19.0)	45 (32.4)
Paresthesia	4 (3.1)	11 (10.5)	16 (11.5)
Syncope	3 (2.3)	1 (1.0)	4 (2.9)
Seizure	2 (1.5)	3 (2.9)	3 (2.2)
Somnolence	2 (1.5)	2 (1.9)	4 (2.9)
Tremor	0	2 (1.9)	2 (1.4)
Psychiatric disorders (SOC)			
Depression	10 (7.6)	8 (7.6)	16 (11.5)
Anxiety	8 (6.1)	3 (2.9)	12 (8.6)
Irritability	5 (3.8)	5 (4.8)	12 (8.6)
Insomnia	4 (3.1)	5 (4.8)	9 (6.5)
Self-Harm	4 (3.1)	3 (2.9)	7 (5.0)
Arthritis	1 (0.8)	1 (1.0)	2 (1.4)
Parasomnia	1 (0.8)	0	2 (1.4)
Psychosis	0	1 (1.0)	1 (0.7)
Study Agent Abuse Potential	0	1 (1.0)	1 (0.7)
Renal and urinary disorders (SOC)			
Renal and Urinary Tract Infection	9 (6.9)	6 (5.7)	14 (10.1)
Urinary Retention	0	2 (1.9)	2 (1.4)
Reproductive system and breast disorders (SOC)			
Abnormal Uterine Bleeding	2 (1.5)	2 (1.9)	5 (3.6)
Bacterial Vaginosis	1 (0.8)	1 (1.0)	1 (0.7)
Decreased Menstrual Bleeding	1 (0.8)	0	1 (0.7)
Erectile Dysfunction	1 (0.8)	0	1 (0.7)
Sexual Dysfunction	1 (0.8)	0	1 (0.7)
Excessive Menstrual Bleeding	0	1 (1.0)	2 (1.4)

System Organ Class	Chronic PVO 5 mg (Nonflare Dosing) N=131 n (%)	PVO 20/10 mg (Flare-up Dosing) N=105 n (%)	*PVO Total (All Exposed Subjects) N=139 n (%)
FMQ (Narrow)			
Respiratory, thoracic and mediastinal disorders (SOC)			
Cough	14 (10.7)	11 (10.5)	25 (18.0)
Dyspnea	6 (4.6)	5 (4.8)	11 (7.9)
Bronchospasm	2 (1.5)	1 (1.0)	3 (2.2)
Respiratory Failure	2 (1.5)	3 (2.9)	5 (3.6)
Skin and subcutaneous tissue disorders (SOC)			
Rash	60 (45.8)	56 (53.3)	86 (61.9)
Pruritus	46 (35.1)	51 (48.6)	79 (56.8)
Alopecia	32 (24.4)	31 (29.5)	59 (42.4)
Erythema	25 (19.1)	34 (32.4)	52 (37.4)
Urticaria	3 (2.3)	1 (1.0)	5 (3.6)
Vascular disorders (SOC)			
Hemorrhage	41 (31.3)	25 (23.8)	56 (40.3)
Hypotension	1 (0.8)	0	1 (0.7)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that developed or worsened after administration of the first dose of study drug to the end of dosing as follows: (first dose date) ≤ (AE start date) ≤ (last dose date) +7 days. For the FOP-FAS, TEAEs also included AEs after enrollment for subjects in Study PVO-1A-202/Part A who were not dosed due to the absence of a flare-up.

Median study duration is 12 weeks for Placebo/Untreated, 165.7 weeks for Chronic PVO 5 mg, 12.1 weeks for Flare-up PVO 5/2.5 mg, 50.4 weeks for Flare-up PVO 10/5 mg, 164.4 weeks for Flare-up PVO 20/10 mg, and 316.3 weeks for PVO Total.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

*Includes all exposed subjects 201, 202A, 202B, 202C, 301

Subjects may overlap between study arms.

Abbreviations: AE, adverse event; FAS, full analysis set; FOP-FAS, fibrodysplasia ossificans progressiva full analysis set; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PVO, Palovarotene; SOC, system organ class; TEAE, treatment-emergent adverse event

The following table lists TEAEs in descending order of frequency by preferred term, with an incidence of at least 5.5%.

Table 50. Patients With Common Adverse Events Occurring at ≥5.5% Frequency, Age at First Entry ≥8/10 Years (FAS), Trial ISS

Preferred Term	Chronic PVO 5 mg (Nonflare Dosing) N=131 n (%)	PVO 20/10 mg (Flare-up Dosing) N=105 n (%)	*PVO Total (All Exposed Subjects) N=139 n (%)
Any AE	127 (96.9)	99 (94.3)	139 (100)
Dry skin	80 (61.1)	60 (57.1)	112 (80.6)
Lip dry	50 (38.2)	30 (28.6)	79 (56.8)
Arthralgia	47 (35.9)	32 (30.5)	68 (48.9)
Pain in extremity	38 (29.0)	29 (27.6)	58 (41.7)
Alopecia	32 (24.4)	31 (29.5)	59 (42.4)
Pruritus	30 (22.9)	34 (32.4)	59 (42.4)
Rash	29 (22.1)	26 (24.8)	46 (33.1)
Upper respiratory tract infection	28 (21.4)	9 (8.6)	37 (26.6)
Nasopharyngitis	26 (19.8)	12 (11.4)	33 (23.7)
Erythema	23 (17.6)	31 (29.5)	48 (34.5)

Preferred Term	Chronic PVO 5 mg (Nonflare Dosing) N=131	PVO 20/10 mg (Flare-up Dosing) N=105	*PVO Total (All Exposed Subjects) N=139
	n (%)	n (%)	n (%)
Pruritus generalized	23 (17.6)	24 (22.9)	43 (30.9)
Headache	22 (16.8)	18 (17.1)	40 (28.8)
Back pain	20 (15.3)	12 (11.4)	29 (20.9)
Nausea	20 (15.3)	14 (13.3)	34 (24.5)
Skin exfoliation	20 (15.3)	30 (28.6)	43 (30.9)
Vomiting	19 (14.5)	14 (13.3)	33 (23.7)
Musculoskeletal pain	18 (13.7)	14 (13.3)	31 (22.3)
Diarrhea	17 (13.0)	8 (7.6)	21 (15.1)
Contusion	16 (12.2)	5 (4.8)	20 (14.4)
Joint swelling	15 (11.5)	14 (13.3)	29 (20.9)
Cough	14 (10.7)	11 (10.5)	24 (17.3)
Eczema	14 (10.7)	9 (8.6)	23 (16.5)
Epistaxis	14 (10.7)	10 (9.5)	21 (15.1)
Neck pain	14 (10.7)	9 (8.6)	23 (16.5)
Skin abrasion	14 (10.7)	23 (21.9)	33 (23.7)
Dry eye	13 (9.9)	23 (21.9)	37 (26.6)
Fall	13 (9.9)	9 (8.6)	21 (15.1)
Paronychia	13 (9.9)	12 (11.4)	22 (15.8)
Drug eruption	12 (9.2)	19 (18.1)	25 (18.0)
Joint range of motion decreased	12 (9.2)	4 (3.8)	15 (10.8)
Abdominal pain	11 (8.4)	10 (9.5)	24 (17.3)
Ear infection	11 (8.4)	7 (6.7)	16 (11.5)
Oropharyngeal pain	11 (8.4)	9 (8.6)	18 (12.9)
Pain in jaw	11 (8.4)	5 (4.8)	14 (10.1)
Pyrexia	11 (8.4)	12 (11.4)	21 (15.1)
Swelling	11 (8.4)	6 (5.7)	15 (10.8)
Chapped lips	10 (7.6)	13 (12.4)	25 (18.0)
Musculoskeletal chest pain	10 (7.6)	9 (8.6)	17 (12.2)
Myalgia	10 (7.6)	8 (7.6)	19 (13.7)
Dry mouth	9 (6.9)	6 (5.7)	18 (12.9)
Urinary tract infection	9 (6.9)	4 (3.8)	12 (8.6)
Gastroenteritis	8 (6.1)	3 (2.9)	11 (7.9)
Peripheral swelling	8 (6.1)	15 (14.3)	23 (16.5)
Skin irritation	8 (6.1)	8 (7.6)	15 (10.8)
Anxiety	7 (5.3)	3 (2.9)	11 (7.9)
Decreased appetite	7 (5.3)	9 (8.6)	17 (12.2)
Depressed mood	7 (5.3)	5 (4.8)	12 (8.6)
Ingrowing nail	7 (5.3)	10 (9.5)	13 (9.4)
Tachycardia	7 (5.3)	4 (3.8)	11 (7.9)
Abdominal pain upper	6 (4.6)	6 (5.7)	10 (7.2)
Decubitus ulcer	6 (4.6)	5 (4.8)	10 (7.2)
Dizziness	6 (4.6)	10 (9.5)	15 (10.8)
Ear pain	6 (4.6)	5 (4.8)	10 (7.2)
Fatigue	6 (4.6)	10 (9.5)	16 (11.5)
Gastroesophageal reflux disease	6 (4.6)	5 (4.8)	11 (7.9)
Hypoacusis	6 (4.6)	4 (3.8)	10 (7.2)
Influenza	6 (4.6)	5 (4.8)	12 (8.6)
Limb injury	6 (4.6)	2 (1.9)	8 (5.8)
Lipase increased	6 (4.6)	4 (3.8)	11 (7.9)
Musculoskeletal discomfort	6 (4.6)	2 (1.9)	9 (6.5)
Musculoskeletal stiffness	6 (4.6)	2 (1.9)	8 (5.8)

Preferred Term	Chronic PVO 5 mg (Nonflare Dosing) N=131	PVO 20/10 mg (Flare-up Dosing) N=105	*PVO Total (All Exposed Subjects) N=139
	n (%)	n (%)	n (%)
Nasal congestion	6 (4.6)	3 (2.9)	8 (5.8)
Nasal dryness	6 (4.6)	2 (1.9)	8 (5.8)
Otitis externa	6 (4.6)	4 (3.8)	9 (6.5)
Pharyngitis	6 (4.6)	2 (1.9)	12 (8.6)
Toothache	6 (4.6)	5 (4.8)	10 (7.2)
Blister	5 (3.8)	5 (4.8)	10 (7.2)
Cheilitis	5 (3.8)	11 (10.5)	15 (10.8)
Dyspnea	5 (3.8)	5 (4.8)	10 (7.2)
Epiphyses premature fusion	5 (3.8)	4 (3.8)	9 (6.5)
Irritability	5 (3.8)	4 (3.8)	11 (7.9)
Joint stiffness	5 (3.8)	5 (4.8)	10 (7.2)
Migraine	5 (3.8)	4 (3.8)	10 (7.2)
Muscle spasms	5 (3.8)	5 (4.8)	9 (6.5)
Onychoclasia	5 (3.8)	4 (3.8)	10 (7.2)
Onychomycosis	5 (3.8)	4 (3.8)	9 (6.5)
Pollakiuria	5 (3.8)	2 (1.9)	9 (6.5)
Skin laceration	5 (3.8)	5 (4.8)	9 (6.5)
Sunburn	5 (3.8)	3 (2.9)	9 (6.5)
Acne	4 (3.1)	4 (3.8)	9 (6.5)
Blood alkaline phosphatase increased	4 (3.1)	6 (5.7)	9 (6.5)
Constipation	4 (3.1)	8 (7.6)	13 (9.4)
Dermatitis	4 (3.1)	5 (4.8)	9 (6.5)
Extraskelatal ossification	4 (3.1)	3 (2.9)	9 (6.5)
Groin pain	4 (3.1)	4 (3.8)	8 (5.8)
Hematuria	4 (3.1)	5 (4.8)	11 (7.9)
Insomnia	4 (3.1)	5 (4.8)	9 (6.5)
Oedema peripheral	4 (3.1)	6 (5.7)	11 (7.9)
Pain	4 (3.1)	4 (3.8)	8 (5.8)
Rash maculo-papular	4 (3.1)	3 (2.9)	9 (6.5)
Rhinorrhea	4 (3.1)	4 (3.8)	8 (5.8)
Skin reaction	4 (3.1)	8 (7.6)	11 (7.9)
Alanine aminotransferase increased	2 (1.5)	7 (6.7)	8 (5.8)
Proteinuria	2 (1.5)	3 (2.9)	9 (6.5)
Skin disorder	2 (1.5)	9 (8.6)	10 (7.2)
Skin infection	2 (1.5)	6 (5.7)	7 (5.0)
Flushing	1 (0.8)	6 (5.7)	7 (5.0)
Ocular hyperemia	1 (0.8)	8 (7.6)	10 (7.2)
Paresthesia	1 (0.8)	5 (4.8)	9 (6.5)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that developed or worsened after administration of the first dose of study drug to the end of dosing as follows: (first dose date) ≤ (AE start date) ≤ (last dose date) +7 days. For the FOP-FAS, TEAEs also included AEs after enrollment for subjects in Study PVO-1A-202/Part A who were not dosed due to the absence of a flare-up.

Median study duration is 12 weeks for Placebo/Untreated, 165.7 weeks for Chronic PVO 5 mg, 12.1 weeks for Flare-up PVO 5/2.5 mg, 50.4 weeks for Flare-up PVO 10/5 mg, 164.4 weeks for Flare-up PVO 20/10 mg, and 316.3 weeks for PVO Total.

Coded as MedDRA preferred terms.

*Includes all exposed subjects 201, 202A, 202B, 202C, 301

Subjects may overlap between study arms.

Abbreviations: AE, adverse event; FAS, full analysis set; FOP-FAS, fibrodysplasia ossificans progressiva full analysis set; N, number of patients in treatment arm; n, number of patients with adverse event; PVO, Palovarotene; TEAE, treatment-emergent adverse event

Severe mucocutaneous AEs were reported in 51% of FOP subjects and included skin exfoliation (31%), drug eruption (i.e., retinoid dermatitis, 18%) and blisters (7%). Mucocutaneous events were the most common reason for dose reductions, especially at the higher 20/10 mg flare-up doses; in almost all cases, subjects were able to continue treatment with lower doses and/or supportive measures such as skin lotions, lip balm, artificial tears, etc.

Because of the association of retinoids with depression and potential suicidality, the C-SSRS was administered to all study participants age ≥ 8 years in Study 301 as well as the NHS. There was no evidence of an increase in suicidal thoughts or behavior. The FMQ for depression identified 11% of subjects, and one subject discontinued treatment after 1 month due to “non-suicidal/intentional self-injury.”

Hearing impairment is a common feature of FOP and was reported by 43% of NHS subjects. Audiometry in Study 301 confirmed high rates of hearing loss at baseline; the incidence and type of abnormal clinically significant findings at 12 months was similar to baseline. Hearing impairment TEAEs were reported in 12% of palovarotene-treated subjects in the FOP-FAS, with similar incidence during chronic and flare-up treatment (7% versus 8%, respectively); none of these events were considered severe or led to discontinuation of treatment. AEs of hearing impairment were much less frequent in subjects with MO or COPD, with no imbalances between palovarotene and placebo.

In Study 201, the only FOP study with a randomized, placebo-controlled design, the highest dose group (10/5 mg), compared to 5/2.5 mg or placebo, reported higher incidence of AEs of pruritis, dry skin and arthralgia; no other apparent imbalances were noted. There were no AEs that led to discontinuation, and only one SAE (vessel puncture site pain, in 10/5 study arm). A summary of AEs among subjects age $\geq 8/10$ in this study is included in Section [17](#).

7.6.1.6. Laboratory Findings

Clinical laboratory evaluations including hematology, serum chemistry and urinalysis showed no clinically meaningful changes from baseline in mean or median values.

Triglycerides

Marked elevations have been reported in patients treated with other retinoids. In the FOP-FAS, hypertriglyceridemia AEs were reported in four subjects at the 20/10 regimen and two subjects during the chronic 5 mg period. Levels over 400 mg/dL were reported in just one subject with baseline high triglyceride (217 mg/dL) and a level of 428 mg/dL at 15 months of treatment with the chronic 5 mg dose. There were no significant trends in mean lipids during chronic or flare-up periods of the FOP studies, or in the prior COPD studies.

Lipase/Amylase

Acute pancreatitis has been reported with other retinoids, sometimes in association with elevated triglycerides. In palovarotene studies in FOP and COPD, the incidence of lipase elevations was similar between the palovarotene and placebo or untreated subjects. Lipase elevations in the FOP-FAS were transient and generally resolved while remaining on palovarotene treatment.

No TEAEs of pancreatitis were identified in the FOP-FAS, MO-FAS or the COPD-FAS populations. However, a 23-year-old white male in the HV-FAS had a SAE of pancreatitis during a DDI study with palovarotene and ketoconazole. The subject had asymptomatic mildly

elevated lipase on Day 2, received paracetamol on Day 14 for headache and initiated ketoconazole on Day 15. Lipase increased to 1084 U/L and the subject was hospitalized with mild abdominal pain. Triglycerides were normal. Palovarotene and ketoconazole were discontinued. The Investigator considered the event of pancreatitis to be possibly related to palovarotene and to paracetamol, with a possible contribution of ketoconazole by way of increasing palovarotene levels

Liver Function Tests

Other retinoids have been associated with moderate elevations of liver enzymes. In FOP studies, TEAEs of elevated alanine aminotransferase (ALT)/aspartate aminotransferase (AST) and GGT were more common during the palovarotene 20/10 mg flare-up treatment compared with chronic treatment and placebo, indicating a possible dose effect. No subjects met Hy's Law criteria for liver transaminases (AST, ALT) or AST/ALT values $>3\times\text{ULN}$ and total bilirubin values $>2\times\text{ULN}$. Hepatic steatosis was identified in the FOP-FAS and COPD-FAS but with a similar incidence between the palovarotene and placebo/untreated groups.

Vital sign measures including systolic and diastolic blood pressure, heart rate, respiratory rate and temperature showed no consistent or clinically meaningful changes from baseline associated with palovarotene treatment.

ECG parameters in FOP studies showed no clinically meaningful changes in intervals including QT, QTcF and QTcB. In addition, a thorough QT study was conducted evaluating the effect of therapeutic and supratherapeutic doses of palovarotene on ECG parameters.

Hearing was tested in Study 301. Hearing impairment TEAEs were reported in 12% of palovarotene-treated subjects in the FOP-FAS, none of which were severe or lead to discontinuation of treatment. Almost half of FOP subjects had a history of hearing impairment.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Premature Physeal Closure in Growing Children, With Potential for Adverse Effects on Growth

Issue

Premature physeal closure was reported in many pediatric subjects treated with palovarotene, with potential for adverse effects on growth

Background

Systemic retinoids, as well as vitamin A toxicity, have long been associated with a variety of adverse musculoskeletal effects. Among these are published case reports of PPC occurrence and impaired growth in children with prolonged exposure to various retinoids prescribed for the treatment of dermatologic conditions or cancer. Growth plate abnormalities and premature closure were also observed in juvenile rats exposed to palovarotene and were consistent with retinoid class effects (see Section [7.1](#)). Prior to palovarotene studies, PPC had not been reported in patients with FOP.

Because of the potential risk, palovarotene FOP studies included a Bone Safety Management Plan (BSMP) in pediatric subjects (<18 years of age). Based on hand/wrist x-rays at screening to assess growth plates, subjects with <90% skeletal maturity (i.e., had achieved <90% of adult height), defined as bone age <12 years (girls) or <14 years (boys), received weight-adjusted dosing and continued monitoring. This included scheduled PA hand/wrist and AP knee radiographs to monitor growth plates and bone age; measurements of standing height (stadiometry) and knee height (knee caliper); and use of whole-body CT scans to measure femur and tibia length and further assess growth plates. In addition, WBCT scans were used (in all subjects, pediatric and adult) to assess potential avascular necrosis (AVN) of the femoral head, due to the association of AVN with corticosteroid use and the reported occurrence of AVN with palovarotene in a rat study. These assessments were conducted every 6 months in Study 301 and every 6 to 12 months in Study 202B/C. Growth assessments were conducted every 12 months in the NHS. Similar monitoring was included in a pediatric study of palovarotene treatment for a different indication, multiple osteochondromas (MO).

Study 301 began enrollment in November 2017. In 2019, multiple instances of PPC among pediatric subjects in this study were reported based on scheduled radiographs. In December 2019, a partial clinical hold was imposed for the dosing of any children under age 14 years in all palovarotene studies, including the FOP Studies 301 and 202C and the MO study. This partial clinical hold remains in effect, and dosing was never resumed except for children who subsequently reached age 14. Protocol amendment 5 added an extended 2-year safety follow-up for pediatric subjects, including annual assessment of growth, hand/wrist radiograph and WBCT.

Assessment

Regarding *bone safety*, 3 pediatric age categories were evaluated in the ISS:

- <8 years (girls)/<10 years (boys), representing a prepubertal population;
- ≥8/10 to <14 years of age, representing an early adolescent population (generally early-to-mid pubertal) which has, on average, attained approximately 80 to 90% of adult height;
- ≥14 to <18 years, representing a late adolescent population.

In Study 301 at baseline, pediatric patients with FOP exhibited generally normal skeletal maturation: mean chronologic age and bone age by x-ray were closely matched (11.4 and 11.5 years, respectively), and all adolescents age ≥14 years had achieved ≥90% skeletal maturity, i.e., bone age ≥12 (girls) or ≥14 (boys). During palovarotene treatment, mean increase from baseline in bone age (BA) was slightly greater than mean increase in chronologic age (CA): mean ratios of Δ BA/ Δ CA were 1.2-1.4 at months 6, 12, 18 and 24. Individual changes were highly variable. Growth plate x-rays were not obtained in FOP NHS patients for comparison.

Standing height was also in the normal range at baseline in most children with FOP. Table 51 presents mean height Z-scores, which ranged from -0.50 to +0.44 at baseline across the three pediatric age categories in Studies 301 and the NHS. Although there was great variability among individual subjects, these data showed a trend toward lower height Z-scores in adolescents compared to younger children at baseline; this may reflect the development of spinal deformities in some adolescents with FOP. At month 12, mean height Z-scores declined moderately from baseline among palovarotene-treated subjects <14 years old; there were slightly smaller mean

declines among untreated NHS subjects. Differences in growth between treated and untreated subjects were most apparent in subjects who developed PPC, as discussed below.

Table 51. Mean Height Z-Score in Pediatric FOP Subjects, Study 301 and NHS (FOP-FAS)

Age group	NHS			Study 301 (Palovarotene-treated)		
	<8/10	≥8/10 to <14	≥14 to <18	<8/10	≥8/10 to <14	≥14 to <18
Baseline, n	23	21	20	21	36	19
Baseline mean	0.44	0.09	0.18	0.34	-0.35	-0.50
Month 12, n	22	17	18	15	31	13
Mean change from baseline	-0.18	-0.30	-0.55	-0.57	-0.36	-0.02

Source: M2.7.4 (03/31/21 NDA submission), Table 32

Age groups are defined by subject age at study entry

Abbreviations: FOP, fibrodysplasia ossificans progressiva; FOP-FAS, fibrodysplasia ossificans progressiva full analysis set; n, number of subjects; NHS, natural history study

Across Studies 301 and 202B/C, there were 25 subjects in the youngest group (age <8/10 years at study entry) who were treated with palovarotene; among these, 14 (56%) developed PPC. There were 39 early adolescent subjects (age ≥8/10 to <14 years); among these, 10 (26%) developed PPC as of the ISS cutoff date (July 31, 2021), and 3 others were reported as of the Safety Update cutoff (January 31, 2022), for a total of 13/39 in this age group (33%). Among 38 older adolescents (age ≥14 to <18 years) in these studies, none were reported to develop PPC.

The mean age at enrollment of subjects who went on to develop PPC was 8.0 years, compared with 12.3 years for subjects <18 years of age who did not develop PPC. There was a similar distribution of females and males in subjects with and without PPC. With one exception, all cases of PPC became first apparent on x-rays of the knee (partial or complete closure of distal femur and/or proximal tibia growth plates), typically on the scheduled x-rays at month 12 of treatment. PPC appeared to be bilaterally symmetric and synchronous at other joints, based on a very limited number of subjects with bilateral or additional x-rays; this issue was not systematically evaluated. Advances in bone age at the hand/wrist were generally similar in subjects with and without PPC. In the ISS, the Applicant evaluated palovarotene exposure (cumulative dose, duration of chronic or flare-up dosing, AUC for concentration versus time curve) for pediatric subjects with and without PPC; no consistent trends were apparent.

Table 52 shows that while palovarotene treatment was associated with trends of slower growth overall in comparison to NHS subjects, the subset that developed PPC accounted for most of the difference, especially among early adolescent subjects (age ≥8/10 to <14 years). In Study 301, mean standing height increase was 1.2 cm/year in this age group with PPC, compared to 3.5 cm/year in treated subjects without PPC and 4.2 cm/year in untreated subjects, and the proportion with growth velocity <4 cm/year was greater (86%, 54% and 41% in these respective groups). It should be noted that this is a small subgroup (seven subjects age ≥8/10 to <14 years with PPC).

Table 52. Standing Height Changes at Month 12, Study 301 and NHS (FOP-FAS)

Variable	NHS (Untreated)		Study 301, no PPC		Study 301, With PPC	
	<8/10 n=22	≥8/10 to <14 n=17	<8/10 n=4	≥8/10 to <14 n=24	<8/10 n=11	≥8/10 to <14 n=7
Height mean change from baseline, cm	5.2	4.2	3.6	3.5	3.4	1.2
Growth velocity <4 cm/year	6 (27%)	7 (41%)	2 (50%)	13 (54%)	6 (55%)	6 (86%)
Growth velocity 4-5 cm/year	1 (5%)	4 (24%)	1 (25%)	2 (8%)	0	0
Growth velocity >5 cm/year	15 (68%)	6 (35%)	1 (25%)	9 (38%)	5 (46%)	1 (14%)

Source: M2.7.4 Table 39 (03/31/21 submission)

Abbreviations: FOP-FAS, fibrodysplasia ossificans progressiva full analysis set; n, number of subjects; NHS, natural history study; PPC, premature physeal closure

Knee height and femur/tibia lengths (by CT) are presumed to be less susceptible than standing height to measurement difficulty in the presence of FOP-related deformities such as scoliosis. Data on these parameters are summarized in Table 53. There were generally only small differences between untreated NHS subjects and treated subjects without PPC. However as with standing height, PPC was associated with trends of smaller gains in these growth parameters among subjects age ≥8/10 to <14 years.

Table 53. Knee Height, Femur Length and Tibia Length: Changes at Month 12, Study 301 and NHS (FOP-FAS)

Variable	NHS (Untreated)		Study 301, no PPC		Study 301, With PPC	
	<8/10	≥8/10 to <14	<8/10	≥8/10 to <14	<8/10	≥8/10 to <14
Knee height, n	20	17	4	24	11	7
Mean change, cm	1.3	2.0	2.2	1.8	1.5	0.6
GV <2 cm/year, n (%)	13 (65%)	9 (53%)	1 (25%)	13 (54%)	7 (64%)	6 (86%)
Femur length, n	18	13	3	20	10	6
Mean change, cm	2.2	1.7	2.0	1.7	1.7	1.1
GV <2 cm/year, n (%)	6 (33%)	9 (69%)	1 (33%)	13 (65%)	6 (60%)	5 (83%)
Tibia length, n	18	14	3	22	10	5
Mean change, cm	1.7	1.7	1.7	1.4	1.5	1.0
GV <1.5 cm/year, n (%)	6 (33%)	7 (50%)	0	13 (59%)	4 (40%)	4 (80%)

Source: M2.7.4 (03/31/21 submission), Tables 40, Tables 14.2.16.3.4 and 14.2.16.3.5

Abbreviations: FOP-FAS, fibrodysplasia ossificans progressiva full analysis set; GV, growth velocity; n, number of subjects with the given length; NHS, natural history study; PPC, premature physeal closure

Table 54 lists the 27 study subjects with reported PPC: 3 who received palovarotene in the phase 2 study, 202B/C, and 24 treated in the phase 3 study, 301. There were five subjects (marked with * in the table) who received only chronic dosing, and the remainder received both chronic and flare-up dosing. All of these subjects received weight-based dose reductions at enrollment based on bone age indicating <90% skeletal maturity. As shown in the table, almost all the subjects who developed PPC experienced declines in height Z-score during treatment, but individual changes were highly variable. The challenges of growth assessment in FOP patients are illustrated in the data for subject # (b) (6), who exhibited a large decline in height Z-score (-4.9) that resulted from an absolute height decline of 17 cm, no doubt reflecting changes in posture and/or deformities.

Following the interruption of palovarotene treatment on or before initiation of the PPC-related clinical hold, growth data are available for up to 2 years off treatment in numerous subjects (and

are included in Table 54 for these subjects). In general, trajectories of height Z-score and other growth parameters continued unchanged in subjects with and without PPC, showing no evidence of a rebound in growth following palovarotene discontinuation.

In addition to the risk of reduced stature based on growth slowing or arrest, PPC at the distal femur and/or proximal tibia has the potential to create leg length discrepancy due to asymmetric effects on the right and left leg, or abnormal knee angulation due to differential growth of medial and lateral aspects of the growth plate. Two parameters included in Table 54 are relevant to these potential risks. The difference between right and left leg length was derived from the sum of femur and tibia length, as measured by whole-body CT scans, on each side. The Applicant postulated that a change from baseline of $> +1.5$ cm or < -1.5 cm in the R-L difference may be of concern; only one of the PPC subjects (among those with available data) exceeded this threshold (subject # (b) (6)), with an apparent change of -1.9 cm from baseline R-L difference but nearly equal R-L length at final assessment (Δ -0.1 cm). Data from palovarotene-treated subjects without PPC and from NHS subjects were similar to these subjects with PPC in not showing evidence of developing leg length discrepancies. The other parameter listed in the table, lateral distal femoral angle, was measured on AP knee radiographs; normal range for this angle in healthy children is approximately 79 to 85°, representing mild valgus. As indicated, all the subjects with PPC had values within or close to this range at last measure, with changes from baseline that were generally small and probably within the normal variability of the measure, which is susceptible to rotation of images; data from subjects without evidence of PPC were similar.

Table 54. Growth Parameters in FOP Subjects With PPC in Studies 301 and 202B/C

Subject	Age/sex (at Study Entry)	Height Z-score		R Leg – L Leg Difference, cm		Lateral Distal Femoral Angle (Degrees)	
		Δ From BL	Last	Δ From BL	Last	Δ From BL	Last
(b) (6), *	4 F	-0.4	-0.5	0.5	0.2	-2.0	79.4
	4 F	-2.0	-3.0	-0.5	0.1	2.1	86.1
	4 F	-1.0	-0.4		0.4	0.3	79.8
	5 F	0.7	-2.8	-0.3	-0.7	-0.1	82.9
	5 F	-0.4	0.1	-0.2	-0.2	-4.2	77.3
	6 F	-2.4	-1.5	0.5	0.4	0.1	80.2
	6 M	-1.8	-0.1		0.3	-1.3	82.7
	7 M	-0.8	-0.1	-1.3	-0.5	1.0	84.9
	7 M	-0.5	3.3	0.4	0.6	-4.2	78.4
	7 M	-1.2	-1.7	-0.2	-0.5	-3.4	81.2
	7 F	-0.9	-1.5	-0.1	0.1	0.9	81.1
	8 M	0.0	2.4	-0.7	-2.5	-1.4	79.3
	9 M	-4.9	-6.1			3.8	81.0
	9 M	-2.1	-3.1		-1.9	-3.5	80.5
	8 F	0.9	2.3	1.0	1.6	-2.5	81.5
	9 F	-1.1	-1.4		-0.2	-0.5	79.8
	10 M	-2.3	-1.0	0.2	1.1	-0.0	81.7
	10 M	-1.1	-2.5		0.9	2.8	82.0

Subject	Age/sex (at Study Entry)	Height Z-score		R Leg – L Leg Difference, cm		Lateral Distal Femoral Angle (Degrees)	
		Δ From BL	Last	Δ From BL	Last	Δ From BL	Last
(b) (6)*	10 F	-0.2	0.5	0.0	-0.4	-0.9	81.4
	10 F	-2.8	-1.4	-0.2	-0.3	1.3	81.3
	11 F	-1.1	-0.8		0.9	0.8	76.4
	11 F	-0.5	0.1	-0.2	0.5	-2.9	80.8
	11M	-1.4	-0.9			-1.0	82.8
	11M	-0.2	0.9	-1.9	-0.1	-0.3	80.3
	11M	0.2	-1.6	-1.0	-1.1	-0.4	82.2
	13M	-0.8	0.4	-0.3	-0.8	0.6	82.1
	13 F	-0.9	-2.6	1.5	0.0	-1.6	79.9

Source: Safety update listings 16.19.16.10.3; 16.19.16.10.1; 16.19.16.1.3.3; 16.19.16.1.3.1; 16.19.16.9.1.1

*Received only chronic dosing (5 mg equivalent)

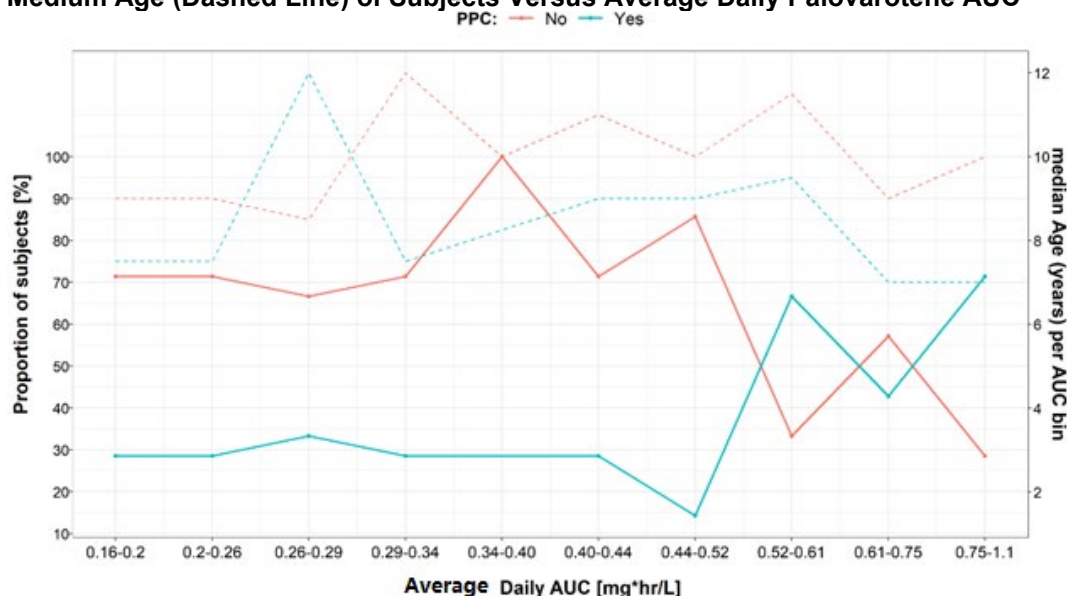
Abbreviations: BL, baseline; FOP, fibrodysplasia ossificans progressiva; L, left; PPC, premature physeal closure; R, right

The Applicant's study of pediatric patients with multiple osteochondromas (MO) enrolled 193 patients ages 2 to 14 years (mean 7.7 years) into 3 randomized groups of palovarotene 2.5 mg and 5 mg, and placebo (N=66, 65 and 62, respectively). During treatment, height changes were generally similar between groups, and height Z-scores showed little change over time with no notable trends. One subject in each dose group had physeal closure by radiograph in some joints; each of these subjects was ≥ 11 years old and the changes were attributed to normal physiologic closure. Changes in bone age were similar between the treatment groups. Because this study was prematurely stopped due to the PPC findings in FOP studies, most subjects did not have data beyond 6 months.

Review of whole-body CT scans in all palovarotene-treated and untreated (NHS) subjects with FOP showed no evidence of femoral head abnormalities related to AVN, through the safety update cutoff date of January 31, 2022.

Further ER analyses were conducted to assess the impact of palovarotene exposure on PPC risks. The results show that the risk of PPC is increased at higher palovarotene AUCs (Figure 12). However, this result is likely to be driven by patients < 8 years old. When only considering patients 8/10 to 13 years, there is absence of a clear relationship between the proportion of subjects with PPC and AUCs (Figure 13).

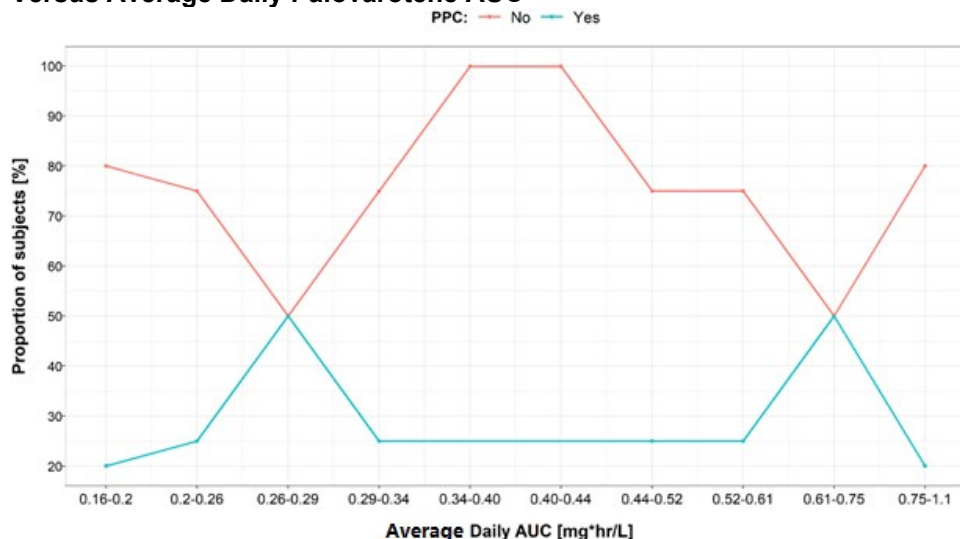
Figure 12. Plots of (1) Proportion of Subjects With or Without PPC Events (Solid Line) and (2) Medium Age (Dashed Line) of Subjects Versus Average Daily Palovarotene AUC



Source: Clinical pharmacology reviewer's analysis.

Abbreviations: AUC, area under the concentration versus time curve; PPC, premature physeal closure

Figure 13. Plots of Proportion of Subjects (Girls 8 to 13 Years/Boys 10 to 13 Years) With PPC Versus Average Daily Palovarotene AUC



Source: Clinical pharmacology reviewer's analysis

Abbreviations: AUC, area under the concentration versus time curve; PPC, premature physeal closure

In general, there is no ER relationship for palovarotene exposure and proportion of patients with PPC events for subjects greater than 8 years of age. Lowering dose of palovarotene dose for subjects younger than 12 years of age is not predicted to reduce risks of PPC for pediatrics. The reviewer acknowledged that this conclusion is limited by the small number of reported PPC events in the clinical studies.

Conclusion

The review team agrees with the Applicant that palovarotene treatment of pediatric patients with FOP is associated with a serious risk of PPC. Premature physeal closure development was most apparent at the active growth plates of the knee (distal femur and proximal tibia), which is consistent with literature reports involving other retinoids. Premature physeal closure was not generally associated with rapid advances in bone age as assessed by x-rays of the hand/wrist.

All patients with open growth plates are likely to be at risk of PPC. Younger children (<8/10 years) may be at greatest risk, but 33% of older pediatric patients (age $\geq$ 8/10 to <14 years) also showed evidence of PPC in the clinical studies. The Applicant could not identify specific risk factors or a safe level of palovarotene exposure. PPC was not reported in any subjects $\geq$ 14 years of age; this may result from difficulty distinguishing premature versus physiologic physeal closure in this age group.

Because PPC involved the knee and appeared to be irreversible, reduced height is expected to result. Growth data in the palovarotene studies were highly variable, which is due in part to measurement difficulty in some FOP patients. While some study subjects with developing PPC were continuing to grow at near-normal rates, others showed near-cessation of growth and sharp declines in height Z-score. Overall, there were trends of reduced growth velocity and declining height Z-score, and greater variability, among palovarotene-treated compared to untreated NHS patients, particularly in early adolescents (age $\geq$ 8/10 to <14 years at study onset) who developed PPC. Measurements of knee height, and of femur and tibia length (CT), were generally consistent with standing height data.

In addition to reduced stature, and potentially disproportionate growth (e.g., short legs relative to trunk), PPC of growth plates at the knee poses a potential risk of leg length discrepancy or abnormal knee angulation. Radiographs have shown no evidence of such effects in study subjects to date, but the duration of treatment and/or follow-up has been limited in most cases, and longer-term data are needed.

PPC and impaired growth represent a major safety risk of palovarotene treatment in children with FOP and open growth plates. Product labeling should include a boxed warning and recommendations for patient monitoring, including height measurements and imaging of growth plates.

7.7.2. Teratogenicity Potential Consistent With the Retinoid Drug Class

Issue

Embryo-fetal toxicity (retinoid class effect)

Background

Embryo-fetal toxicity has been reported with multiple retinoids and may result in irreversible fetal malformations, adverse pregnancy outcomes and stillbirths. The labeling of all approved retinoids (isotretinoin, acitretin, tretinoin, bexarotene) includes Boxed Warnings for pregnancy and teratogenicity.

Assessment

Embryo-fetal toxicity consistent with retinoid effects was observed in fetal rat studies of palovarotene (Section [7.7.1](#)).

The disease burden of FOP appears to result in low reproductive fitness, and there are only rare reports of pregnancy in women with FOP (almost all known cases of FOP result from new spontaneous mutations). FOP poses life-threatening risks for both the mother and fetus, including cardio-respiratory complications, thromboembolism, delivery complications, fetal distress, and premature birth. Consensus guidelines for FOP advise of these life-threatening risks and urge serious consideration and family planning before attempting a pregnancy. As a result of the high-risk nature of pregnancy to both mother and fetus, reports of miscarriage are fairly common amongst the small number of FOP pregnancies documented in case reports. The risk of embryo-fetal toxicity from palovarotene would potentially add to the incidence of these events in the population likely to use the drug.

Clinical studies of palovarotene included frequent pregnancy testing and contraception requirements as a precaution. To date, there are no reports of pregnancy or in utero exposure to palovarotene. Based on a phase 1 study showing very low palovarotene levels in semen, administration to a male is considered to be of low risk to female partners who become pregnant.

Conclusion

The risk of teratogenicity, and other pregnancy-related risk in FOP patients, warrants a Boxed Warning. The Applicant has proposed a risk management plan with the goal of educating prescribers, pharmacists and patients, which does not include a REMS. This is a reasonable approach based on the following: the FOP patient population is very small and is largely managed by experts in the disease; the pregnancy risks of FOP and importance of family planning discussions are already included in consensus guidelines; pregnancy is very infrequent in FOP patients due to low reproductive fitness; and off label use of palovarotene for other indications such as acne is not expected to occur.

7.7.3. Increased Rate of Reported Flare-ups During Palovarotene Treatment; Potential for Retinoid-Induced Myositis

Issue

Increased rate of reported flare-ups during palovarotene treatment; potential for retinoid-induced myositis

Background

The rate of new FOP flare-up episodes was assessed in the NHS and palovarotene studies and is relevant to both efficacy and safety. Flare-up incidence and rate were designated in phase 3 as secondary efficacy endpoints to assess whether chronic palovarotene treatment may suppress the initiation of new flare-ups, in addition to potentially suppressing formation of new HO. However, retinoids, and vitamin A in toxic doses, 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, sometimes associated with strenuous physical activity. Because FOP flare-ups are frequently triggered by local inflammation or trauma and are characterized by ossification of muscle and other soft tissues, there is a theoretical concern for induction or exacerbation of flare-ups by palovarotene.

Assessment

In all FOP studies, subjects were instructed to call the site immediately for potential flare-up symptoms. The process by which flare-ups were treated and reported varied among the FOP studies.

NHS

Subjects reporting potential flare-ups were evaluated in clinic or monitored with weekly phone contacts. Subjects were also contacted by phone every 6 months between the yearly clinic visits but were not systematically asked about new flare-ups at visits and did not record symptoms in diaries.

Phase 2 Studies 201/202A/B

In these studies, flare-ups were treated if they met the following criteria: had at least 2 out of 6 predefined symptoms (pain, soft tissue swelling, decreased ROM, stiffness, redness and warmth), were within 7 days of symptom onset, symptoms were consistent with the subject's previous flare-ups, and flare-ups were confirmed by the investigator. Flare-ups that were not treated (i.e., not meeting these criteria, or intercurrent flare-ups at a different location during flare-up treatment) were recorded not as flare-ups *per se*, but as AEs under the MedDRA preferred term of "condition aggravated."

Phase 3 Study 301 and Phase 2 Study 202C

In these studies, the criteria for initiating flare-up treatment were expanded such that only one symptom (or traumatic event likely to lead to a flare-up) was required, if consistent with previous flare-ups and confirmed by the investigator, with no requirement to start treatment within 7 days of onset. Intercurrent (or markedly worsened) flare-ups were recorded as new flare-ups and treated as such, so that there were no AEs of "condition aggravated."

Flare-up Incidence and Rate in Phase 2 Studies

During the 12-week period of treatment/follow-up of the index flare-up in Study 201, new symptoms consistent with a flare-up (i.e., condition aggravated AEs) were reported by more subjects randomized to the palovarotene 10/5 mg regimen (13/21, 62%) in comparison to the 5/2.5 mg regimen (2/9, 22%) or placebo (3/10, 30%). In addition, some of the subjects treated with the 10/5 mg regimen experienced more than one new flare-up event within the 12-week observation period, therefore the rate of new events was highest in this treatment group. The majority of these events occurred at a new location rather than at the original flare-up location. New events, particularly those involving a new location, occurred somewhat more frequently in the first 4 weeks of treatment, compared to Weeks 5-8 or Weeks 9-12. Two of the events in the 10/5 group were categorized as SAEs of condition aggravated.

Table 55. Study 201: New Flare-up Events Reported During Treatment of an Initial (Index) Flare-up (FOP-F-FAS)

	Placebo	PVO 5/2.5 mg	PVO 10/5 mg
Number of treated (index) flare-ups	10	9	21
Number of index flare-ups that were followed by $\geq$ one new event within 12 weeks	3 (30%)	2 (22%)	13 (62%)
Total number of new events within 12 weeks	3	2	24
Number of new events per 12-week treatment period	0.30	0.22	1.14
Number at new location/number worsening at original location	2/1	2/0	18/6
Time interval of onset of new events: Weeks 0-4/Weeks 5-8/Weeks 9-12	0/1/2	1/1/0	11/7/6

Source: Study 201 CSR, and RTQs submitted on 08/23/22 and 10/05/22

Abbreviations: FOP-F-FAS, fibrodysplasia ossificans progressiva flare-up full analysis set; PVO, palovarotene

To address the issue of a possible triggering of new flare-ups by higher palovarotene doses, the ISS analyzed these events by regimen across the NHS and phase 2 studies (Table 56). Within the 12 weeks following an index flare-up, new events (i.e., condition aggravated AEs) were reported more frequently when the index flare-up was treated with 10/5 mg or 20/10 mg, compared to 5/2.5 mg or placebo/untreated flare-ups. Most of these new events occurred at a different location from the index flare-up.

Table 56. New Flare-up Events Occurring Within 12 Weeks of a Treated or Imaged Flare-up Across Studies (FOP-F-FAS)

	Untreated NHS	Placebo	PVO 5/2.5 mg	PVO 10/5 mg	PVO 20/10 mg
Number of treated or imaged (index) flare-ups	53	10	9	52	66
Number of index flare-ups that were followed by $\geq$ one new event within 12 weeks	12 (23%)	3 (30%)	2 (22%)	19 (37%)	24 (36%)
Total number of new events within 12 weeks	17	3	2	38	33
Number of new events per 12-week treatment period	0.32	0.30	0.22	0.73	0.50

Source: ISS Table 14.9.7 (original 03/31/21 NDA), RTQs submitted on 08/23/22 and 10/05/22

The FOP-F-FAS includes all subjects with at least one flare-up (from teleconferencing and imaged flare ups) from the NHS and from treated flare-ups in the interventional studies 201, 202A and 202B. Numbers and percentages are based on number of flare-ups, not number of subjects.

Abbreviations: FOP-F-FAS, fibrodysplasia ossificans progressiva flare-up full analysis set; NHS, natural history study; PVO, palovarotene

In subjects receiving the chronic/flare-up regimen in Study 202 Parts B and C, new flare-ups (or condition aggravated AEs) occurred at a higher rate during 20/10 mg treatment of an index flare-up, than during chronic 5 mg dosing:

Table 57. Study 202, Parts B and C: Flare up Rate, by Dosing Period

	Chronic Dosing Period*	Flare-up Dosing Period**
Study 202 Part B		
N at risk / n with $\geq$ one flare-up	44/28	28/14
Total number of flare-ups	64	28
Total number of subject dosing-months	641	142
Flare-up rate per subject-month exposure, mean (95% CI)	0.10 (0.08-0.12)	0.20 (0.12-0.27)
Study 202 Part C		
N at risk / n with $\geq$ one flare-up	43/30	33/17
Total number of flare-ups	47	68
Total number of subject dosing-months	488	233
Flare-up rate per subject-month exposure, mean (95% CI)	0.10 (0.07-0.12)	0.29 (0.22-0.36)

Source: IR/SE Supplemental Tables 3a and 3b

*The chronic period includes treated and untreated (i.e., condition aggravated in Part B) flare-ups with a start date during chronic dosing. Any flare-up that occurred during chronic dosing that resulted in the start of flare-up dosing (i.e., treated flare-ups) was allocated to the chronic period.

**The flare-up period includes new flare-ups (or condition aggravated AEs in Part B) with a start date during the flare-up dosing. Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects

Flare-up Incidence and Rate in Phase 3 Study

For the Study 301 secondary endpoints of flare-up incidence and rate in comparison to the NHS, the SAP defined qualifying flare-ups as the presence of at least 2 flare-up symptoms. As noted above, this criterion had been used to determine treatment in earlier phase 2 studies, but any number of symptoms (≥ 1) was sufficient to define a flare-up in the NHS or Study 301, and upon request the Applicant submitted analyses based on $\geq$ one symptom and on $\geq$ two symptoms. These two studies were similar with regard to the number of reported symptoms per event (mean and median were 3.0 in both studies), and the proportion of flare-ups with only one reported symptom (13%, 14% respectively).

Flare-ups were reported by a slightly greater proportion of palovarotene-treated versus untreated subjects through month 12: 67% in Study 301 and 56% in the NHS, based on $\geq$ one relevant symptom (Table 56). The proportions based on $\geq$ two symptoms were slightly lower: 65% and 54%, respectively. Among subjects with $\geq$ one flare-up event, the number of reported events per subject (based on $\geq$ one symptom) was also greater in Study 301 (mean 4.2, range 1-23) versus the NHS (mean 2.5, range 1 to 9). Therefore, among all patients (with or without flare-ups), the rate of flare-ups per month of study participation was greater in Study 301 compared to the NHS (0.15 versus 0.07 per subject-month, respectively). Data were similar for the subset of 39 subjects who crossed over from the NHS to Study 301.

Table 58. Study 301 and NHS: Incidence and Rate of New Flare-ups

	Untreated NHS	Palovarotene Study 301
All subjects, Principal Safety Set		
Proportion of subjects who reported at least one flare-up through Month 12	62/111 (56%)	66/99 (67%)
Flare-up rate per subject-month of exposure (95% CI)	0.07 (0.06, 0.08)	0.15 (0.13, 0.17)
Subjects who transferred from NHS to study 301 (N=39)		
Proportion of subjects who reported at least one flare-up through Month 12, within each study	23/39 (59%)	26/39 (67%)
Flare-up rate per subject-month of exposure (95% CI)	0.08 (0.07, 0.10)	0.15 (0.12, 0.18)

Source: IR/ISE Supplemental tables E8.1, E8.2, E10.1 and E10.2

Based on ≥ one reported flare-up symptom

Abbreviations: CI, confidence interval; N, number of subjects; NHS, natural history study

As noted by the Applicant, these differences in flare-up rate may be explained, at least in part, by differences in reporting related to study design and conduct. NHS subjects generally had less frequent contact with study staff compared to Study 301 subjects. Phone contacts were primarily every 6 months in the NHS; in Study 301, subjects were contacted every 3 months during chronic dosing and every 4 weeks during flare-up dosing. Study 301 subjects were asked to maintain daily symptom diaries, which were reviewed at clinic visits; NHS subjects did not use diaries and may have been less motivated to report symptoms that were not intended for any treatment. In addition, worsening of flare-ups was not systematically recorded in the NHS, unlike Study 301. Other aspects of care, such as the use of high-dose prednisone to treat flare-ups, were generally similar between the two studies.

There are limited data supporting the Applicant's position that flare-ups were under-reported in the NHS. Among the 39 crossover subjects, the mean number of flare-ups recorded prospectively in the last 12 months of the NHS was 0.6; at the time of enrollment in Study 301, the same 39 subjects reported (retrospectively) a mean of 1.1 flare-ups during the previous 12 months (the same time period) (Table 20.1.35.1 in ISE resubmission)

In Study 301, many subjects experienced multiple flare-ups, often in succession, whereby a new event within 12 weeks of the onset of the last event would restart the 20/10 dosing regimen before chronic dosing (5 mg) could resume. Thus, a flare-up "cycle" could include one or multiple flare-ups; the mean number of flare-ups per cycle in the study was 2.2 and the maximum was 23. Table 59 compares the rates of new flare-ups occurring during chronic dosing (i.e., the first or index flare-up of a new cycle) and during flare-up dosing (any subsequent flare-ups within a cycle). The rate of reported new flare-ups was greater during the higher dosing periods (0.33 versus 0.12 events/month). Among these follow-on events within a flare-up cycle, 82 (42%) were categorized as worsening of the initial flare-up, and 114 (58%) were categorized as intercurrent flare-ups at a new location. New events were generally distributed evenly by time interval throughout the flare-up treatment cycle.

Table 59. Study 301: Flare-up Rate, by Dosing Period (PSS, N=99)

	Chronic Period*	Flare-up Period**	Overall
Flare-up rate per subject-month of exposure (95% CI)	0.12 (0.10-0.14)	0.33 (0.28-0.38)	0.18 (0.16-0.20)

Source: IR/ISE Supplemental Table 4.1

*The chronic period includes flare-ups with a start date during chronic dosing. Any flare-up that occurred during chronic dosing that resulted in the start of flare-up dosing (i.e., treated flare-ups) was allocated to the chronic period.

**The flare-up period includes new flare-ups with a start date during flare-up dosing.

Abbreviations: CI, confidence interval; N, number of subjects; PSS, Principal Safety Set

The clinical significance of the number of flare-ups in these studies with regard to disease progression is unclear. Subjects reporting $\geq$ one flare-up, compared to subjects reporting no flare-ups, developed larger quantities of new whole-body HO, both in the NHS (mean 40.8 versus 6.7 cm³ at month 12), and also in Study 301 (mean 9.0 versus 2.9 cm³) (ISE Table 30). Otherwise, however, the number of flare-ups did not appear to be closely related to the quantity of new whole-body HO in these studies. Among the five subjects in either NHS or Study 301 with annualized new HO >100 cm³/year, 3 of the 4 NHS subjects had reported only 1 or 2 flare-ups. The only Study 301 subject (# (b) (6)) with >100 cm³/year of new HO (236.8 cm³/year) was an exception, having reported 13 flare-ups.

Among the 39 subjects who transferred from the NHS to Study 301, the change in number of flare-ups for a given subject did not appear to predict the change in new HO. The two subjects ((b) (6) and # (b) (6)) with the largest increases in number of flare-ups between NHS and Study 301 (one event to 18 events, and one event to 14 events, respectively) nevertheless had large declines in rates of new HO from the NHS to Study 301. In such cases, extended high-dose treatment of the numerous flare-ups (encompassing nearly all of these two subjects' time of participation in Study 301) may have suppressed the formation of new HO, if not the rate of clinical events or symptoms.

Conclusion

FOP flare-up episodes were reported by a greater proportion of palovarotene-treated subjects in the phase 3 study, 301, compared to untreated subjects in the NHS, and at a higher frequency (0.15 versus 0.07 per month). However, flare-ups appear to have been under-reported in the NHS based on the study design. This may be supported by findings of a published survey in which untreated FOP patients reported an average of 1.9 flare-ups in the preceding 12 months, which is a rate of 0.16 events per month (*J Bone Miner Res.* 2016; 31:650).

Within Study 301, flare-ups were reported at higher rates during cycles of flare-up treatment (0.33 new events per month, versus 0.12 per month during chronic dosing). Data from Study 202B/C subjects receiving the chronic/flare-up regimen were consistent with this finding, with 0.20-0.29 new events per month during flare-up dosing, versus 0.10 per month during chronic dosing. In the randomized Study 201, more new events (condition aggravated AEs, mostly at a new location) were reported in subjects receiving the highest dose flare-up regimen (10/5 mg) compared to 5/2.5 mg or placebo.

There are several possible explanations for these findings. According to the Applicant, some FOP experts have reported anecdotally that flare-ups may occur in clusters or in rapid sequence, although this is not well documented in the literature. Higher palovarotene doses may trigger inflammatory processes leading to new flare-ups, or could result in musculoskeletal adverse

events related to retinoid effects that could be misinterpreted as flare-up symptoms, or could potentially result in musculoskeletal adverse events that trigger new flare-ups. Flare-up symptoms may rebound following withdrawal of the high dose corticosteroids which are administered during most flare-ups. Additionally, patients may have a tendency to over-report symptoms during treatment, perhaps related to frequent contacts with study staff and questioning about possible adverse events while already experiencing symptoms of the initial flare-up in the cycle.

The clinical significance of the apparent increase in flare-ups in these studies is uncertain, given that the overall rate of flare ups in Study 301 of 0.15 events per month is similar to the reported rate for untreated FOP patients in the literature (approximately 2 per year). To gain further insight, DGE has asked the Applicant to analyze the relationships between flare-ups (“index” and subsequent events during flare-up dosing) and new HO (both at and away from flare-up sites), in Studies 301, 202B, 202C and the NHS. This information is not available during this review cycle and is planned to be submitted at a later date.

7.7.4. Apparent Adverse Effects of Palovarotene on Vertebral Bone Mineral Density, Bone Mineral Content, and Fractures

Issue

Apparent adverse effects of palovarotene on vertebral bone mineral density (BMD), bone mineral content (BMC), and fractures.

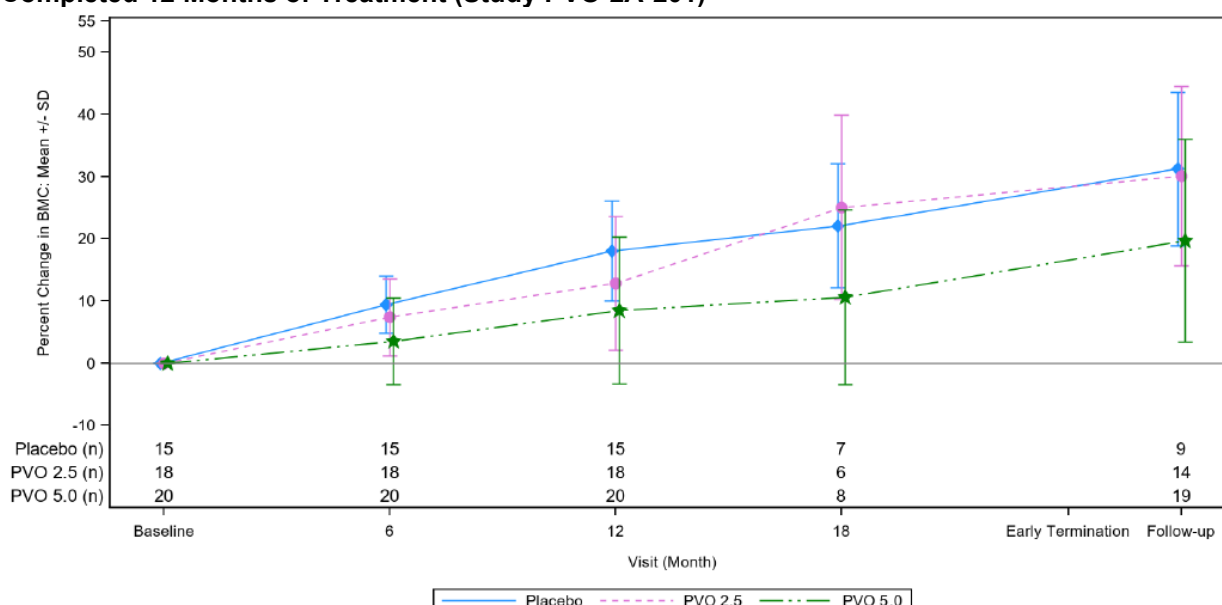
Background

Literature reports indicate that retinoids and vitamin A toxicity may cause bone demineralization, osteoporosis, or “slender long bones” in children. Labeling for isotretinoin in the treatment of acne includes a Warning for negative effects on BMD seen in clinical trials. There is no definitive evidence of an increase in fractures related to retinoid use.

Assessment

Assessments of BMD and BMC by DXA were not included in the palovarotene FOP studies because of the likely confounding effects of extensive HO in overlying soft tissues. DXA was conducted on subjects with MO (age 2 to 14 years) in study PVO-2A-201. Although treatment duration was limited in most subjects due to early termination of the trial, there were discernable trends of reduced BMC accrual in the palovarotene 5 mg treatment group compared to the 2.5 mg and placebo groups. Figure 14 shows that lower BMC in the 5 mg group appeared to persist at the follow-up visit 6 months after discontinuation of the drug.

Figure 14. Lumbar Spine BMC, Percent Change From Baseline, in Subjects With MO Who Completed 12 Months of Treatment (Study PVO-2A-201)



Source: Study PVO-2A-201 CSR Figure S27B.1C

Abbreviations: BMC, bone mineral content; MO, multiple osteochondromas; PVO, palovarotene; SD, standard deviation

Because of this adverse BMC trend in the MO trial, the FOP DMC requested retrospective re-evaluation of the WBCT scans from FOP Studies 301 (palovarotene treated) and the NHS (untreated), which had been obtained to measure HO, for the assessments related to vertebral structural integrity listed below. It should be noted that these measures have not been validated by FDA for assessment of fractures or estimation of fracture risk in clinical trials; standard radiographs are considered the gold standard for assessment of vertebral fractures. In addition, as discussed above (see Section 6.3.3), the populations of Studies 301 and the NHS differed in age and possibly other factors due to the lack of randomization.

Biomechanical CT (BCT) analysis was conducted at L1, L2 or adjacent vertebrae (i.e., T12 if either L1 or L2 was not evaluable) to derive the following parameters:

- Estimated bone compressive strength (Newtons) by finite element analysis
- Trabecular volumetric BMD (mg/cm^3) of the central vertebral body
- BMC (g) of the entire vertebral body

The Applicant analyzed the data for changes from baseline, with adjustments for covariates, and reported nominally significant associations of palovarotene treatment with lower values for each of these parameters.

Vertebral fracture analysis (VFA) of T4 through L4 vertebrae was conducted using automated placement of 6 points to outline vertebral morphometric shape, which were used to calculate deformity ratios for grading using established criteria of Genant:

- Normal (Grade 0; deformity $<20\%$)
- Mild (Grade 1; deformity $\geq 20\%$ to $<25\%$)
- Moderate (Grade 2; deformity $\geq 25\%$ to $<40\%$)
- Severe (Grade 3; deformity $\geq 40\%$)

The prevalence of these fractures on baseline imaging was 21.5% in palovarotene-treated subjects (Study 301) and 23.6% of untreated subjects (NHS). At 12 months, 28.4% of palovarotene-treated subjects (Study 301) and 11.6% of untreated subjects (NHS) were found to have at least one new-onset vertebral fracture that was not present at baseline. For the target $\geq 8/10$ -year-old population, these proportions were 24.2% and 11.8%, respectively. The 12-month incidences of at least one new-onset moderate/severe fracture (Grade 2 or 3) were 8.6% (palovarotene) and 4.7% (untreated) overall, or 9.1% and 4.4% for the $\geq 8/10$ population. The report indicates that all of these apparent fractures were asymptomatic.

The Applicant also analyzed clinical fracture AEs in the FOP-FAS: normotopic bone fractures were reported in 13/164 subjects (7.9%), including 2/23 subjects (8.7%) in the placebo arm.

Conclusion

The results of the BCT analysis suggest that palovarotene treatment may be associated with decreases in vertebral bone strength, BMC and BMD. Prior vertebral fractures appeared to be highly prevalent at baseline in FOP studies given the young age of the population, which may be disease related, and new abnormalities occurred at a higher rate in palovarotene-treated versus untreated patients over 12 months. These effects are consistent with some data involving other retinoids, but do not establish a definitive causal association due to the post hoc nature of the analyses, use of nonvalidated measures, and differences between the populations of the two nonrandomized studies.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Hepatic Impairment

FOP is an ultrarare disease with approximately 800 known patients worldwide. The median lifespan of FOP patients is 56 years. The Applicant claimed that hepatic impairment is not a known complication of patients with FOP. In the NHS, none of the 114 patients with FOP with available hepatic medical history had cirrhosis, and only one of 114 subjects (0.9%) reported a history of mild hepatitis. The effect of hepatic impairment on the PK of palovarotene has not been evaluated in a dedicated study. According to the Applicant's population PK analyses, there was no evidence that serum albumin, ALT, AST, alkaline phosphatase (ALP), or bilirubin affected palovarotene PK.

Per the Applicant, in an exploratory covariate analysis of the population PK analyses, mild and moderate hepatic impairment did not affect palovarotene PK. However, most subjects (healthy subjects and patients) in the population PK dataset (N=577) had normal hepatic function and only a small number of subjects (~2%) had elevated baseline AST (40-75 U/L) or ALT (50-90 U/L), with a total of five subjects classified as moderate hepatic impairment and none of subjects classified as severe hepatic impairment. Therefore, due to limited sample size of subjects with moderate hepatic impairment, the effect of moderate (Child-Pugh B) hepatic impairment on the PK of palovarotene is not conclusive from the submitted population PK analyses.

The Applicant also conducted a physiological based PK (PBPK) analysis and concluded that the moderate hepatic impairment status would not significantly affect the PK of palovarotene. The review team, however, concludes that the PBPK analyses are inadequate to evaluate the effect of hepatic organ impairment, as the metabolic pathways of palovarotene have not been well characterized. Specifically, six unidentified metabolites accounted for approximately 28.4% of the dose in feces according to the human mass balance study, and there is uncertainty about the contribution of CYP2C8 and CYP2C19 to the elimination pathway of palovarotene (see Section [14.4](#) for more detailed assessment). Since palovarotene is significantly metabolized in the liver, the exposure may be expected to be higher in moderate-to-severe hepatic impaired patients. Due to the lack of PK data, the use of palovarotene in patients with moderate-to-severe hepatic impairment is not recommended. The Applicant should conduct a hepatic impairment study to evaluate the effect of moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) on the PK of palovarotene to inform the dosing recommendations in patients with hepatic impairment.

Renal Impairment

Renal impairment is not a known complication of FOP patients. None of the 114 subjects in the NHS with available renal medical history reported renal impairment. Furthermore, in the mass balance study, only 3% of radioactivity was recovered in urine, indicating renal excretion is a minor elimination route of palovarotene. No dedicated PK study was conducted in subjects with renal impairment. According to the Applicant's population PK analyses, there was no evidence that serum creatinine affected palovarotene PK. Most subjects in the population PK dataset (N=577) had baseline serum creatinine <1.2 mg/dL and only <5% of subjects had baseline serum creatinine between 1.2 – 1.6 mg/dL. Due to the minor role of renal excretion in palovarotene elimination, an increased palovarotene exposure is not expected in patients with mild-to-moderate renal impairment. However, since severe renal impairment may potentially affect the drug's hepatic metabolism, there is a concern of increased exposure in severely renally impaired patients. While no dose adjustment is needed for patients with mild-to-moderate renal impairment, the use of palovarotene in patients with severe renal impairment is not recommended.

Body Weight

According to the population PK analysis, body weight has a significant impact on palovarotene PK, resulting in increasing exposure with decreasing weight at the same dose. For the range of body weights in the analysis population (13-130 kg), CL/F ranged from 8.85-26.8 L/h, which was 56% lower to 35% higher compared to the typical value of CL/F (19.9 L/h) for a 70-kg subject. The simulation results showed that following 20 mg daily dosing under fed state, steady-state AUC was 8% higher for a 51 kg subject and 18% lower for a 98 kg subject compared to a 70 kg subject, respectively. ([Table 60](#)).

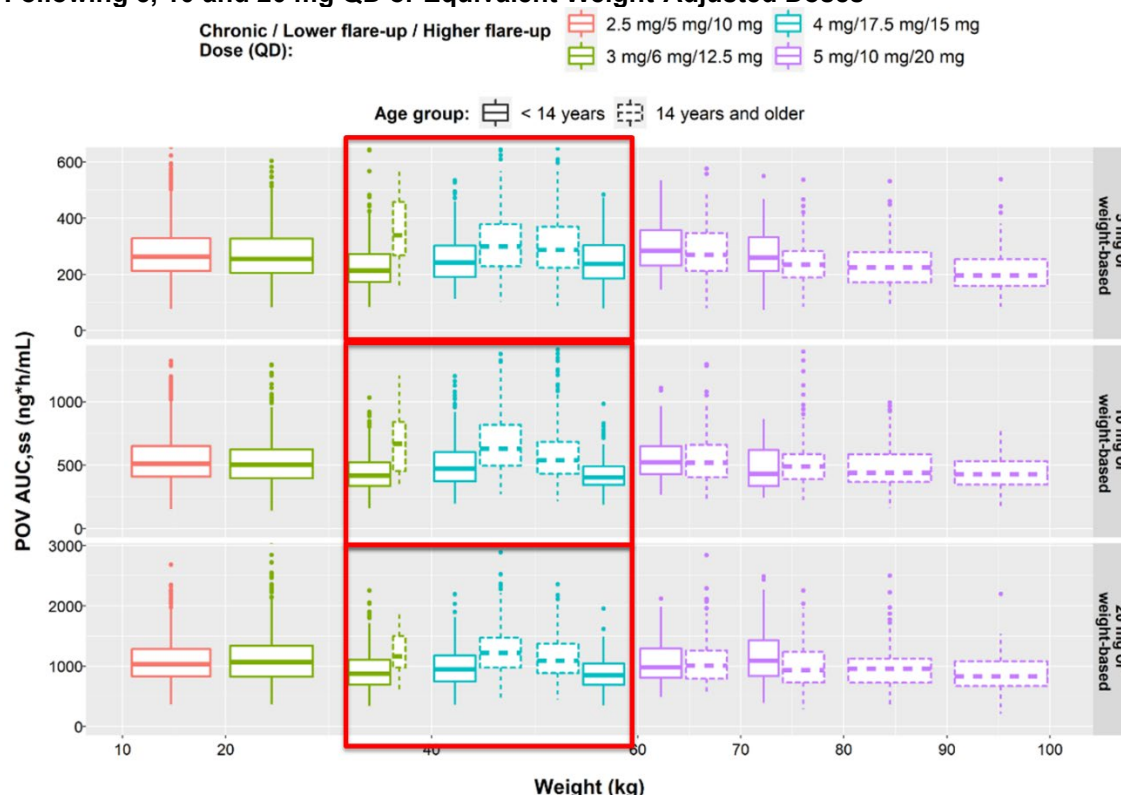
Table 60. Weight-Adjusted Palovarotene Chronic and Flare-up Doses

Body Weight Group	Chronic Dosing	Flare-up (Weeks 1 to 4)	Flare-up (Weeks 5 to 12)
≥60 kg	5 mg	20 mg	10 mg
40-<60 kg	4 mg	15 mg	7.5 mg
20-<40 kg	3 mg	12.5 mg	6 mg
10-<20 kg	2.5 mg	10 mg	5 mg
(b) (4)			

The PK data from Study 202 showed that skeletally immature patients receiving weight-adjusted doses had systemic exposure comparable to that in adults receiving chronic 5 mg and flare-up 10/20 mg doses (Refer to Appendices 14.3). Consistently, population PK simulations showed comparable palovarotene exposure between patients <14 years and patients ≥14 years who are greater than 60 kg ([Figure 15](#)). However, the exposures of palovarotene in patients ≥14 years were higher than that in subjects <14 years in the same body weight categories (i.e., body weight 30 kg– 40 kg, 40 kg – 50 kg, and 50 kg – 60 kg). Since body weight rather than age is a significant covariate affecting palovarotene PK in the population PK model, there is not sufficient rationale supporting 14 years of age to be included in the weight-adjusted dosing regimen. In addition, in phase 3 clinical studies, patients ≥18 years of age received orally administered 5 mg palovarotene once daily and 20 mg/10 mg dosing at flare-up, whereas weight-adjusted dose was used for skeletally immature subjects under 18 years of age.

Based on this information, the review team recommends that the weight-adjusted doses be applied for FOP patients <18 years of age, while patients ≥18 years of age receive orally administered 5 mg palovarotene once daily and 20 mg/10 mg dosing at flare-up. This recommendation follows the same recommendations as in Study 301.

Figure 15. Simulated Steady-state AUC of Palovarotene in Patients ≥ 14 Years or < 14 Years Following 5, 10 and 20 mg QD or Equivalent Weight-Adjusted Doses



Source: Clinical pharmacology reviewer's analysis

Note: In this simulation, patients ≥ 14 years (dashed boxplots) received 5, 10 and 20 mg QD dose; patients < 14 years (solid boxplots) received equivalent weight-adjusted doses.

Abbreviations: AUC, area under the concentration versus time curve; POV, palovarotene; QD, once daily

Age, Sex, Race, and Health Status

In a single-dose PK study (Study NP17726), no significant difference in palovarotene exposure was observed between young males (21 to 40 years) and elder males (65 to 74 years). The geometric mean AUC of palovarotene in elder women (65 to 73 years) was 20% higher than that in elder males. The difference in palovarotene exposure between elder males and females can be explained by the differences in body weight. In another single-dose PK study (Study PVO-1A-101), the PK parameters of palovarotene were similar between Japanese and non-Asian groups at either the 10 mg or 5 mg dose. Based on a population PK analysis of palovarotene plasma concentration data from 577 subjects with baseline age ranging from 2 to 85 years, there was no evidence that age affected palovarotene pharmacokinetics. Similarly, population PK analysis showed that neither sex, race (Asian, black, white, and other), nor health status (healthy volunteers, FOP, chronic obstructive pulmonary disease, and multiple osteochondromas) were significant covariates on the PK of palovarotene.

8.2. Extrinsic Factors

Food Effects

The food effect study (Study PVO-1A-102) was conducted in healthy volunteers using the to-be-marketed formulation (TBM) of palovarotene. In addition to the effect of food on the PK of palovarotene capsules, the study evaluated the effect of swallowing intact capsule versus sprinkling the contents on apple sauce on the PK of palovarotene. Following oral administration of two 10 mg palovarotene capsules after a high-fat breakfast, palovarotene C_{max} and AUC_{0-inf} were 15% and 39% higher, respectively, when compared to exposures under fasting conditions (Table 61). Following administration of the palovarotene capsules by sprinkling the contents onto one teaspoon of apple sauce after a high-fat breakfast, both AUC and C_{max} were comparable to when the capsules were swallowed whole after a high-fat breakfast (Table 61).

In Study 301, patients were instructed to take palovarotene capsules with a full meal. For FOP patients with difficulty swallowing intact capsules due to ankylosis of the jaw, the contents of capsules were sprinkled on soft foods (i.e., apple sauce) and administered with a meal. In the drug label, the Applicant proposed that palovarotene should be administered with food, preferably at the same time each day. If a patient cannot swallow whole capsules, he/she can sprinkle the contents of capsules onto a teaspoon of soft food and take with a meal. The Applicant's dose administration instructions are supported by the food effect data and phase 3 trial.

Table 61. Statistical Analysis of Bioavailability of Palovarotene Under Fed and Fasted Conditions

Test/Reference	Pharmacokinetic Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CIs)
		Test	Reference	
Fed/Fasted	AUC_{0-inf} (ng•h/mL)	1071.0	770.2	139.1 (128.5 – 150.5)
	AUC_{0-t} (ng•h/mL)	1059.8	751.4	141.0 (132.5 – 150.1)
	C_{max} (ng/mL)	139.4	121.0	115.2 (100.5 – 132.1)
Sprinkling/Capsules	AUC_{0-inf} (ng•h/mL)	1052.3	1071.0	98.26 (91.09 – 106.0)
	AUC_{0-t} (ng•h/mL)	1042.1	1059.8	98.33 (92.38 – 104.7)
	C_{max} (ng/mL)	131.9	139.4	94.66 (82.57 – 108.5)

Source: Clinical study report PVO-1A-102

Abbreviations: AUC_{0-inf} , area under the concentration versus time curve from time 0 to infinity; AUC_{0-t} , area under the concentration versus time curve from time 0 to time t; CI, confidence interval; C_{max} , maximum observed concentration

Smoking

In Study RB16327, a single dose of 5 mg palovarotene was administered to smokers (N=6) and nonsmokers (N=6) under fed state. Compared to nonsmokers, smokers showed a 22% increase in mean AUC (271±75 ng*h/mL versus 222±29 ng*h/mL), and 32% increase in mean C_{max} (39.7±9.83 ng/mL versus 30.1±8.21 ng/mL) (refer to Section 14.2.1 for more information of Study RB16327). Population PK analysis based on the PK data of 66 smokers and 370 nonsmokers did not detect smoking status as a significant covariate on the PK of palovarotene. No dose adjustment is needed for smokers.

Drug-Drug Interaction (DDI)

In vitro drug interaction studies showed that palovarotene is mainly metabolized by CYP3A4 and metabolized by CYP2C8 and 2C19 to a minor extent. At clinically relevant plasma concentrations, palovarotene did not significantly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 in vitro. Palovarotene at clinically relevant concentration (0.32µM) did not induce CYP1A2, CYP2C8, CYP2C9 and CYP2C19, but induced CYP3A4 and CYP2B6 mRNA expression by 3.8 – 5.0 folds and 1.8 - 2.4 folds in vitro, respectively.

The Applicant submitted four clinical DDI study reports and a physiological based pharmacokinetic (PBPK) model report that evaluated the DDI liability of palovarotene as a victim of CYP3A4, CYP2C8, and CYP2C19.

Effect of CYP3A4 Inhibition and Induction on Palovarotene PK

Study 17041B showed that co-administration of ketoconazole 400 mg QD (a strong CYP3A4 inhibitor) and palovarotene 1 mg QD caused an increase of palovarotene AUC by 3.1-fold. Study NP17040 showed co-administration of rifampin 600 mg QD (a strong inducer of CYP3A4, 2C8, 2C19 and several transporters) and palovarotene 1 mg QD caused a decrease of palovarotene AUC by 89%. The PBPK model simulated the scenarios of single oral doses of 5 mg and 20 mg palovarotene in the absence of any perpetrator and on the 15th day of 21 days of dosing of erythromycin (moderate CYP3A4 inhibitor) or efavirenz (moderate CYP3A4 inducer) in healthy subjects. The simulated geometric mean ratios of AUC_{0-inf} and C_{max} for palovarotene in the absence and presence of erythromycin (500 mg QID) are 2.54 (90%CI of 2.39, 2.69) and 1.64 (90% CI of 1.59, 1.69), respectively, and for efavirenz (600 QD) are (b) (4) and (b) (4) respectively.

The review team agrees that the Applicant's PBPK analyses are adequate to evaluate the effects of the moderate CYP3A inhibitor erythromycin on the PK of palovarotene. However, the review team concluded that the PBPK analyses are inadequate to evaluate the effect of the moderate CYP3A inducer efavirenz on the PK of palovarotene for the following reasons: (1) The PBPK model underpredicted the effect of the strong CYP3A inducer rifampin on the AUC and C_{max} of palovarotene by (b) (4) (the reason for the underprediction is unclear), thus, the ability of the palovarotene model to predict the effect of other inducers is in question; (2) efavirenz is also a clinical inducer of CYP2C19 ; however, the current efavirenz PBPK model is not validated for CYP2C19 induction predictions; and (3) there is uncertainty about the contribution of CYP2C19 in the elimination of palovarotene (see Section 14.4 for more detailed assessment).

The Applicant proposed to avoid concomitant use of moderate-to-strong CYP3A4 inhibitors or inducers. The review team agrees with the proposal to avoid concomitant use of moderate-to-strong CYP3A inhibitors and moderate CYP3A inducers. However, since rifampin decreased the AUC of palovarotene by 89%, the review team recommends that the use of strong CYP3A inducers with palovarotene should be prohibited. Since a moderate CYP3A inhibitor is expected to increase the AUC of palovarotene by approximately 2.54-fold based on the PBPK simulation using erythromycin, the dose of palovarotene should be reduced by half ([Table 62](#)). Since the effect of moderate CYP3A inducer on the PK of palovarotene is unknown, the concomitant use of palovarotene with moderate CYP3A inducers is not recommended.

During the late cycle communication, the review team recommended the Applicant to conduct a clinical DDI trial to evaluate the effect of a moderate CYP3A4 inducer on the pharmacokinetics of palovarotene in healthy adult subjects, to assess the magnitude of exposure change of palovarotene, and to determine the appropriate dosing recommendations for palovarotene when used concomitantly with a moderate CYP3A4 inducer. However, the Applicant indicated that common CYP3A moderate inducers are not expected to be routinely co-administrated with palovarotene in patients with FOP. The Applicant prefers to keep the current recommendation in the USPI to “avoid the concomitant use of moderate CYP3A4 inducers with SOHONOS”, rather than to conduct a clinical DDI trial. The review team agrees with the Applicant’s approach.

Table 62. Dose Reduction of Palovarotene for Use With Moderate CYP3A Inhibitors

Body Weight	Chronic Dosing	Flare up (Weeks 1 to 4)	Flare up (Weeks 5 to 12)
≥60 kg*	2.5 mg	10 mg	5 mg
40-<60 kg	2 mg	7.5 mg	4 mg
20-<40 kg	1.5 mg	6 mg	3 mg
10-<20 kg	1 mg	5 mg	2.5 mg

Source: Clinical pharmacology reviewer’s recommendation

In Study NP21025, a single oral dose of 40 mg prednisone decreased the AUC of co-administered palovarotene by 14%. However, maximum induction of CYP3A4 was not achieved with a single dose of prednisone. The results from Study NP21025 cannot be used to justify that co-administration of multiple-dose prednisone does not affect the PK of palovarotene. Population PK analyses of the PK data of 59 subjects concomitantly taking prednisone did not detect the use of prednisone as a significant covariate on the PK of palovarotene. The review team agrees that no dose adjustment is needed for palovarotene in patients who concomitantly use prednisone.

Effect of CYP2C9 and CYP2C19 Inhibition and Induction on Palovarotene PK

The Applicant conducted PBPK modeling to predict the scenarios of single oral doses of 5 mg and 20 mg palovarotene in the presence of gemfibrozil (strong CYP2C8 inhibitor), fluoxetine (strong CYP2C19 inhibitor) and fluconazole (moderate CYP3A inhibitor and strong CYP2C19 inhibitor) in healthy subjects. However, the review team concluded that the PBPK analyses are inadequate to evaluate the effects of CYP2C8 and CYP2C19 inhibitors on the PK of palovarotene due to the uncertainty about the contribution of CYP2C8 and CYP2C19 to elimination of palovarotene (see Section [14.4](#) for more detailed assessment). Considering the strong CYP3A4 inhibitor ketoconazole increased the AUC of palovarotene by 3.1-fold, (b) (4)

, it is reasonable to expect that coadministration of a specific inhibitor of CYP2C8 or CYP2C19 would result in a weak interaction effect (i.e., increase on the AUC of palovarotene by (b) (4)). Additionally, in the phase 3 trial, concomitant use of strong inhibitors of CYP2C8 and CYP2C19 was allowed and the intersubject variability in AUC was 40%. The review team agrees with the Applicant that no dose adjustment is needed for palovarotene when patients concomitantly use a specific strong CYP2C8 or 2C19 inhibitor. However, concomitant use of palovarotene with a dual strong CYP2C19 and moderate CYP3A4 inhibitor (e.g., fluconazole, fluvoxamine) should be avoided. If co-administration is unavoidable, the dose of palovarotene should be reduced by half (Table 63).

Effect of Palovarotene on Other Drugs

Prednisone

Study NP21025 showed that co-administration palovarotene 5 mg QD did not change the PK of prednisone. However, the effect of palovarotene 10 mg or 20 mg QD on co-administered prednisone was not evaluated.

Midazolam

In Study PVO-1A-102, palovarotene 20 mg QD reduced the AUC and C_{max} of co-administered midazolam by 14% and 10%, respectively. Palovarotene is not a clinical inducer of CYP3A4. The review team agrees with the Applicant that no dose adjustment is needed for concomitantly used CYP3A4 substrates.

The clinical DDI study findings and management strategies are summarized in [Table 63](#).

Table 63. Major Clinical Drug Interaction Study Findings and Management Strategies for Palovarotene

Evaluation	GMR	The Applicant's Management Strategies	Review Team's Recommendation
The Effects of Other Drugs on Palovarotene			
CYP3A4 inhibition by ketoconazole, 400 mg QD x 7 days (Study 17041B)	C_{max} 2.2 (1.98, 2.44) AUC3.1 (2.96, 3.27)	Avoid concomitant use of strong CYP3A4 inhibitors	Agree with the Applicant
CYP3A inhibition by erythromycin, 500 mg QID x 21 days (PBPK Report IPN-3B)	C_{max} 1.64 (1.59, 1.69) AUC2.54 (2.39, 2.69)	Avoid concomitant use of moderate CYP3A4 inhibitors	Avoid concomitant use. If concomitant use is unavoidable, reduce the dose of palovarotene by half
CYP450 enzyme induction by rifampin, 600 mg QD x 10 days (Study NP17040)	C_{max} 0.19 (0.16, 0.23) AUC0.11 (0.10, 0.13)	Avoid concomitant use of strong CYP3A4 inducers.	Do not administer strong CYP3A inhibitors
CYP450 enzyme induction by efavirenz, 600 mg QD x 21 days (PBPK Report IPN-3B)	C_{max} 0.52 (0.50, 0.54) AUC0.40 (0.38, 0.42)	Avoid concomitant use of moderate CYP3A4 inducers	The use of palovarotene is not recommended
CYP450 enzyme induction by a single dose of prednisone, 40 mg (Study NP21025)	C_{max} 0.87 (0.72, 1.05) AUC0.87 (0.76, 0.99)	No dose adjustment for palovarotene is needed for patients on prednisone treatment.	Agree with the Applicant based on population PK analysis.
The Effects of Palovarotene on Other Drugs			
CYP3A4 induction by palovarotene 20 mg QD x 14 days (Study PVO-1A-102)	C_{max} 0.90 (0.84, 0.98) AUC0.87 (0.80, 0.94) (midazolam)	Palovarotene is not a clinical inducer of CYP3A4 at 20 mg QD dose and no dose adjustment is needed for concomitantly used CYP3A4 substrates.	Agree with the Applicant
Effect of palovarotene 5 mg QD on co-administered prednisone (Study NP21025)	No change in C_{max} and AUC of prednisone or prednisolone	Palovarotene has no effect on the pharmacokinetics of prednisone or its metabolite prednisolone	The dose of palovarotene in Study NP21025 was lower than the recommended maximum daily dose (20 mg QD). The effect of palovarotene 10 mg or 20 mg QD on co-administered prednisone is unknown.

Source: Clinical pharmacology reviewer's recommendation

*Results presented as GMR geometric mean ratio with (90% CI)

Abbreviations: AUC, area under the concentration versus time curve; CI, confidence interval; C_{max} , maximum observed concentration; GMR, geometric mean ratio; PK, pharmacokinetics; QD, once daily; QID, four times a day

Transporter-Mediated Drug Interactions

In vitro data showed that palovarotene is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3 or OCT1. Substrate interaction assessments with renal transporters OAT1, OAT3, OCT2, MATE1 and MATE2-K transporters were not conducted because only 3.2% of the dose was recovered in urine. Palovarotene is not an in vitro inhibitor of P-gp, OAT1, OAT3, OCT2, MATE1, or MATE2-K transporters. Palovarotene inhibited BCRP, OATP1B1, OATP1B3, OCT1, and BSEP transporter with IC_{50} values of 9.69 μ M, 1.83 μ M, >3 μ M, >3 μ M, and 14.7 μ M, respectively. The steady-state C_{max} of palovarotene following 20 mg QD oral dosing was 0.333 μ M to 0.487 μ M. At the recommended maximum dose (20 mg QD), palovarotene does not pose a clinically relevant risk with respect to the inhibition of OATP1B1, OATP1B3, OCT1, or BSEP transporters. Also, the Applicant measured the solubility of palovarotene in fed-state simulated intestinal fluid at 37°C and pH 5, which was 2.37 ± 0.23 μ g/mL or 5.8 μ M. The ratio of I_{gut}/IC_{50} (I_{gut} : the intestinal luminal concentration of the interacting drug calculated as the dose/250 mL) for intestinal BCRP transporter is 0.60 and the calculated palovarotene R value is 1.60, which is below the threshold value of 11. No BCRP-mediated DDI is expected for palovarotene at 20 mg QD.

8.3. Plans for Pediatric Drug Development

Palovarotene is indicated for the treatment of adults and children (females 8 years and older, and males 10 years and older) with FOP. A six-week toxicity study was conducted in juvenile rats with oral palovarotene administered daily at 0.1, 0.5 or 1.2 mg/kg/day from postnatal Weeks 3 through 9 (prior to the closure of epiphyses, which normally occurs between Weeks 15 to 16). Palovarotene adversely affected skeletal growth and development resulting in abnormal bone size, shape, mass and/or geometry in juvenile rats treated at ≥ 0.5 mg/kg/day (below the clinical exposure, based on AUC). Palovarotene caused dose-related thinning/closure of the physis, physeal hypertrophy and chondrodysplasia in multiple bones, decreased endochondral ossification and hypertrophic hyaline cartilage, and hypertrophy and chondrodysplasia in articular cartilage. Additionally, decreased bone density, avascular necrosis in the femoral head and neck region, and microfractures were notable at 1.2 mg/kg/day. These changes occurred with correlating decreases in bone formation markers, radiological changes (abnormal shape, diffuse bone loss, increased/decreased physis thickness, and increased space between bones). No recovery for effects on thinning/closure of the physis or chondrodysplasia were observed at ≥ 0.5 mg/kg/day; partial to complete recovery of decreased bone growth were seen in animals at 0.5 mg/kg/day.

Table 64. Juvenile Toxicity Safety Margins

Study	Adverse Effects	NOAEL (mg/kg/day)	AUC Exposure (ng.h/mL)	Safety Margins* (Multiples)
Juvenile rat	Skeletal toxicities including reduction in bone size, BMC, BMD, thinning/closure of the physis, physeal hypertrophy and chondrodysplasia in multiple bones, decreased endochondral ossification and hypertrophic hyaline cartilage, hypertrophy and chondrodysplasia in articular cartilage and decreased bone at ≥ 0.5 mg/kg/day; avascular necrosis in the femoral head and neck region and microfractures were notable at 1.2 mg/kg/day. Thinning/closure of the physis and chondrodysplasia did not recover; decreased bone partial to complete recovery of were seen in animals at 0.5 mg/kg/day.	0.1	681	0.7

Source: Reviewer derived from data from Study # 6700132

*The maximum recommend human dose is 20 mg; Safety margin calculated based on $AUC_{0-4} = 1060$ ng.h/ml at steady state in phase 3 study PVO-1A-301

Abbreviations: AUC, area under the concentration versus time curve; BMC, bone mineral content; BMD, bone mineral density; NOAEL, no observed adverse effect level

8.4. Pregnancy and Lactation

Animal Data

The Applicant conducted fertility and early embryonic development studies in male and female rats and an embryofetal development study in a single species (rat). The Agency agreed that there was no benefit in conducting an EFD study in pregnant animals of a second species, as palovarotene adversely affected fetal development in pregnant rats, which was consistent with the retinoid class known to carry fetal development risks.

The following section summarizes the outcomes and conclusions of these studies. Greater details of the reproductive toxicity studies are provided in the Section [13.1](#).

Table 65. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	In an embryo-fetal developmental toxicity study in rats, palovarotene was administered orally during the period of organogenesis (gestation day 6 to 17) at doses of 0.01, 0.25 and 1.25 mg/kg/day. Palovarotene caused multiple fetal malformations including cleft palate, protruding tongue, eye defects (anophthalmia, microphthalmia), skull abnormalities (exencephaly, abnormal head shape, dilated cerebral ventricles, misshapen brain), abnormalities of blood vessels, kidney, ureter, and skeletal malformations and variations (short, unossified/incomplete ossification of bones) at ≥ 0.25 mg/kg/day (below clinical exposure). Maternal toxicities in the form of reductions in body weight gains were noted at ≥ 0.25 mg/kg/day and lower food consumption at the 1.25 mg/kg/day. The teratogenic findings with palovarotene are consistent with malformations noted with the class (retinoids). The NOAEL for effects on fetal development was 0.01 mg/kg ($AUC_{0-24h} = 8.7$ ng.h/mL, below clinical exposure).
8.2 Lactation	The partitioning of palovarotene into animal milk was not studied.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	In a male fertility and early embryonic development study, palovarotene was administered orally to male rats prior to and during mating for total of 11 weeks at doses of 0.3, 1 and 3 mg/kg/day. Males did not tolerate 3 mg/kg/day and this group was terminated prematurely on Day 39 due to the death of a male on Day 30, with adverse skin and hair coat related clinical signs, and substantially reduced BW gain. Paternal toxicities including significant reduction (up to 18%) in BW gains and skin changes (thin cover, red skin and scab) were seen at 0.3 and 1 mg/kg/day. Therefore, the NOAEL for paternal general toxicity was not identified. Palovarotene did not affect mating, fertility indices, or reproduction parameters. The NOAEL for reproductive effects in males was 1 mg/kg/day ($AUC_{0-24h} = 421$ ng.h/mL) based on the absence of adverse effects on fertility and reproduction parameters. In a female fertility and early embryonic development study, palovarotene was administered orally to female rats 14 days prior to mating with drug naïve males and up to GD 7 at dose levels of 0.3, 1 and 3 mg/kg/day. Palovarotene caused prolonged periods of diestrus, slightly lower ovulation rates, fewer implantation sites, and reduced numbers of live embryos at 3 mg/kg/day. No effect was observed on mating and fertility indices or the conception rate in females at any dose level. Maternal toxicities, including skin, hair/coat related clinical signs, reduced BW gain and lower food consumption were noted at ≥ 1 mg/kg/day. The NOAEL for female fertility was 3 mg/kg/day ($AUC_{0-24h} = 918$ ng.h/mL).

Source: Reviewer derived from data from Study # 9001429, 9001478, 1003177

Abbreviations: AUC_{0-24h} , area under the concentration versus time curve from time 0 to time 24 hours; BW, body weight; GD, gestation day; NOAEL, no observed adverse effect level

The safety margins identified from fertility and embryo-fetal development studies conducted in rat are shown in Table 66. The reproductive toxicities (teratogenicity) will be addressed in Section 8 and 13 of the label.

Table 66. Palovarotene Reproductive Toxicity Exposure Margins

Study	NOAEL (mg/kg)	Nonclinical Exposure (µg.h/mL)	Exposure Margins ¹ (Multiples)	Basis for NOAEL
Fertility male rat	3	918 ²	~0.9	No adverse effect on male fertility indices.
Fertility female rat	1	421	0.4	Adverse female reproductive indices (prolonged periods of diestrus, slightly lower ovulation rate, fewer implantation sites and live embryos) at 3 mg/kg/day.
EFD rat	0.01	8.7 ³	0.008	Adverse fetal external, visceral and skeletal malformations skeletal at ≥0.25 mg/kg/day.

Source: Reviewer derived from data from Study # 9001429, 9001478, 1003177

¹The maximum recommend human dose is 20 mg; the safety margin is based on AUC₀₋₄ = 1060 ng.h/mL at steady state in phase 3 study PVO-1A-301

²No PK data; based on 6-month study

³K data: GD17 exposure rat EFD study

Abbreviations: EFD, embryo-fetal development; NOAEL, no observed adverse effect level

9. Product Quality

Drug Substance

The Palovarotene drug substance is a new chemical entity. It is a poorly soluble achiral compound with a molecular formula of C₂₇H₃₀N₂O₂ and a molecular weight of 414.5 g/mol. It is manufactured as a single crystalline form (b) (4). The review confirmed the identity of the drug substance based on infrared (IR) spectroscopy, ¹H and ¹³C nuclear magnetic resonance (NMR) spectroscopy, mass spectroscopy (MS), ultraviolet (UV) spectroscopy, elemental analysis and x-ray powder differentiation (XRPD) data. The review also assessed starting material design, manufacturing process, in process controls, characterization, impurities, and physicochemical properties as adequate to support the quality of the drug substance. The drug substance specification includes appropriate tests and acceptance criteria to support the identity, strength, purity, and quality of the drug substance. Related substances are limited at levels recommended in ICH Q3A, except for (b) (4), which is proposed at a limit of ≤ (b) (4) %. This limit has been determined to be reasonable by the Pharmacology/Toxicology review team. Solvents used during the manufacturing process are controlled as per the ICH Q3C Guidelines. The risks associated with potential genotoxic impurities in the drug substance were assessed following ICH M7 and were determined to be extremely low. A retest date of (b) (4) months is granted for palovarotene drug substance when stored at (b) (4).

The Applicant proposed high acceptance criteria (original plan (b) (4) and current proposal (b) (4) %) for the impurity (b) (4) in the drug substance as compared to the qualification threshold (0.15%) established, as per ICH Q3A recommendations. (b) (4) is a process impurity of the drug substance which persists in the final drug substance at levels exceeding the ICH qualification threshold of 0.15%. It is (b) (4). It was identified in palovarotene batches late in the drug development phase and it was not present in drug substance batches used for pivotal repeat dose 26-week rat and 39-week dog toxicity studies. The toxicology batch (R0042674) used for the male and female fertility and early embryonic development (FEED) studies contained (b) (4), but at a much lower level ((b) (4) %) than in the proposed specification. Moreover, the toxicity endpoints assessed in the FEED study were limited compared to standard toxicity studies. On the other hand, (b) (4) was detected ((b) (4) %) in drug substance material used for clinical studies PVO-1A-202/204, PVO-2A-201 (MO-Ped) and PVO-1A-301 (Study 301). Based on the absence of an already established PDE, comprehensive toxicology data from the palovarotene nonclinical program or published studies, the safety of this impurity was not considered qualified at the time of the initial palovarotene NDA submission. In the NDA resubmission, the Applicant conducted and submitted nonclinical studies with (b) (4) and implemented manufacturing process changes and proposed a new acceptance limit of (b) (4) % for the commercial product.

Nonclinical toxicology studies to assess the safety profile of (b) (4) consisted of genotoxicity studies (QSAR in silico analyses and in vitro bacterial Ames and chromosomal aberration in human lymphocyte assays) and a dedicated 4-week oral general repeat dose toxicity study with the purified impurity, (b) (4). No structural alert for mutagenicity was detected on (b) (4) when tested by QSAR performed with expert- and statistical-based models (DEREK and SARAH). (b) (4) was neither mutagenic nor clastogenic in the in vitro Ames and chromosomal aberration assays in the presence and absence of metabolic activation. In the rat oral repeat dose general toxicity study, there was no (b) (4)-induced toxicological finding noted up to the highest dose tested (b) (4) mg/kg/day (≥ 10 -times maximum clinical exposure). Moreover, no finding of concern was reported up to (b) (4) mg/kg/day in the DRF 7-day rat toxicity study.

Overall, no safety hazard was identified in (b) (4) toxicology studies. The NOAEL dose identified in the confirmatory 4-week rat toxicity study with (b) (4) was (b) (4) mg/kg/day, providing >10 -fold the maximum level of (b) (4) calculated at the MRHD using the (b) (4) % specification limit. The completed nonclinical studies support the proposed impurity acceptance criteria of (b) (4) % (b) (4) and the safety of (b) (4) is considered qualified nonclinically.

Drug Product

The drug product is an immediate release capsule composed of the drug substance and inactive ingredients, including croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate. The hard gelatin capsule (size 0) is composed of titanium dioxide ((b) (4)) and gelatin ((b) (4)). The formulation contains no phthalates. The drug product was assessed with respect to its critical quality attributes and risks associated with drug product formulation, specification for quality control, stability for shelf-life determination, impurities, packaging, and compatibility with soft food for a pediatric patient population.

The review assessed the physicochemical risks to the drug product such as possible degradation during manufacturing and product shelf-life source of impurities in the drug product, and

compatibility with soft food. Absence of drug product compatibility data with soft food, and risk of nitrosamine impurity were identified during the review cycle. These issues were satisfactorily addressed by the Applicant. Labeling was revised as follows: “*SOHONOS may be swallowed whole, or capsules may be opened, and the contents emptied onto a teaspoon of soft food and taken within 1 hour of opening provided it was maintained at room temperature and not exposed to direct sunlight.*”

The drug product specification included acceptable tests and acceptance criteria to assure the identity, strength, purity, and quality of all strengths of the drug product. Analytical method validations for all tests were found to be acceptable. The shelf-life of 36 months is supported based on 36 months of long-term, 36 months of intermediate and 6 months of accelerated stability data. Photostability study shows that the drug product is sensitive to light. Therefore, appropriate instruction on container closure has been added. Finally, the in-use stability results show that drug product stays within the specification when blisters are exposed for 10 minutes to fluorescent light for 28 consecutive days.

Quality Labeling

The quality aspects of the labeling were reviewed and found to be adequate.

Manufacturing

Process

Manufacturing process utilizes (b) (4)

. The review assessed the critical manufacturing unit operation that can possibly impact the critical quality attributes of the drug product, risk assessment, process parameters, in-process control, sampling, executed master batch records, packaging, and manufacturability (i.e., yield and reconciliation). The reviewer identified absence of certain critical manufacturing information such as reconciliation data for each manufacturing unit operation, in-process controls for (b) (4).

These issues were satisfactorily resolved during the review cycle. Based on manufacturing knowledge gained with the experimental batch and historical data from the clinical batches, the Applicant has adequately established a viable commercial manufacturing process with acceptable operational targets and ranges for process parameters.

Facilities

All facilities were found to be acceptable based on previous inspection history.

Biopharmaceutics

The biopharmaceutics review focused on the acceptability of the in vitro dissolution test method and acceptance criteria. No biowaiver for lower strengths of the drug product was requested as clinical and TBM (to be marketed) drug product batches were administered in various clinical safety/pharmacokinetic studies.

Bridging of clinical and TBM drug products manufactured at different manufacturing sites is supported by pharmacokinetic (PK) data in healthy and FOP patient populations that were assessed by the Office of Clinical Pharmacology (OCP). In response to several information

requests, the Applicant provided adequate justification for the final test method parameters and acceptance criteria, as well as data to support the discriminating power of the method with respect to variations in manufacturing and drug substance particle size variation. Because the drug is a BCS class II compound, the Applicant Team Lead (ATL) initiated a discussion between the OPQ sub discipline reviewers regarding the acceptability of the drug substance particle size distribution (PSD) limit and its possible impact on bioavailability (BA). Both the biopharmaceutics and drug substances reviewers agreed with the Applicant's proposed PSD limit of D90-NMT (b) (4) μm for the drug substance specification.

Life-Cycle Considerations

Palovarotene is a BCS class II drug. Therefore, any change in the drug substance particle size distribution and polymorphism may require appropriate bridging to establish bioequivalence and a prior approval supplement (PAS).

Overall Recommendation by Subdiscipline

Drug Substance	Adequate
Drug Product	Adequate
Quality Labeling	Adequate
Manufacturing	Adequate
Biopharmaceutics	Adequate
Microbiology	N/A

Environmental Assessment

Categorical Exclusion	Adequate

Conclusions Regarding Drug Quality

The Office of Pharmaceutical Quality Review team has assessed NDA 215559 with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that the drug product purports to have. As such, OPQ recommends approval of this NDA from a quality perspective.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

The clinical studies (NHS, 201, 202A/B/C, 301) were conducted in accordance with the ethical principles of the Declaration of Helsinki, and that are consistent with the ICH Good Clinical Practice (GCP) and FDA regulations.

The original NDA submitted on March 31, 2021, was withdrawn on August 21, 2021, due to issues of data quality and integrity involving missing WBCT scan readings, which were identified during the review cycle and required extensive updating of the datasets and efficacy analyses. The resubmission includes a Data Integrity Quality Review Report which outlines the steps that were taken to assure the accuracy and reliability of the data. During this second review cycle, no additional issues involving data quality or integrity were identified.

Financial disclosure information was provided (in the original NDA submission) for the covered clinical studies 001, 201, 202A/B/C and 301, as defined by 21 Code of Federal Regulations (CFR) 54.2(e), which establish the effectiveness and safety of palovarotene (See Section [23](#)). No concerns are raised about the integrity of the data.

11. Advisory Committee Summary

Not applicable. An originally schedule Advisory Committee meeting was postponed until after the Applicant submits additional data and data analyses as requested in multiple Information Requests from the Division during this review cycle.

III. Appendices

12. Summary of Regulatory History

The investigational new drug (IND) 120181 was submitted by Clementia Pharmaceuticals Inc. (Clementia) on March 28, 2014, to investigate palovarotene for the treatment of fibrodysplasia ossificans progressiva (FOP). Palovarotene was previously under development by Roche Pharmaceuticals Inc. (Roche) under IND (b) (4)

. Clementia licensed palovarotene from Roche (b) (4)

On July 21, 2014, U.S. Food and Drug Administration (FDA) designated palovarotene as an orphan drug product for the treatment of FOP. Fast Track designation was subsequently granted on November 25, 2014, for prevention of heterotopic ossification following preosseous flare-ups in patients with FOP. In a meeting held on May 14, 2015, Clementia updated FDA on the development of palovarotene for the treatment of FOP as it pertained to the pediatric population and discussed the overall development plan to support product registration. During this meeting FDA reiterated concerns with Clementia's methodology for selecting doses for pediatric patients and suggested that Clementia could use nonclinical data on the reversibility of growth effects to help justify their pediatric dose selection.

A subsequent type C meeting was held on March 1, 2017, to gain agreement on the formation of new heterotopic ossification (HO) as a clinically meaningful outcome that would be appropriate as the primary endpoint in a phase 3 study, and the potential to utilize Clementia's natural history study (NHS) as a control group. During the meeting, FDA conveyed that in principle, they agreed with the use of new HO for the primary endpoint; however, FDA requested additional clarification on the specifics of how new HO data would be obtained for use as the primary efficacy endpoint. FDA also stated that additional discussion would be needed regarding the use of the NHS as an external control group for the phase 3 study.

An end-of-phase 2 (EOP2) meeting was held on June 27, 2017, to discuss key design features of the phase 3 study, including enrollment criteria, dosing regimen, control group, and safety monitoring. FDA conveyed that use of the NHS study as an external control group may be acceptable; however, the FDA reiterated the preference for randomized controlled data. FDA further noted that the acceptability of NHS data and comparability of NHS and phase 3 patients will be review issues. With regards to dosing, FDA commented that chronic dosing for adult patients appeared reasonable, but the chronic dosing regimen for the pediatric population, especially skeletally immature children, was a safety concern. FDA conveyed to Clementia that the phase 3 protocol should have clear criteria, schedules, and algorithms for dose interruption and dose de-escalation. Additionally, FDA recommended stringent safety monitoring, including the Columbia-Suicide Severity Rating Scale (C-SSRS) and evaluation of growth in the pediatric population. During this meeting, FDA also noted that a food effect study was conducted in the COPD program; Clementia agreed to perform a food effect study with the to-be-marketed formulation specific for the FOP program. Breakthrough Therapy designation for the prevention of HO in patients with FOP was granted on July 11, 2017.

At a type B meeting held on October 23, 2018, under the Breakthrough Designation program, Clementia requested FDA concurrence for the potential of the phase 2 outcomes data for the episodic flare-up 20/10 mg palovarotene regimen to support a New Drug Application (NDA) for full approval of this dosing regimen for the treatment of FOP in children and adults. It was agreed that the available phase 2 data would support the filing of an NDA for prevention of heterotopic ossification associated with flare up symptoms in patients with FOP. Clementia proposed, and FDA agreed, that the ongoing phase 3 trial could be submitted as a supplemental NDA for a chronic dosing regimen. This meeting also included discussion about the different imaging modalities that were used in the studies and the image acquisition guidelines and adjudication processes.

Another type B meeting held under the Breakthrough Designation program on February 5, 2019, focused discussion on nonclinical aspects of the planned NDA. FDA stated that nonclinical studies to assess the effects of palovarotene on female fertility, early embryonic development, and male fertility, would be required. Clementia responded with a request to conduct these studies as a postmarketing commitment. The requested studies were conducted subsequently and submitted with the NDA.

Rare Pediatric Disease designation was granted on February 7, 2019. Pre-NDA meetings were held with CMC and clinical on February 7 and February 14, 2019, respectively. During the February 14, 2019, meeting, the format and content of the planned NDA for all relevant disciplines was discussed. FDA recommended that a thorough QT (TQT) study should be conducted, as the available nonclinical data might not support waiver of a TQT study. FDA also continued to recommend that Clementia conduct a food effect study with the to-be-marketed formulation of palovarotene to support labeling that the drug may be swallowed whole or sprinkled on soft foods. There were no agreements made for late submission of application components.

In April 2019, Clementia was acquired by Ipsen. Ipsen Biopharmaceuticals, Inc. is the US commercial branch of Ipsen. On December 4, 2019, a teleconference was held during which a partial clinical hold (PCH) was issued by the FDA for children under 14 years of age participating in the palovarotene clinical trials following reports of premature epiphyseal closure. Ipsen submitted a complete response to the PCH on April 16, 2020. FDA issued a correspondence on May 15, 2020, to continue the PCH. This partial clinical hold remains in effect.

A subsequent pre-NDA Meeting was held on July 28, 2020, to discuss the adequacy of Ipsen's drug development program to support their future NDA. Ipsen's updated proposal included changes to the following: indication (b) (4)

_____ dosing regimen (to include chronic and flare-up dosing regimens), and the proposed safety and efficacy data to be included in the submission. During this meeting, FDA communicated the need to review bone safety and other safety data on pediatric subjects ≥ 12 years old. There were no agreements made for late submission of application components.

Ipsen submitted NDA 215559 on March 31, 2021, and the application was filed on May 30, 2021. An informal teleconference was held with Ipsen on August 6, 2021, to discuss FDA concern about the reliability of the data submitted with the NDA. The concerns stemmed from the issues regarding the imaging vendor wherein Ipsen informed FDA that rereads for one or multiple timepoints for subjects in the trial were required. Due to these concerns, FDA

recommended that Ipsen withdraw their NDA and resubmit following further investigation with the imaging vendor to include a complete root cause analysis of the processes that may have led to the issues described. On August 12, 2021, Ipsen submitted a request for withdrawal of the application. The NDA was subsequently resubmitted on April 29, 2022, and filed on June 28, 2022.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

Data from a series of in vitro and in vivo nonclinical pharmacology studies completed with palovarotene and published scientific literature cited by the Applicant support the mechanism of action and potential benefits of palovarotene for the proposed indication in FOP patients.

13.1.1. Primary Pharmacology

Data from a series of in vitro and in vivo nonclinical pharmacology studies completed with palovarotene and published scientific literature cited by the Applicant support the mechanism of action and potential benefits of palovarotene for the proposed indication in FOP patients.

Table 67. In Vitro Pharmacological Studies of Palovarotene

Study	Findings
Receptor binding and transactivation assay	Palovarotene is selective for binding to RAR γ (6 to 10-fold) as compared to RAR α and RAR β , based on IC ₅₀ values (450, 4700, and 2900nM, respectively). Palovarotene demonstrated 3 to 12-fold greater in vitro functional activity at RAR γ as compared to RAR α and RAR β , with EC ₅₀ values of 8.0, 94.2 and 25.0nM, respectively). The main metabolites M2, M3, M4a and M4b demonstrated reduced RAR γ activity (1.2, 1.7, 14, and 4.2% of parent, respectively).
Effect of RAR γ agonist on cell differentiation and Smad signaling	Published study provided evidence that treatment with RAR γ agonists (e.g., CD1530) inhibited BMP-induced differentiation of chondrogenic (ATDC5) cells. In the treated ATDC5 cells, reductions (>80%) in the levels of phosphorylated Smad (pSmad 1, 5, and 8) and decreases in Smad proteins were noted. The response in ATDC5 cells was abrogated in the presence of proteasome inhibitors, suggesting that RAR γ agonists might potentially promote proteasome mediated Smad protein degradation. Similarly, palovarotene also reduced BMP-induced pSmad1/5 proteins in human FOP fibroblast cell line carrying an overactive ALK2 ^{R206H} mutation (replicates the codon 206 mutation present in most patients with FOP).

Source: Reviewer derived from Study # AT-7801, Study # CLM001-PD-001 and .

Abbreviation: BMP, bone morphogenetic protein; EC₅₀, dose at half-maximum response; FOP, fibrodysplasia ossificans progressiva; IC₅₀, half-maximal inhibitory concentration; RAR, retinoic acid receptor

The in vivo efficacy of palovarotene was evaluated by the Applicant and in published research studies in three distinct injury-based (BMP-implant, ALK^{Q207D} and ALK2^{R206H}) and one spontaneous (Prrx1-R206H) mouse models of HO.

Table 68. In Vivo Activity of Palovarotene

Study	Findings
<i>Injury-based HO models</i>	
BMP-2 implant mouse model	In BMP-implant mouse model, a wild-type mouse was implanted with matrigel containing skeletogenic factor recombinant rBMP-2 inside the calf muscle to induce injury. Mice received various daily doses of retinoids and palovarotene by oral gavage for 12 days. Suppression of HO was evaluated by measuring bone volume/total volume in ectopic masses by microcomputed tomography (microCT) on Day 12. In general, activation of the RAR receptor including by palovarotene at 0.12 to 4 mg/kg or HED 0.6 to 19 mg was effective in preventing the formation of ectopic mineralized tissue masses at the operation sites. The effectiveness of retinoids was highest for RARγ selective agonists (CD1530, palovarotene). The pan-agonist, all-transretinoic acid, and RARα agonist (NRX185183) inhibited HO as well, but their effectiveness was partial and required high doses. This was likely attributed to the high expression of RARγ in chondrogenic cells and chondrocytes as compared to other RAR members (Koyama et al. 1999). Mice treated with various doses of palovarotene showed dose-dependent HO inhibition. Inhibition of HO was mediated exclusively via the RARγ as the effect was completely abolished in RARγ null mice.
ALK ^{Q207D} mouse model	The ALK^{Q207D} transgenic mice carry Cre-inducible Q207D mutant (change in amino acid residue 207 from glutamine to aspartic acid) that constitutively activates ALK2 in the absence of ligand. HO was induced in homozygous ALK^{Q207D} mice at 16 days of age by intramuscular injection with adenovirus expressing Cre- recombinase (Adeno-Cre) into the posterior femoral muscle region to activate the transgene plus cardiotoxin to initiate an inflammatory triggering event (i.e., muscle injury). Oral administration of palovarotene to ALK^{Q207D} mice starting from the day of muscle injury and for 15 consecutive days resulted in dose-dependent reductions in injury-induced HO volume (75 to 100%) at the injury site, with ED₅₀ of 2 mg/kg/ day (HED =7 mg/day). Treatment with palovarotene is most effective (up to 93.5% HO inhibition) when initiated early (prior to and up to 3-days post injury), but effectiveness was decreased to 71% inhibition of heterotopic bone volume when initiating treatment 7-days post injury. The data suggest that RARγ agonists block HO by preventing chondrogenic cell differentiation and cartilage formation, but are not effective in the osteogenic phase of HO.

Study	Findings
ALK2 ^{R206H} mice model	The conditional-on knock-in ACVR1/ALK2^{R206H} mouse was developed to encode mildly activating gain-of-function classical FOP R206H mutant allele (substitution of arginine with histidine in codon 206). One month old ALK2^{R206H} mice were treated with doxycycline to induce global expression of the mutant allele and cardiotoxin into quadriceps muscle to induce local inflammation and HO. HO volume was measured by microCT and 3D image reconstruction at Day 14. Treatment with oral palovarotene starting from Day 1 to Day 3 of injury at 4 mg/kg (HED =19 mg) followed by 0.6 mg/kg (HED =3 mg) from Day 4 to Day 14 diminished heterotrophic bone formation by more than 86%, based on bone volume/total volume quantification. In vehicle-treated ALK2^{R206H} mice movement of the HO-affected leg was impaired whereas in drug treated group joint mobility of the HO-affected leg was maintained. Moreover, histochemical analysis showed that newly formed heterotopic cartilaginous tissue and endochondral bone were present in vehicle-treated but not in palovarotene-treated ALK2^{R206H} mice.
Spontaneous HO models	
Prrx1-R206H spontaneous HO mice model	Additional studies were conducted in Prrx1-R206H mice, that contain the R206H mutation in a tissue specific manner in skeletal mesenchymal progenitor cell (Prrx1⁺). Prrx1-R206H mice recapitulate many of the phenotypic features of FOP patients (e.g., malformed hindlimb at birth and spontaneous postnatal development of HO in the absence of injury). Palovarotene blocked spontaneous HO in pups when nursing dams were dosed orally with 50 µg/mouse/day from birth to 14 days and pups were dosed orally with 20µg Q2D from Day 15-30. It also prevented skeletal defects and improved mobility with markedly reduced HO. It also reversed histologic growth plate abnormalities compared to those observed in untreated Prrx1-R206H mice.

Source: Reviewer derived from Study # CLM001-PD-002, Study # 001,
Abbreviations: ACVR1, Activin receptor 1A/ also known as ALK2, activin-I kinase 2; EC₅₀, dose at half-maximum response; HED, human equivalent dose; HO, heterotopic ossification; microCT, microcomputed tomography; Q2D, every 2 days; RAR, retinoic acid receptor; rBMP-2; recombinant bone morphogenetic protein-2

13.1.2. Secondary Pharmacology

Screening for off-target binding sites indicated interaction with adenosine A3, benzodiazepine and the delta opioid receptor with high IC₅₀ values of 3.94, 2.12, 1.85µM, respectively, when tested up to 10µM. Of note, the IC₅₀ for RARγ binding is 450nM. Inhibition (>10%) of phosphodiesterase I, phosphodiesterase IV, cathepsin G, human immunodeficiency virus type 1 protease and increased guanylate cyclase activity were noted at high concentrations (30-fold higher than human exposure observed at MRHD). Therefore, palovarotene is not considered to possess clinically relevant secondary pharmacology activity.

13.1.3. Safety Pharmacology

Based on safety pharmacology studies conducted to assess the potential for cardiovascular, neurobehavioral, gastrointestinal and urinary effects, palovarotene did not appear to pose any

acute safety concerns at clinically relevant exposures. A respiratory safety pharmacology study was not conducted; however, no evidence of adverse respiratory function was noted in repeat dose toxicity studies.

Table 69. Summary of Safety Pharmacology Studies

Study/ Study No.	Findings
hERG assay in CHO cells	The effect of palovarotene on hERG current was tested on CHO cells expressing hERG potassium channel at concentrations ranging from 1 to 10μM using whole cell patch clamp method. Palovarotene significant reduced inward and outward K⁺ currents, with IC₅₀ of 7.2μM (~2985 ng/mL), which results in wide safety margin (>30-fold between hERG IC₅₀ and the free C_{max} at the MRHD). Based on the absence of in vivo CV effects, low in vitro potency, and absence of effects on hERG or action potential in the subsequently conducted assays, palovarotene is unlikely to affect CV functions in patients.
hERG assay in HEK293 cells	The effects of palovarotene and its major metabolites (M2, M3, M4a and M4b) on hERG current were tested on HEK293 cells expressing hERG potassium channel at 0.3, 1, 3, 10 and 30μM. Palovarotene and its metabolites did not produce more than 38% reduction in hERG current. IC₅₀ could not be calculated, but it is >30μM. The discrepancy in blocking hERG channel may be due to the differences in the hERG receptor structure between the cell lines. The positive controls in both test systems blocked hERG current, which confirmed the sensitivity of the test systems.
Action potential assay in Canine Purkinje fibers	In ventricular cardiac fibers isolated from dogs, palovarotene had no effect on resting membrane potential, depolarization rate, upstroke amplitude, or action potential duration at concentrations up to 10μM (30-fold C_{max} at MRHD).
Potential neurobehavioral effects in male Wistar rats Wistar Han rats 6/males/Group 0, 0.2, 1, 5 mg/kg Oral; single dose	Wistar Han rats were administered with a single oral dose of palovarotene at 0.2, 1 or 5 mg/kg. Irwin-type assessments were conducted at 0.5 to 5 h postdose. Palovarotene did not affect central or peripheral nervous system endpoints.
Potential cardiovascular effects in male beagle dogs Beagle dogs 4/males/Group 0, 0.04, 0.2, 1 and 10 mg/kg Oral; single dose	Conscious and telemetered dogs were administered with a single oral dose of palovarotene at 0.04, 0.2, 1 or 10 mg/kg. Cardiovascular parameters (heart rate, blood pressure, and electrocardiograms) were monitored through 8 hours postdose. Palovarotene did not cause any changes in heart rate, blood pressure or ECG parameters up to 10 mg/kg (1-fold C_{max} and 28-fold AUC at MRHD).

Study/ Study No.	Findings
Potential renal and urinary system effects in male Wistar rats Wistar Han rats 10/males/Group Dose: 0, 0.2, 1, 5 mg/kg Oral; single dose	Wistar rats were given a single oral dose of palovarotene at 0.2, 1 or 5 mg/kg. Renal function was assessed for up to 24 h postdose. Decreases (9 to 21%) in urine electrolytes levels of Na, K and Cl were observed at 5 mg/kg. This finding was not of toxicologic concern as no changes in urine electrolyte or kidney histology were observed in repeat dose toxicity studies.
Potential gastrointestinal system effects in male Wistar rats Wistar Han rats 10/males/Group Dose: 0, 0.2, 1, 5 mg/kg Oral; single dose	GI function was assessed in Wistar rats given single doses of palovarotene at 0.2, 1 or 5 mg/kg. Palovarotene slightly slowed gastric emptying with no changes of intestinal motility at all doses. No effect on GI emptying was present in chronic toxicity studies.

Source: Reviewer derived from data from Studies 1006456, 1005681, 1006565, 1004719, 1007995, 1006978, 1008099, and 1007751

Abbreviations: AUC, area under the concentration versus time curve; CHO, Chinese hamster ovary cell; Cl, chloride; C_{max}, maximum observed concentration; CV, cardiovascular; ECG, electrocardiogram; GI, gastrointestinal; hERG, human Ether-à-go-go-Related Gene; IC₅₀, half-maximal inhibitory concentration; K, potassium, MRHD, Maximum Recommended Human Dose; Na, sodium

13.1.4. ADME/PK

Palovarotene absorption, distribution, metabolism, excretion (ADME) and PK parameters were characterized in humans, rats, dogs, and monkeys. Palovarotene was quantified using protein precipitation extraction HPLC/MS/MS assay with solid phase extraction. Metabolites were assayed by HPLC/UV or HPLC/MS/MS.

Absorption

- Contrary to humans, food did not significantly affect the pharmacokinetics of palovarotene in the animal species evaluated.
- In both fasted and fed animals, oral bioavailability (BA) was medium in mouse (44 to 56%), rat (28 to 32%), dog (63 to 70%) and low in monkey (8 to 13%). Relative and absolute BA were not determined in human.
- Palovarotene was rapidly absorbed in mice, rat and dog (T_{max}=0.25 to 2 h) and slightly slower in monkeys (T_{max}=5 to 13 h) and 8 h in human.
- Palovarotene had a high apparent volume of distribution in human (237 L), rats and monkeys (1.5 to 4.2 L/kg) and low in dogs (0.3 L/kg).
- The terminal elimination half-life (t_{1/2}) values were 3 h in rats, 4 h in rat and dog, 8 h in monkey and 9 h in human.

Table 70. Comparison of Palovarotene PK Parameters Across Nonclinical Species, Absorption After a Single Dose (1 mg/kg)

PK Parameter	Single Dose PK summary			
	Species			
	Mouse	Rat	Dog	Monkey
<i>Oral gavage (fasted; male)</i>				
C _{max} (ng/ml)	64.2	90.4	1030	16.5
AUC _{0-last} (ng.h/ml)	281	362	9530	138
T _{max} (h)	0.5	2.0	2.3	5
t _{1/2} (h)	NC	NC	NC	NC
Bioavailability (%)	56	32.4	62.9	8.4
CL (L/h/kg)	3.6	2.8	0.12	7.0
<i>Oral gavage (fed; male) *</i>				
C _{max} (ng/ml)	37.1	65.2	990	21.6
AUC _{0-last} (ng.h/ml)	222	308	10400	200
T _{max} (h)	0.25	0.25	3	12.7
t _{1/2} (h)*	2.9	3.7	4.4	7.5
Bioavailability (%)	44.2	27.5	70.3	13
CL (L/h/kg)	3.8	3.3	0.09	0.12
<i>Intravenous (fed; male)</i>				
AUC _{0-last} (ng.h/ml)	502	1120	15400	1550
t _{1/2} (h)	NC	NC	4	7.5
CL (L/h/kg)	2	0.9	0.07	0.7
V _{ss} (L/kg)	2.5	4.2	0.3	1.5

NC: not calculated; *dog data for fed state is derived from female

Source: Reviewer derived from Study # 1008704, 1008700 and 1008701

Abbreviations: AUC_{0-last}, area under the concentration versus time curve from time 0 to last; CL, clearance; C_{max}, maximum observed concentration; NC, not calculated; t_{1/2}, half-time; T_{max}, time to maximum observed concentration; PK, pharmacokinetics

Distribution

- In autoradiography tissue distribution studies, palovarotene exhibited a slow but extensive distribution into the tissues.
- Maximal blood and tissue levels were attained 4 to 8 hours post-dose in the adrenal cortex, adrenal medulla, liver, and the walls of the small intestine and caecum.
- The mean blood to plasma ratios of palovarotene in mouse, rat, dog, monkey and human ranged from 0.52 to 0.63, indicating that palovarotene did not partition into erythrocytes
- There was no evidence of retention in, or affinity for, melanin-containing tissues.
- Palovarotene was highly (97 to 99%) bound to proteins in mouse, rat, dog, monkey and human plasma.

Metabolism

- Palovarotene is extensively metabolized by CYP3A4, and to a minor extent by CYP2C8 and CYP2C19.
- The in vitro metabolic profiles of palovarotene in liver microsomes and hepatocytes from mice, rats, dogs, monkeys, and humans were qualitatively similar but quantitatively different across species. The in vivo metabolite profiles were similar in rats and dogs. No metabolites unique to humans were identified.
- The four major metabolites identified were: M2 (6-OH) and M3 (7-OH) which are further metabolized to M4a (6-oxo) and M4b (7-oxo), M5, the carboxyl β-glucuronide of the

parent compound, was also detected after incubation with cryopreserved hepatocytes. Exposure to each of the metabolites, M2, M3, M4a and M4b was much lower than the parent in all species. The in vivo metabolite-to-parent drug ratios were 2 to 13% in rats and 1 to 27% in dogs.

- The pharmacological activity of main metabolites M2, M3, M4a, M4b was lower than that of parent (1.2%, 1.7%, 14%, and 4.2% of parent activity, respectively) in an in vitro RAR γ transactivation assay.

Excretion

In rats and dogs, palovarotene was primarily eliminated through the biliary and fecal routes, and recovery was complete within 7 days, with most of the administered radioactivity recovered within the first 24 hours. In both species, small fractions of the dose (<1%) were recovered in urine.

Table 71. Excretion of Palovarotene Following Single Oral Doses in Rats and Dogs

Report Number	1008705		1008692	
	Rats (2 mg/kg)		Dog (0.2 mg/kg)	
	Intact (N=5)	Bile D-C (N=5)	Intact (N=4)	Bile D-C (N=3)
Collection	0-168 hours	0-48 hours	0-168 hours	0-72 hours
Urine	0.234	0.736	0.554	2.34
Feces	101	26.1	101	46.7
Bile	N/A	57.0	N/A	47.8
Carcass	N/A	10.4	N/A	N/A
Total	102	94.4	102	97.1

D-C=duct-cannulated; N/A=not applicable.

Source: Applicant pharmacokinetic summary

Data are presented as percentages

Abbreviations: N, number of subjects

Pharmacokinetic drug interaction and transporter studies

- Palovarotene is mainly metabolized by CYP3A4, and its in vitro biotransformation could potentially be influenced by strong inhibitors and inducers of CYP3A4.
 - Ketoconazole (a strong inhibitor of CYP3A4) competitively inhibited the metabolism of palovarotene, with K_i of 0.2 μ M.
 - Palovarotene's exposure was increased (3-fold) and decreased (9-fold) in the presence of ketoconazole and rifampin (strong inducer of CYP3A4) and human DDI studies.
- In vitro, palovarotene did not significantly inhibit CYP1A2, CYP2B6, CYP3A4, CYP2C9, CYP2C19, and CYP2D6. For CYP3A4, IC_{50} values of palovarotene and its metabolites
- (M1 through M4) were >100 μ M (300-fold C_{max} at the MRHD), suggesting that palovarotene is not likely to inhibit the CYP3A4-dependent elimination of other drugs.
- Palovarotene was not an inducer of CYP1A2, CYP2C8, CYP2C9 and CYP2C19 but induced CYP2B6 and CYP3A4. A clinical DDI study was conducted and has

demonstrated that palovarotene is not a CYP3A4 inducer in vivo. For CYP2B6, the risk assessment of all available data suggests that the likelihood of palovarotene to induce CYP2B6 in vivo is negligible.

- Palovarotene does not appear to be a significant substrate of UGTs and does not pose a clinically relevant risk with respect to their inhibition.
- Palovarotene was not a substrate of the following efflux and uptake transporters: P-gp, BCRP, OATP1B1, OATP1B3 and OCT1.
- As palovarotene is essentially excreted by biliary route, the interaction with renal transporters (OAT1, OAT3, OCT2, MATE1 and MATE2-K) was not warranted. Of the transporters tested, palovarotene inhibited BCRP, OATP1B1, OATP1B3, OCT1, and BSEP, with IC₅₀ values of 9.69µM, 1.83µM, >3, >3µM, and 14.7µM, respectively. An evaluation of the DDI risk was performed and showed that clinically significant interaction of palovarotene with other drugs was unlikely.

13.1.5. Toxicokinetic Data

Toxicokinetics of palovarotene were evaluated in repeat-dose toxicity studies in rats and dogs, developmental and reproductive toxicology studies in rats, and juvenile animal toxicity studies.

Table 72. TK Data From General Toxicity and Reproductive Studies

Study/Study No.	Major Findings
<i>General toxicology studies</i>	
26-week repeat-dose oral toxicity study in rats	
Accumulation: None	
Dose-proportionality: All doses	
Sex differences: Exposure to the parent, M3, and M4b in females was up to 2x higher than in males	
Metabolite:parent ratio: 2 to 13%	
NOAEL: <0.3 mg/kg/day	
Safety Margin: <0.2	

Table 73. TK Parameters for Palovarotene and its Metabolites in the Rat 26-Week Study

Sex	Parameters	0.3 mg/kg /day			0.6 mg/kg/day			1 mg/kg/day		
		Day 1	Day 86	Day 177	Day 1	Day 86	Day 177	Day 1	Day 86	Day 177
Males	C _{max} (ng/mL)	22.7	20.7	16.5	47.2	31.4	33.1	64.0	51.4	82.6
	AUC ₀₋₂₄ (ng·h/mL)	85.9	133	129	191	282	242	301	366	421
Females	C _{max} (ng/mL)	33.8	35.7	29.7	48.7	57.6	60.7	79.5	107	96.6
	AUC ₀₋₂₄ (ng·h/mL)	133	211	207	292	351	445	501	673	716

Metabolite-to-Parent Ratio (%) Based on AUC₀₋₂₄ (Dose: 1 mg/kg/day)

Sex	M2			M3			M4a			M4b		
	Day 1	Day 86	Day 177	Day 1	Day 86	Day 177	Day 1	Day 86	Day 177	Day 1	Day 86	Day 177
Males	3.82	3.44	3.71	3.69	3.11	3.40	10.6	12.8	11.6	2.53	3.42	2.61
Females	2.63	4.96	4.22	4.07	8.42	7.14	2.71	8.60	7.58	1.77	7.95	5.95

Study/Study No.

39-week repeat-dose oral toxicity study in dogs

Accumulation: Decreased exposure (0.5 to 0.7) at 12 µg/kg/day at Day 170 and 268

Dose proportionality: less than (HD)

Sex differences: Exposure to M2, M4a in females ~2x males

Metabolite: parent ratio: 1 to 27%

NOAEL <12 µg/kg/day

Safety Margin <0.1

Major Findings

Table 74. TK Parameters for Palovarotene and its Metabolites in the Dog 39-Week Study

	0.012 mg/kg/day			0.025 mg/kg/day		
	Day 1	Day 89	Day 268	Day 1	Day 89	
Males						
C _{max} (ng/mL)	9.68	10.6	10.3	15.3	18.0	
AUC ₀₋₂₄ (ng•h/mL)	102	126	117	137	189	
	0.040 mg/kg/day			0.120 mg/kg/day		
	Day 1	Day 89	Day 268	Day 1	Day 170	Day 268
C _{max} (ng/mL)	38.4	40.7	35.1	96.5	52.8	86.9
AUC ₀₋₂₄ (ng•h/mL)	443	466	384	1020	412	752
Females						
C _{max} (ng/mL)	9.87	9.83	8.07	16.2	21.7	
AUC ₀₋₂₄ (ng•h/mL)	103	109	88.2	188	237	
	0.040 mg/kg/day			0.120 mg/kg/day		
	Day 1	Day 89	Day 268	Day 1	Day 170	Day 268
C _{max} (ng/mL)	31.2	37.1	40.3	121	95.3	56.7
AUC ₀₋₂₄ (ng•h/mL)	335	343	401	1450	948	718
Metabolite-to-Parent Ratio (%) Based on AUC ₀₋₂₄ (Dose: 0.040 mg/kg/day)						
	M2		M3		M4a	
	Day 1	Day 89	Day 268	Day 1	Day 89	Day 268
Males	4.36	7.47	8.18	2.82	5.36	5.42
Females	7.97	13.4	15.9	4.12	6.94	6.73

Reproductive toxicology studies

Oral embryo-fetal developmental toxicity study in rats

NOAEL: 0.01 mg/kg/day

Safety Margin: 0.008

Table 75. TK Parameters for Palovarotene and its Metabolites in Pregnant Rat (Rat EFD Study; GD 17)

Parameter	0.01 mg/kg/day	0.25 mg/kg/day	1.25 mg/kg/day
	GD17	GD17	GD17
Females C _{max} (ng/mL) ¹	0.721	22.3	80.1
AUC ₀₋₂₄ (ng•h/mL) ²	8.65	268	1000

Oral rat juvenile toxicity and toxicokinetic study

Accumulation: Decreased exposure (0.3 to 0.7) on Day 62; maturation of drug metabolizing enzymes

Dose proportional: All doses

Sex differences: Slightly higher exposure in females (1.3 to 2x) than males.

NOAEL: 0.1 mg/kg/day

Safety Margin: 0.6

Table 76. TK Parameters in Juvenile Rat Toxicity Study

	0.1 mg/kg/day		0.5 mg/kg/day		1.2 mg/kg/day	
	Males 18+6	Females 18+6	Males 18+6	Females 18+6	Males 18+6	Females 18+6
Day 21 pp (Day 1 of dosing)						
C _{max} (ng/mL)	20.6	22.3	98.5	113	316	295
AUC _{0-last} (ng•h/mL) ²	120	129	912	800	1490	1810
Day 62 pp (Day 42 of dosing)						
C _{max} (ng/mL)	10.8	14.0	47.8	99.1	92.0	138
AUC _{0-last} (ng•h/mL) ²	57.9	87.0	300	430	575	787

Source: Toxicokinetic data from toxicology Study reports 1013603, 1013980, 1003177 and 6700132

Safety margins are based on exposure based on AUC₀₋₂₄ at steady state in phase 3 study (PVO-1A-301) is 165 ng/mL and 1060 ng•h/mL, respectively at MRHD of 20 mg.

Abbreviations: AUC_{0-last}, area under the concentration versus time curve from time 0 to last; AUC₀₋₂₄, area under the concentration versus time curve from time 0 to 24 hours; C_{max}, maximum observed concentration; MRHD, Maximum Recommended Human Dose; NOAEL, no observed adverse effect level; pp, per protocol

13.1.6. Toxicology

13.1.6.1. General Toxicology

13.1.6.1.1. 26-Week Toxicity Study in Rats, Study 1013603

Key Study Findings

- Groups of Wistar rats were given oral daily doses of vehicle (Miglyol 812 with 0.01% BHA and 0.01% BHT), or palovarotene at 0.3, 0.6 and 1 mg/kg/day for 26 weeks, including groups terminated after 13-weeks. Recovery was assessed for an additional 8 weeks.
- Adverse drug-related skin lesions lead to early termination of one male and two females treated at 1 mg/kg/day.
- The target organs were the skin, growth plate of stifle or knee joints and sternum, and nonglandular forestomach during the interim and terminal sacrifices at all doses.
 - Skin: Lesions including hypergranulosis, epidermal hyperplasia (acanthosis), chronic active skin inflammation and skin ulceration were noted at all doses.
 - Growth plate: Dose-dependent chondrodystrophy in the growth plate of knee joints were observed at all dose levels. Chondrodystrophy in the growth plate in sternum was seen in both sexes at 1 mg/kg/day.
 - Forestomach: Degeneration/dyskeratosis and acute keratin layer inflammation of nonglandular stomach epithelium were noted in both control and treated animals but with increasing incidence and severity at ≥ 0.6 mg/kg/day. The lesion in rat forestomach was considered rodent-specific and not clinically relevant due to the absence of comparable structure in human.
 - The growth plate chondrodystrophy and forestomach lesion were still present in recovery animals.
- In general, the findings in this study were consistent with the class and those noted in subchronic studies in this species.
- Based on area under the concentration-time curve (AUC) ratios, exposure to each of four metabolites (M2, M3, M4a, and M4b) was generally <13% of the exposure to palovarotene itself.
- While evidence of testicular toxicity was seen in male rats given daily oral doses at 5 mg/kg in the 4-week study, this dose level produced severe toxicity and deaths, so it is possible that the findings were related to the underlying poor conditions of the animals rather than a direct palovarotene effect. There was no evidence of testicular toxicity in rats or dogs in chronic toxicity studies
- The NOAEL was not established and was considered <0.3 mg/kg/day (AUC_{0-24h} <168 ng.h/mL) due to only partially recoverable growth plate chondrodystrophy of the stifle joint and persistent forestomach degeneration/dyskeratosis observed at all doses. Adverse findings in the animals were considered consistent with exaggerated pharmacology.

GLP compliance: Yes

Table 77. Methods of 26-Week Oral Toxicity Study in Rats

Study Feature	Method Details
Dose and frequency of dosing	0 (vehicle), 0.3, 0.6 and 1 mg/kg/day; Once daily for 13 or 26 weeks
Route of administration	Oral gavage
Formulation/vehicle	Miglyol 812 with 0.01% BHA and 0.01% BHT
Species/strain	Rat/Wistar Han [CrI:WI(Han)]
Number/sex/group	Interim (13-week): 8/group/sex Final (26-week): 12/group/sex Recovery: 8/group/sex
Age	7 weeks old (at initiation)
Satellite groups/unique design	TK: 12/sex/group
Deviation from study protocol affecting interpretation of results	None

Source: Compiled by the reviewer

Abbreviations: BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; TK, toxicokinetics

Table 78. Observations and Results of 26-Week Oral Toxicity Study in Rats

Parameter	Major Findings
Mortality	Palovarotene caused deaths in three animals treated at 1 mg/kg/day. One HD male sacrificed on Day 94 due to drug-related limb injury and present with histological slight hemorrhage and moderate inflammation in the right humeroradial joint. One HD male and female HD sacrificed in moribund condition during Week 22 due to skin lesions (sores/scab on the skin, red focus areas and dark red and drug crusted areas, epidermal hyperplasia, chronic active inflammation, ulceration, hemorrhage and hypergranulosis). Deaths in four animals (control male, LD female, MD male and female) was considered incidental as these died on Days 92, 24, 23 and 92 following blood collections.
Clinical signs	Skin and pelage lesions (red/rough hair coat, red skin and sores/scabs) were seen in all treated males and females at ≥ 0.6 mg/kg/day: The onset time ranges from Days 6 to 13 across groups. Incidences was higher during the first 13 weeks (interim) and decreased over the course of the treatment period. The head, mouth, and dorsal-cervical and thoracic regions were most affected. Skin findings resolved largely during the recovery period.
Body weights	Lower mean BW (9 to 15%) were observed in males and females treated at 1 mg/kg/day. All treated males (6 to 22%) and females (12 to 18%) at ≥ 0.6 mg/kg/day had a reduced BW gain. BW changes were considered adverse based on $>10\%$ and the absence of any change in food consumption at the end of dosing. Body weight loss did not fully recover in HD males and females. There was a transient decrease (up to 9%) in FC noted at 1 mg/kg/day during the first 3 months but not at the end of dosing.
Ophthalmoscopy	Unremarkable
ECG	Not measured
Hematology	Modest increases in neutrophil counts were seen throughout dosing, predominately in males (33 to 88%), and females (13 to 80%) at 1 mg/kg/day. The neutrophil changes suggest immune or inflammatory change and correlate with skin lesions observed clinically or inflammatory stomach lesions observed microscopically or both. All hematological changes were reversible.
Coagulation	Unremarkable

Parameter	Major Findings
Clinical chemistry	There were increases in UN (11 to 13%), lower A/G ratio (up to 5%), and TG (up to 17%) in males at ≥ 0.6 mg/kg/day noted either in Week 4 or 14. Not considered adverse due to the transient nature and absence of correlative histological changes.
Urinalysis	Nonadverse, transient, and moderately lower urine volume (60%), mildly higher urine specific gravity, low urine pH (3%) were noted only during Week 14. Occur with no correlative kidney histological changes. These changes in conjunction with serum urea nitrogen might indicate slight dehydration relative to the control animals.
Gross pathology	Interim sacrifice: Single red linear focus at the left lip commissure was noted in a male at 1 mg/kg/day. Terminal sacrifice: Crusted area of the skin was notable in male at 1 mg/kg/day and females at ≥ 0.6 mg/kg/day. Thickened wall of the non- glandular stomach was seen in male at 1 mg/kg/day. The skin and stomach changes correlated with inflammatory microscopical changes noted in the respective organs. No macroscopic change was evident in the recovery animals.
Organ weights	No remarkable findings.

Parameter	Major Findings
Histopathology Adequate battery: Yes	Drug-related histologic findings were observed in the skin, bone (sternum), stifle (knee) joint, and forestomach during the interim as well as terminal sacrifices. At recovery sacrifice, test article-related microscopic findings persisted in the stifle joint, sternum, and nonglandular stomach. Recovery was attained for the skin lesions. Stifle (knee joint): Minimal to moderately severe dose-dependent growth plate chondrodystrophy was seen in the stifle joint (knee) in all treated animals at the terminal sacrifice and in males at ≥ 0.6 mg/kg/day and all treated females during interim sacrifice. Severity did not show trend with the duration of treatment. The chondrodystrophy was characterized by thickened, disorganized growth plate, increased amount of pale staining cartilaginous matrix, and abnormal endochondral ossification. Partial recovery of chondrodystrophy of stifle was achieved. Sternum: Minimal to moderate growth plate chondrodystrophy was seen in the sternum of rats treated at 1 mg/kg/day during interim and terminal sacrifices. Chondrodystrophy of sternum persisted in recovery animals but with lower grade (minimal) severity. Skin lesions: Dose dependent hypergranulosis (increased keratohyalin granules in the superficial epithelium) was seen at ≥ 0.6 mg/kg/day in both sexes at the interim analysis (minimal to slight), and at all dose levels and increased severity during terminal sacrifice (minimal to moderate). Epidermal hyperplasia (acanthosis) was observed at 1 mg/kg/day at interim and all doses in males and ≥ 0.6 mg/kg/day in females at terminal sacrifices. Chronic active inflammation was seen at 1 mg/kg/day in both sexes during interim and at 1 mg/kg/day males and all females at terminal sacrifice. Skin ulcerations was notable in males treated at 1 mg/kg/day and females ≥ 0.6 mg/kg/day only at terminal sacrifices. All skin lesions cleared in recovery animals. Forestomach: Degeneration/dyskeratosis of nonglandular stomach epithelium was present in control and treated groups at the interim terminal, and recovery sacrifices, suggesting that it was a spontaneous finding. However, palovarotene increases in the incidence and severity of these findings were noted at all doses. Test article related acute keratin layer inflammation consisting of neutrophils and lymphocyte infiltration were seen in interim animals at ≥ 0.6 mg/kg/day and all terminal males. Stomach lesions persisted at the end of recovery. The lesion in rat forestomach was considered species-specific and not clinically relevant as this organ has no human equivalent.

Source: Compiled by the reviewer
Abbreviations: BW, body weight; FC, food consumption

13.1.6.1.2. 39-Week Oral Toxicity Study in Dogs, Study 1013980

Key Study Findings

- A group of male and female beagle dogs were orally treated with vehicle (Miglyol 812 with 0.01% BHA and 0.01% BHT) or palovarotene doses of 12, 25 or 40 $\mu\text{g/kg/day}$ for at

least 13 or 39 weeks. Due to the lack of significant toxicity, the mid dose was increased from 25 to 120 µg/kg/day for at least 39 weeks (Week 13 through Week 52). Recovery was assessed for an additional 13 weeks in animals treated at 12 and 40 µg/kg/day. Recovery was not evaluated in animals administered 25/120 µg/kg/day.

- Skin findings were noted at all dose levels, with frequency and severity increasing with doses.
- Adverse skin clinical signs at 120 µg/kg/day necessitated early euthanasia of seven dogs (two males and five females between Week 26 to 33 and Week 19 to 52, respectively) due to repetitive occurrences of clinical otitis externa, conjunctivitis, and severe skin lesions, which were manifested systemically with an inflammatory response and hypergranulosis of the skin.
- The surviving animals also presented with skin related clinical signs including aural discharge (black), ocular discharge, red conjunctivae, alopecia, black/red/broken skin and scabs, predominantly at ≥12 µg/kg/day.
- Drug-related conjunctivitis of the eye was noted after 39 and 52-weeks of treatment in one male at 120 µg/kg/day.
- Histological findings related to palovarotene were only noted in the skin, and included dose-related hypergranulosis at all doses, lymphohistiocytic/neutrophilic infiltrates, parakeratosis predominantly in animals treated at 40 and 25/120 µg/kg/day. Moreover, skin histopathology (erosion, epithelial hyperplasia, cell infiltrates, inflammatory exudate) occurred in limited number of animals treated at 12 and 25/120 µg/kg/day
- The skin findings were largely reversible except lymphohistiocytic infiltrates at 12 µg/kg/day and inflammatory exudate noted at 40 µg/kg/day.
- The NOAEL was <12 µg/kg/day (AUC_{0-24h} <103 ng.h/mL) based on in-life and histological skin lesion (hypergranulosis) noted at all tested doses.

GLP compliance: Yes

Table 79. Methods of 39-Week Oral Toxicity Study in Dogs

Study Feature	Method Details
Dose	1 to 13 weeks: 0 (vehicle), 12, 25 and 40 µg/kg/day 13 to 39 weeks: 0 (vehicle), 12, 40 µg/kg/day 13 to 52 weeks: 25/120 µg/kg/day
Frequency of dosing	Once a day
Route of administration	Oral gavage (capsule)
Formulation/vehicle	Miglyol 812 with 0.01% BHA and 0.01% BHT
Species/strain	Dog/Beagle dog
Number/sex/group	Interim: 3/sex/group Terminal: 4/sex/group
Age	At least 12 months at initiation
Satellite groups/ unique design	TK samples were collected from the study animals. Animals in the 25/120 µg/kg/day were treated with 25 µg/kg/day for the first 13 weeks; and dose is increased to 120 µg/kg/day for at least 39-Week of treatment (total~52 weeks). No recovery group for the 25/120 µg/kg/day group.
Deviation from study protocol affecting interpretation of results	None

Source: Compiled by the reviewer

Abbreviations: BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; TK, toxicokinetics

Table 80. Observations and Results of 39-Week Oral Toxicity Study in Dogs

Parameter	Major Findings
Mortality	There were seven drug-related unscheduled deaths and one incidental death: Two males and five female dogs administered with palovarotene at 25/120 µg/kg/day were sacrificed during Weeks 19 to 52 for humane reasons due to aural and skin lesions secondary to microscopic inflammatory skin lesions and hypergranulosis of the skin. Mortality was attributable to effects at 120 µg/kg/day as deaths occurred after Week 13 dose escalation in this group. Observations prior to sacrifice include repetitive occurrences of aural discharge (black), swollen ears, ocular discharge, red conjunctivae, alopecia, severe skin lesions (broken skin, red and black skin and scabs). Most of these animals exhibited findings consistent with an inflammatory response including mildly increased WBC (neutrophil and monocyte counts), TP, globulin and decreases in A:G ratio. Test article-related macroscopic findings included squamous epithelial surfaces of the skin, skin overlaying the pinna, and conjunctiva. Microscopically, there were test article-related findings involving the pinna were erosion, hemorrhage, lymphohistiocytic infiltrates, neutrophilic infiltrates, epithelial hyperplasia, hypergranulosis, parakeratosis, and inflammatory exudate.
Clinical signs	Interim phase (Week 1 to 13): Red skin was noted in dose-independent manner in animals treated at 25 and 40 µg/kg/day. Alopecia, broken skin (head, muzzle, ears, periorbital area, cervical region, limbs and paws), red and black skin, scabs, red conjunctivae, and aural discharge in animals given 40 and 25/120 mg/kg/day from Week 13 to 39 (Days 94 to 275). Similar profile of skin changes was also apparent in animals treated at 25/120 mg/kg/day during the study period Weeks 39 to 52 (Days 276 to 373). The skin clinical findings correlated with macroscopic changes (crusted skin) and microscopic alterations (epidermal hyperplasia and inflammation). Recovery phase: Black aural discharge, ocular, alopecia, scabs and red skin persisted in animals at 40 µg/kg/day.
Body weights	Unremarkable
Ophthalmoscopy	One male at 120 µg/kg/day had conjunctivitis noted during Week 39 and 52 examinations. This was considered drug-related as similar swelling of the eyelids with conjunctival hyperemia and/or induration were noted in the 4-week dog study.
ECG	Unremarkable
Hematology	Unremarkable
Clinical chemistry	Unremarkable
Urinalysis	Unremarkable
Gross pathology	Interim sacrifice: The only test article-related macroscopic finding at the interim sacrifice was crusted areas on the skin of the ears and cranium of one male given 40 mg/kg/day. Terminal sacrifice: Crusted areas on the skin for one male given 12 µg/kg/day Crusted areas on the pinna for one male given 12 µg/kg/day Focal alopecia in one female at 25/120 µg/kg/day Red focus area of nongranular stomach in one male at 25/120 µg/kg/day
Organ weights	Unremarkable

Parameter	Major Findings
Histopathology Adequate battery: Yes	Treatment-related microscopic findings were limited to the skin during interim, unscheduled and terminal sacrifices. Interim sacrifice: There were minimal to slight fibrosis and hypergranulosis, minimal to moderate hyperplasia of the epidermal epithelium and fibrosis, minimal neutrophilic infiltrates and inflammatory exudates of the skin noted predominantly at 40 µg/kg/day. Additionally, minimal to slight lymphohistiocytic infiltrates were seen in male at 40 µg/kg/day and females at 25 and 40 µg/kg/day. Terminal sacrifice: Histological finding with clear relation to treatment during terminal sacrifice include dose-related minimal to slight to hypergranulosis of the skin in all treated males and females at ≥40 µg/kg/day. Parakeratosis and neutrophilic infiltrate were seen in one female at 25/120 µg/kg/day. Additional skin findings which lacked dose-dependency but with probable relation with treatment due to similar observation in the interim sacrifice animals are erosions, epithelial hyperplasia, lymphohistiocytic infiltrates and inflammatory exudate. Recovery sacrifice: Some animals treated with 12 µg/kg/day showed lymphohistiocytic infiltrates and some male dogs treated with 40 µg/kg/day showed inflammatory exudates.

Source: Compiled by the reviewer

Abbreviations: A:G ratio; albumin/globulin; WBC, white blood cell

13.1.6.2. Genetic Toxicology

The Applicant completed a battery of in vitro and in vivo genotoxicity study with Palovarotene. The in vitro Ames assay and in vivo mouse micronucleus assays were negative. Although an in vitro chromosomal aberration assay was positive, a clastogenic response was only evident at cytotoxic concentrations (mitotic index ≥50%).

Table 81. Genotoxicity Studies

Study Title/Study No.	Key Study Findings
In Vitro Reverse Mutation Assay in Bacterial cells GLP compliance: Yes Study is valid: Yes	Palovarotene was tested in five strains of <i>Salmonella typhimurium</i> strains (TA98, TA100, TA1535, TA102 and TA1537) at 50 to 5,000 µg/plate concentration with and without S9 metabolic activation. Negative: No mutagenicity was observed in any strain at all tested doses with or without metabolic activation.
Chromosomal Aberrations Assay In Vitro in the Human Peripheral Blood Lymphocytes (HPBL) GLP compliance: Yes Study is valid: Yes	HPBL were exposed to palovarotene at 20 to 30 µg/mL for 3 with and without metabolic activation, at 10 to 30 µg/mL for 24 h without metabolic activation or at 30 to 88 µg/mL for 5 h in the presence of metabolic activation. Positive: Clastogenic response was observed with metabolic activation at ≥60 µg/mL and without metabolic activation ≥50 µg/mL. However, this response was considered not biologically relevant since chromosomal aberrations were observed at cytotoxic concentration (relative mitotic index ≥50%). Moreover, these concentrations were 149 to 248-fold higher than estimated plasma C_{max} at MRHD (although in vitro genetic toxicity studies are considered useful for hazard identification but are not typically considered quantitative in nature).

Study Title/Study No.	Key Study Findings
In Vivo Mouse Micronucleus Assay	Groups of CD-1 mice (10/sex/dose) were administered orally at daily palovarotene doses of 5, 12.5 and 25 mg/kg (MTD in the DRF) for two consecutive days and bone marrow preparations were made on the following day.
GLP compliance: Yes	
Study is valid: Yes	Negative: There was no increase in MN PCE in the bone marrow up to 25 mg/kg dose. No bone marrow cytotoxicity was observed. Exposure to palovarotene was confirmed in plasma as 25 mg/kg (C_{max} and AUC were 412 ng/mL and 4545 ng.h/mL, respectively).

Source: Reviewer derived from Studies 1003192, 1002681, and 55016-500-013

Abbreviations: AUC, area under the concentration versus time curve; C_{max} , maximum observed concentration; DRF, Dose-range-finding study; GLP, good laboratory practice; HPBL, Human Peripheral Blood Lymphocytes; MTD, maximum tolerated dose; MN, micronucleus; MRHD, maximum recommended human dose; PCE, polychromatic erythrocytes

13.1.6.3. Carcinogenicity

Palovarotene's nonclinical package did not include rodent carcinogenicity studies. Instead, the Applicant conducted a WOE assessment to address the carcinogenic potential of palovarotene using the available information from the completed nonclinical studies, published literature and the intended patient population. In brief, the Applicant argued that palovarotene is unlikely to pose a carcinogenic hazard to patients and lifetime rodent carcinogenicity studies are not necessary based on:

- Absence of preneoplastic and neoplastic lesions in palovarotene's nonclinical chronic toxicology program in rats and dogs,
- The lack of strong mechanism-based evidence linking RAR γ activation with increased risk of cancer from publicly available information, no significant risks identified from review of class effects of retinoids for nonchronic indications
- No evidence of hormonal effects or immunosuppression
- Negative overall genotoxicity assessment

The Agency review of the WOE assessment suggested that the human carcinogenic potential of palovarotene is uncertain considering:

- Target biology: RAR γ is a member of the nuclear receptor superfamily that act as transcription factors and mediate pleiotropic effects of retinoids in cellular hemostasis and early development (organogenesis). It has been shown to regulate the balance between cellular proliferation, differentiation and apoptosis of normal and malignant cells .
- Published studies provide evidence of the potential role of RAR γ in cancer both as an oncogene and tumor suppressor gene depending upon the type of cancer studied (Marinelli et al. 2007). Overexpression of RAR γ was shown in multiple human cancers such as hepatocellular carcinoma, esophageal cancer, and cholangiocarcinoma. In these models, RAR γ facilitated the progression of tumors through multiple signaling pathways including PI3K/Akt, NF- κ B, and Wnt/ β -catene . On the other hand, treatment with retinoic acid, a RAR γ ligand, was shown to increase death of SH-SY5Y neuroblastoma cells and induce apoptosis of pancreatic cancer cells .
- Preneoplastic histological findings were noted in the skin, as epidermal hyperplasia in the context of chronic active skin inflammation in rats, which were supported by similar

findings in dogs at clinically relevant exposures. In addition, dyskeratosis/inflammation were seen in the stomach of rats in the 26-week study at clinically relevant exposures.

- The available tumor outcome data from rodent carcinogenicity studies with approved oral and topical retinoids described tumor findings in the skin, liver, blood vessels and adrenal glands.
- Indication: palovarotene is the first in class molecule for the treatment of chronic disease.

The initial nonclinical review of the WOE did not completely exclude the carcinogenic risk of palovarotene with high certainty, hence rodent carcinogenicity studies in two species were recommended as a post marketing requirement, should palovarotene be approved for the indicated FOP population. However, the Applicant submitted additional information late in the review cycle requesting reconsideration of the requirement for carcinogenicity studies. The nonclinical team will review the information amendment and request consultation from the Executive Carcinogenicity Assessment Committee upon NDA resubmission.

13.1.6.4. Reproductive and Developmental Toxicity

13.1.6.4.1. An Oral Gavage Fertility and Early Embryonic Development Study of Palovarotene in Male Rats, Study 9001429

Key Study Findings

- Palovarotene was orally administered to male rats prior to mating, during mating, and up to scheduled termination (approximately 11 weeks in total) at 0.3, 1 and 3 mg/kg/day.
- The high dose exceeded the MTD as it caused premature termination of the group on Day 39 due to death, adverse skin and hair coat-related clinical signs, and substantially (up to 70%) reduced BW gain.
- Significant nondose related reductions in BW gain (18%) and skin changes (thin cover, red skin and scab) were noted at both 0.3 and 1 mg/kg/day doses. Therefore, the NOAEL for paternal general toxicity was not identified.
- Palovarotene did not cause adverse effects on mating, fertility indices, conception rate, reproductive organ weights, or sperm parameters.
- No drug-related effects were observed on reproductive parameters (implantation sites, live embryos, dead embryos, early resorptions or the rate of pre- or postimplantation loss) in untreated females mated with treated males.
- The NOAEL for reproduction in males is 1 mg/kg/day ($AUC_{0-24h}=569$ ng.h/mL) based on the absence of adverse effects on fertility and reproduction parameters up to this dose level (the highest tolerated dose).

GLP compliance: Yes

Table 82. Methods of Fertility and Early Embryonic Development to Implantation

Parameter	Method Details
Dose and frequency of dosing	0 (vehicle), 0.3, 1 and 3 mg/kg/day, Once daily
Route of administration	Oral gavage
Formulation/vehicle	Miglyol 812 with 0.01% BHA and 0.01% BHT
Species/strain	Rat/ Sprague-Dawley CD (CrI:CD[SD])
Number/sex/group	Control: 10/sex/group Treatment: 22/sex/group Recovery: 22/sex/group (control and MD and HD)
Satellite groups	None
Study design	Standard: Males were treated with daily oral doses of palovarotene from 9 weeks before cohabitation through 2 weeks after mating with a drug naïve female. Histology was conducted on testes and epididymides TK analysis was not conducted.
Deviation from study protocol affecting interpretation of results	Noted and not considered to have affected the quality or integrity of the study.

Source: Compiled by the reviewer

Abbreviations: HD, high dose; MD, mid dose; TK, toxicokinetics

Table 83. Observations and Results Fertility and Early Embryonic Development to Implantation

Parameters	Major Findings
Mortality	Palovarotene at the high dose of 3 mg/kg/day was not tolerated and the group was prematurely terminated on Day 39 due to the following: Death of one male on Day 30 The occurrence of adverse clinical observations (fur thin cover/skin red/skin scab of the muzzle, urogenital area and/or hindlimbs) and significantly reduced body weight gains (up to 19%), and BW loss (up to 70%) and food intake as compared to the controls.
Clinical signs	Palovarotene-related skin observations similar to those observed in the unscheduled euthanized males were observed in the surviving rats at both 0.3 and 1 mg/kg/day doses. These clinical signs included thin cover of the fur and/or skin red, scab on the muzzle, forepaws/forelimbs, hindpaws/hindlimbs and red discoloration of the pinnae. These changes were observed after at least 2 weeks of dosing and persisted until beyond the end of the dosing period. In addition, red staining/thinness of the fur of the periorbital area(s) was seen occasionally in males at 0.3 mg/kg/day between Days 42 and 45 and at 1 mg/kg/day at 59 to 81. Thin cover was noted in urogenital area at 1 mg/kg/day and 3 mg/kg/day. There was an increased frequency and/or incidence of males noted with hypersensitivity between Days 10 and 122 and vocalization between Days 56 and 108.
Body weights	Palovarotene caused nondose related reduction in BW gains (18%) and absolute BW (6%) at both 0.3 and 1 mg/kg/day doses. Marginal decreases in food consumption (3 to 5%) were noted at the same dose levels.
Gross pathology, organ weight and Histology	There were no effects noted on reproductive organ weight, gross pathologic and histopathologic finding in the testes or epididymides of males and 0.3 and 1 mg/kg/day.
Mating and fertility	Palovarotene did not affect the mean number of days to mating, fertility indices, conception rate, sperm motility, morphology or concentration when tested up to 1 mg/kg/day.

Parameters	Major Findings
Ovarian and Uterine Data	The number of implantation sites, live embryos, dead embryos, early resorptions or the rate of the pre- and postimplantation losses were not changed in the pregnant females mated with male partners treated at ≥ 0.3 mg/kg/day.

Source: Compiled by the reviewer

Abbreviations: BW, body weight; HD, high dose; MD, mid dose

13.1.6.4.2. An Oral Gavage Fertility and Early Embryonic Development Study of Palovarotene in Male Rats, Study 9001429

Key Study Findings

- Palovarotene was administered to female Sprague-Dawley (SD) rats for 14 days prior to mating with drug naïve male and up to GD 7 at the dose levels of 0.3, 1 and 3 mg/kg/day.
- Skin and hair coat related clinical signs, reduced BW gain and lower food consumption were noted at ≥ 1 mg/kg/day.
- The maternal NOAEL for general toxicity was 0.3 mg/kg/day [$AUC_{0-24h}=207$ ng.h/mL] based on the increased incidence of maternal skin changes and lower BW/food consumption at ≥ 1 mg/kg/day.
- Palovarotene caused prolonged periods of diestrus, a slightly lower ovulation rate, fewer implantation sites, and fewer live embryos at 3 mg/kg/day.
- No effect on mating, fertility indices and conception rate were seen in females at any dose level.
- The NOAEL for reproduction in females was 1 mg/kg/day [$AUC_{0-24h}=421$ ng.h/mL] based on adverse effects noted in estrus cycle and reduced embryofetal survival at 3 mg/kg/day.

GLP compliance: Yes

Table 84. Methods of Fertility and Early Embryonic Development to Implantation

Parameter	Method Details
Dose and frequency of dosing	0 (vehicle), 0.3, 1 and 3 mg/kg/day; once daily
Route of administration	Oral gavage
Formulation/vehicle	Miglyol 812 with 0.01% BHA and 0.01% BHT
Species/strain	Rat/ Sprague-Dawley CD (CrI:CD[SD])
Number/sex/group	Control: 10/sex/group Treatment: 22/sex/group Recovery: 22/sex/group (control, MD and HD)
Satellite groups	None
Study design	Standard; Female rats were treated with daily oral doses of palovarotene for 14 days before cohabitation during cohabitation and continuing until GD 7. TK analysis was not conducted.
Deviation from study protocol affecting interpretation of results	Noted and not considered to have affected the quality or integrity of the study.

Source: Compiled by the reviewer

Abbreviations: BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; GD, gestation day; HD, high dose; MD, mid dose; TK, toxicokinetics

Table 85. Observations and Results Fertility and Early Embryonic Development to Implantation

Parameters	Major Findings
Mortality	None
Clinical signs	During the premating period, the following clinical signs were noted: Thin fur cover of the cranium, dry skin of the tail and flaking skin of the tail at all doses, Fur staining of the muzzle and cranium, discolored skin of pinna at ≥ 1 mg/kg/day, dry skin of the mouth and decreased activity at 3 mg/kg/day. During gestation, similar portfolio of clinical signs and dehydration were notable at 3 mg/kg/day. Dry skin of tails, thin fur cover/staining and skin scabs was observed at all doses.
Body weights	Premating BW gain was reduced 28 to 88% of the controls at ≥ 1 mg/kg/day; whereas BW loss only reduced by 7% in females treated at 3 mg/kg/day. Gestation BW gain was transiently lower (18 to 34%) on GD 0 to 7 at ≥ 1 mg/kg/day. There was a slight reduction in food consumption during premating (9%) and gestation phase (6% to 15%) at ≥ 1 mg/kg/day.
Gross pathology, organ weight and histology:	There were no gross pathologic or organ weight (ovary) findings noted on reproductive organs.
Mating and fertility:	Estrous cycle: There was an increased number of females with prolonged periods of diestrus (5 or more days) at 3 mg/kg/day. This contributed to slightly lower values for the number of days in estrus (37% fewer) and the number of cycles seen (25% fewer) as compared to the control. Fertility: Mean number of days to mating, the mating and fertility indices, and conception rate were not affected at any dose.
Ovarian and Uterine Data:	There were reductions in the numbers of corpora lutea, total number of implantation sites, and live embryos at ≥ 1 mg/kg/day. However, all these ovarian parameters were within test facility historical control data (HCD) at 1 mg/kg/day and at the borderline of HCD at 3 mg/kg/day. Hence, these changes were considered unlikely related with the test article. There were no palovarotene-related effects on the number of early resorptions, dead embryos or pre- and postimplantation losses.

Source: Compiled by the reviewer

Abbreviations: BW, body weight; MD, mid dose; GD, gestation day; HCD, historical control data; HD, high dose

13.1.6.4.3. Developmental Toxicity Study in Rats With Toxicokinetic Evaluation, Study 1003177

Key Study Findings

- Palovarotene was orally administered to pregnant female rats during the period of organogenesis (GD 6 to 17) at doses of 0.01, 0.25 and 1.25 mg/kg/day.
- Modest maternal toxicities characterized by reduced body weight gain (10% to 20% lower) were noted at ≥ 0.25 mg/kg/day and decreased food consumption (10%) was seen at 1.25 mg/kg/day.
- Palovarotene was teratogenic in rats as it caused multiple fetal external, visceral and skeletal malformations at ≥ 0.25 mg/kg/day, consistent with the pattern of retinoid-mediated embryopathy.

- Fetal NOAEL =0.01 mg/kg/day [AUC_{0-24h} =8.7 ng.h/mL] based on the increases in the incidence and severity of fetal malformations at ≥ 0.25 mg/kg/day.
- Maternal NOAEL =0.01 mg/kg/day [AUC_{0-24h} =8.7 ng.h/mL] based on decrease in maternal body loss at ≥ 0.25 mg/kg/day.

GLP compliance: Yes

Table 86. Methods of Oral Embryo-Fetal Developmental Study in Rats

Parameter	Method Details
Dose and frequency of dosing	0 (vehicle), 0.01, 0.25, 1.25 mg/kg/day; Once daily; GD 6 to GD 17
Route of administration	Oral gavage
Formulation/vehicle	Miglyol 812 with 0.01% BHA and 0.01% BHT
Species/strain	Time mated female rats/ Wistar Han [CrI:WI(Han)]
Number/sex/group	24/sex/group
Satellite groups	TK: 3 time-mated females
Study design	Standard; Pregnant female Wistar Han rats were dosed from GD 6 to GD 17 and euthanized on GD 21.
Deviation from study protocol affecting interpretation of results	Deviations reported did not affect the interpretation of the study findings.

Source: Compiled by the reviewer

Abbreviations: BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; GD, gestation day; TK, toxicokinetics

Table 87. Observations and Results of Oral Embryo-Fetal Developmental Study in Rats

Parameters	Major Findings
Mortality	None
Clinical signs	A dose-related encrustation in the angle of mouth was noted during treatment (GD 6 to 17) and persisted during the post-treatment period (GD 18 to 21) albeit with lower incidences.
Body weights	Maternal body weight gains were lower than control in animals treated at ≥ 0.25 mg/kg/day during treatment GD 6-17 (10% to 20% lower) and over the study period GD 6-21 (9% to 14% lower). Body weight losses were unremarkable (4% to 5%) in these groups as compared to vehicle control. Food consumption was reduced 5% to 9.5% in HD animals throughout the gestation period (GD 6 to 21).
Necropsy findings: Cesarean-section data [Implantation sites, pre- and postimplantation loss, etc.]	No drug-related maternal necropsy findings. The numbers of corpora lutea, implantations, pre- and postimplantation loss and live litter size were comparable among all experimental groups.
Necropsy findings: offspring	Multiple fetal external, visceral and skeletal malformations and variations were noted at 1.25 mg/kg/day that were typical of retinoid embryopathy. The fetal findings at HD are listed below and fetus and litter incidences are shown in: External malformations: Cranium—exencephaly, abnormal head shape and meningoencephalocele Mouth/Jaw—protruding tongue Limbs/Paw—malrotated limb and oligo/syndactyly Visceral malformations and variations: Palate/mouth - cleft palate Eyes - anophthalmia, microphthalmia

Parameters	Major Findings
	Brain/skull - dilated cerebral ventricle, misshapen brain Blood vessels- interrupted aortic arch, absent brachiocephalic trunk, short brachiocephalic trunk, retroesophageal subclavian, and persistent truncus arteriosus Kidney-small renal papilla, hydronephrosis, malpositioned kidney Ureters-convoluted ureter, hydroureter Sex organs-undescended testis Skeletal malformations and variations: Skull-incomplete ossification of supraoccipital and skull bone (>80% of litters at all doses), small mandible, misshapen mandible/skull bone, cleft palate, fused skull bones, acrania Thoracic vertebra- supernumerary vertebra, incomplete ossification/unossified center, hemivertebra, incomplete ossification/fused arch, premature fusion of vertebral body to neural arches Lumbar vertebra- bipartite/ incomplete ossification of center, hemivertebra, incomplete ossification and fused center Scapula-misshapen scapula, premature ossification of coracoid process Clavicle-misshapen clavicle Sternum-incomplete, unossified, fused, misaligned, additional, connected, and misshapen sternal element Ribs-short, full supernumerary, absent/rudimentary rib 13, cervical, fused, absent rib, intercostal, and misshapen rib Forelimbs-misshapen/ short humerus, short radius Phalanges-incomplete ossification/small phalanx Hindlimbs-short femur, short tibia Pelvis-misshapen ilium The MD of 0.25 mg/kg/day induced a low incidence of malformations (eye), and variations (kidney, ureter and skeletal). No malformation was noted at the low dose of 0.01 mg/kg/day, but this dose was associated with minor and likely reversible kidney, ureter, and skeletal variations/retardations which are not considered adverse. Incidence of fetal external, visceral and skeletal malformation in rat EFD

Parameters Major Findings
Table 88. Summary of result from Oral Embryo-Fetal Developmental Study in Rats

dose (mg/kg)		0		0.01		0.25		1.25	
		Litter	Fetus	Litter	Fetus	Litter	Fetus	Litter	Fetus
Change site									
External	Cranium	0	0	0	0	0	0	43%	14%
	Mouth/Jaw	0	0	0	0	0	0	100%	98.6%
	Limbs/paw	20%	2.2%	6.7%	0.6%	11.8%	1%	90.5%	59.8%
Visceral	Palate/Mouth	0	0	0	0	0	0	95.2%	90.2%
	Eyes	0	0	0	0	5.9%	1%	33.3%	8.2%
	Brain/Skull	0	0	0	0	0	0	9.5%	3.2%
	Blood vessels	6.7%	1.1%	20%	3.5%	11.8%	4%	42.9%	13.9%
	Kidney	6.7%	1%	40%	9.4%	41%	10%	76%	27.9%
	Ureters	6.7%	1.06%	20%	4.7%	47%	11%	53.2%	25%
	Sex organs	0	0	0	0	0	0	4.8%	0.8%
	Skull	60%	21%	80%	23%	82%	51%	100%	100%
Skeletal	Cervical vertebra	0	0	0	0	5.9%	1.1%	4.8%	0.9%
	Thoracic vertebra	40%	8.2%	6.7%	1.3%	29.4%	10.2%	100%	82.2%
	Lumbar vertebra	6.7%	1.1%	0	0	11.7%	2.2%	76.2%	51.4%
	Scapula	0	0	0	0	0	0	100%	100%
	Clavicle	0	0	0	0	0	0	100%	100%
	Sternum	40%	10.6%	46.7%	10.4%	88.2%	38.6%	100%	79.4%
	Ribs	66.7%	22.3%	46.7%	13%	100%	84.1%	100%	99.1%
	Forelimbs	0	0	0	0	0	0	100%	100%
	Phalanges fore	66.7%	52.9%	66.7%	44.2%	100%	89.7%	100%	100%
	Hindlimbs	0	0	0	0	0	0	100%	100%
	Pelvis	0	0	0	0	0	0	100%	100%

Source: Compiled by the reviewer

Abbreviations: BW, body weight; EFD, embryo-fetal development; GD, gestation day; HD, high dose; MD, mid dose; LD, low dose.

13.1.6.4.4. A 6-Week Oral Gavage Toxicity Study of Palovarotene in 3- to 9-Week-Old Rats, Followed by a 6-Week Recovery Period

Juvenile rats were treated orally with 0 (vehicle), or palovarotene at the doses of 0.1, 0.5 and 1.2 mg/kg/day from postnatal Weeks 3 through 9 (covering human development period of 2 to 12-year years old). Recovery was assessed for an additional 6 weeks.

- Palovarotene adversely affected skeletal growth and development in a dose-dependent manner in juvenile rats treated at ≥ 0.5 mg/kg/day. The findings included the following:
 - Decreases in bone formation markers (OC and PINP)
 - Reduction in bone size (femur and tibia length/width)
 - Decreases in bone densitometry area, BMC, and BMD at the proximal, mid and distal femur, total/cortical/subcortical femoral diaphysis, vertebral body
 - Radiological changes in several bones (abnormal shape, diffuse bone loss, increased/decreased physis thickness, and increased space between bones)
- Dose-related increases in the incidence and severity of histopathologic findings were noted in physeal, articular, hyaline cartilages and bone in animals treated at 0.5 and 1.2 mg/kg/day.
 - Physis: Dose-related thinning/closure of the physis, physeal hypertrophy, and chondrodysplasia were observed in multiple bones (humerus, radius, ulna, femur, tibia, hindpaw, vertebrae, and sternum)
 - Hyaline cartilage (Vertebral epiphysis): Decreased endochondral ossification and hypertrophic hyaline cartilage

- Articular cartilage: Hypertrophy and chondrodysplasia were seen in the sternbrae, osteochondral junctions, humeral/scapular, femoral/acetabular joints and proximal tibial articular cartilage.
- Bone: Decreases in bone was noted in all bones except nasal cavity and calvarium, and necrosis in the femoral head and neck region.
- Histomorphometry measurement: thickening of proximal tibial physis at ≥ 0.5 mg/kg/day.
- These effects reflect the intended pharmacodynamic activity (inhibition of chondrocyte differentiation) of palovarotene. Changes in bone mass and geometry could be secondary to effect on skeletal growth.
- Effects on physal closure and decreased vertebral epiphyseal bone did not reverse.
- Of note, skeletal effects chondrodystrophy were noted in 4 and 6 weeks repeat dose toxicity study conducted on adolescent rats (7 weeks old ~older than 12 years old human).
- The NOAEL is 0.1 mg/kg/day ($AUC_{0-t} = 681$ ng.h/mL) based on the adverse pathologic changes observed in the skeleton at ≥ 0.5 mg/kg/day.

GLP compliance: Yes

Table 89. Methods of Pre-and Postnatal Study in Rats

Parameter	Method Details
Dose and frequency of dosing	0 (vehicle), 0.1, 0.5, 1.2 mg/kg/day, once daily for 6 weeks
Route of administration	Oral gavage
Formulation/vehicle	Miglyol solution (Miglyol 812 99.98% [w/w], butylated hydroxytoluene 0.01% [w/w] and hydroxyanisole 0.01% [w/w])
Species/strain	Rat: Wistar Han [CrI:WI(Han)]
Number/sex/group	Main: 11/group/sex Recovery: 11/group/sex TK: 6 to 18/group/sex
Satellite groups	TK: 9 to 32 sex/group
Study design	Juvenile rats were orally dosed with palovarotene for 6 weeks from postnatal Weeks 3 to 9 (covering the period of human development from 2 to 12 years of age). The study included comprehensive bone related parameters including: Serum and urine markers of bone turnover Whole-body radiography. Femoral and tibial length and width Radiological evaluation: whole skeleton Histomorphometry: left proximal tibial growth plate thickness Densitometry methods (DXA and pQCT): right femur and L4 lumbar vertebra
Deviation from study protocol affecting interpretation of results	Deviations reported to not have affected the interpretation of the study findings.

Source: Compiled by the reviewer

Abbreviations: DXA, dual x-ray absorptiometry; PND, postnatal day; pQCT, peripheral quantitative computed tomography; TK, toxicokinetics

Table 90. Observations and Results

Parameters	Major Findings
Mortality	None

Parameters	Major Findings
Clinical signs	Red discoloration of the fur in the muzzle area was observed in males at 1.2 mg/kg/day and red skin was noted in females at 1.2 mg/kg/day
Body weights	BW gains were reduced in males (8% to 29%) and in females (10% to 34%) treated at ≥ 0.5 mg/kg/day; onset was Day 3 after treatment initiation. Absolute BW was lower in males (4% to 26%) and females (6% to 26%) at ≥ 0.5 mg/kg/day. Not reversible; BW gains in recovery were reduced in males (17%) and females (23%) at 1.2 mg/kg/day. FC was reduced up to 29% in males and females treated at 1.2 mg/kg/day; low FC was noted starting from Week 1 and persisting until recovery periods (24 to 27%).
Clinical pathology	Minimal changes in hematology (lower RBCs, Hgb, Hct and higher reticulocytes and RDW), increases in platelet (11 to 15%) and lymphocytes counts (31%), decreases in ALP (0.6 to 0.7x), elevations in AST/ALT (up to 1.6x); these were not toxicologically relevant as no histological changes noted for these changes. ALP isoenzyme analysis was not conducted; however, decreases in ALP levels in palovarotene treated animals might reflect decreased bone formation. Higher urea (25%) decreases in glucose, cholesterol (20%) and TG (34%); these changes were likely due to decreased food consumption. Substantial dose-related decreases in urine output (45% to 90%) were noted at ≥ 0.5 mg/kg/day. This was accompanied with higher urine specific gravity (26% to 73%) at ≥ 0.5 mg/kg/day in males and at 1.2 females. pH was also lower in both HD males and females. These changes were likely due to decreased food consumption evident at HD and possibly secondary decreased in water consumption. Clinical chemistry changes were absent or had resolved in part by the end of the recovery period.
Sexual Maturation	Unremarkable
Bone and Growth Evaluation	Growth: The increase in crown-rump length (20 to 27%) and absolute (11 to 13%) crown-rump length (growth) were reduced at 1.2 mg/kg/day in both sexes; not reversible Bone biochemical markers: Dose-related decreases in bone turnover markers (osteocalcin; 15 to 31% and PINP; 17 to 31%) and bone resorption marker (CTx; 16 to 21%; females only) were observed at ≥ 0.5 mg/kg/day; reversible Bone measurement: Reductions in bone size (femur and tibia length/width) were seen in both sexes at ≥ 0.5 mg/kg/day; not reversible. Radiology: Moderate to severe radiological changes of the entire skeleton (except the skull) were reported at 1.2 mg/kg/day, and limited bones at 0.5 mg/kg/day. These included: abnormal shape (shortened, thin, decreased cortical thickness, bent), decreased/increased physis thickness, bone production/enlargement, increased intervertebral or intersternbral spaces); not reversible. DXA: Decreases in area, BMC and BMD were seen at the proximal, mid and distal femur at ≥ 0.5 mg/kg/day. PQCT: Decreases in total area, cortical area, and diaphysis and vertebral body at 1.2 mg/kg/day. Inconsistent changes (low total area, BMC (cortical/subcortical) and high BMD (total/ cortical/subcortical) were noted in femoral metaphysis of females at 1.2 mg/kg/day. Histomorphometry measurement: Thickening of proximal tibial physis was seen at ≥ 0.5 mg/kg/day.

Parameters	Major Findings
Histopathology	Histological findings were noted in cartilage (physeal, hyaline, articular) and bone at ≥ 0.5 mg/kg/day. The incidence and severity increased with dose. These include: Physis: Dose-related thinning/closure of the physis, physeal hypertrophy, and chondrodysplasia were observed in multiple bones (humerus, radius, ulna, femur, tibia, hindpaw, vertebrae, and sternum). Hyaline cartilage (Vertebral epiphysis): Decreased endochondral ossification of the vertebral bodies and hypertrophic hyaline cartilage in sternebrae. Articular cartilage: Hypertrophy and chondrodysplasia were seen in the sternebrae, osteochondral junctions, humeral/scapular, femoral/acetabular joints and proximal tibial articular cartilage. Bone: Decreased bone was noted in all bones except nasal cavity and calvarium, necrosis in the femoral head and neck region and microfractures of the trabeculae.

Source: Compiled by the reviewer

Abbreviations: ALP, alkaline phosphatase; AST/ALT, aspartate transaminase/alanine transaminase; BMC, bone mineral content; BMD, bone mineral density; BW, body weight; CTx, cardiotoxin; DXA, dual energy x-ray absorptiometry; FC, food consumption; GFA, global femur area; Hct, hematocrit; HD, high dose; Hgb, hemoglobin; MCH, mean cell hemoglobin; PINP, procollagen type I N-terminal propeptide; RBC, red blood cell; RDW, red cell distribution width; TG, triglycerides;

13.2. Individual Reviews of Studies Submitted to the NDA

13.2.1. Impurities

The Applicant proposed a high acceptance criterion earlier during development (originally (b) (4) and current proposal (b) (4) %) for a drug substance impurity, (b) (4). This impurity was present at very low levels (up to (b) (4) %) in batches used for nonclinical toxicity studies but was detected in batches used in the clinical studies at levels up to (b) (4) %. In order to qualify the drug substance impurity (b) (4), the Applicant conducted and submitted genotoxicity assessments including QSAR, in vitro (Ames and chromosomal aberration), and 4-week oral repeat dose general toxicity study in rats.

13.2.1.1. Genotoxicity Studies With (b) (4)

No structural alert for mutagenicity was detected on (b) (4) when evaluated by QSAR performed using expert-based and statistical-based models (DEREK and SARAH). (b) (4) was neither mutagenic nor clastogenic in the in vitro Ames and chromosomal aberration assays in the presence and absence of metabolic activation systems.

Table 91. Summary of Genotoxicity Studies With (b) (4)

Study Title/Study No.	Key Study Findings
QSAR/20264821B	In silico toxicity assessment of (b) (4) using DEREK and SARAH analysis did not show structural alert for mutagenicity.
In Vitro Reverse Mutation Assay in Bacterial cells/8462655	(b) (4) was tested in four strains of <i>Salmonella typhimurium</i> strains (TA98, TA100, TA1535 and TA1537) and Escherichia coli, strain WP2 uvrA up to (b) (4) µg/plate concentration with and without S9 metabolic activation.
GLP-compliance: Yes Study is valid: Yes	Negative: No mutagenicity was observed in all the tested strains and doses with or without metabolic activation.
Chromosomal Aberrations Assay In Vitro in the Human Lymphocytes/8462656	Human lymphocytes were exposed to (b) (4) up to (b) (4) µg/mL for 3 and 21 hours in the absence of S9 and for 3 hours in the presence of S9.
GLP compliance: Yes Study is valid: Yes	Negative: (b) (4) did not induce structural chromosome aberrations up to the highest concentration (b) (4) µg/mL, maximum recommended dose as per ICH S2.

Source: Compiled by the reviewer

Abbreviations: GLP, good laboratory practice; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; (b) (4)

13.2.1.1.1. 4-Week Oral (Gavage) Administration General Toxicity Study With (b) (4) in the Rat, 8462660

Key Study Findings

- Groups of male and female Wistar rats were given oral daily doses of vehicle (water for injection), or (b) (4) (in isolation with no palovarotene) at (b) (4) and (b) (4) mg/kg/day for 4 weeks. (b) (4) doses selected for this study based on a preliminary 7-day dose range finding study conducted with (b) (4) at (b) (4) mg/kg/day (study # 8462659). No adverse effect was noted with (b) (4) doses up to 0.75 mg/kg/day.
- (b) (4) was well tolerated with no mortality, clinical, or ophthalmic observations noted. No abnormal changes in body weights and food consumption, or clinical pathology parameters were noted.
- The NOAEL was the highest dose tested (b) (4) mg/kg/day (≥10-fold higher than maximum estimated clinical exposures based on the proposed drug substance impurity specification).

GLP compliance: Yes

Table 92. Methods of 4-Week Oral Toxicity Study With (b) (4) in Rats

Study Feature	Method Details
Dose and frequency of dosing	0 (vehicle), (b) (4) mg/kg/day; Once daily for 4 weeks
Route of administration	Oral gavage
Formulation/vehicle	Water for injection
Species/strain	Rat/Wistar Han [CrI:WI(Han)]
Number/sex/group	10/sex/group
Age	6 to 7 weeks old (at initiation)
Satellite groups/unique design	TK analysis was not conducted.
Deviation from study protocol affecting interpretation of results	None

Source: Compiled by the reviewer

Abbreviations: (b) (4); TK, toxicokinetics

Table 93. Observations and Results of 4-Week Oral Toxicity Study With (b) (4) in Rats

Parameter	Major Findings
Mortality	All animals survived till scheduled sacrifice.
Clinical signs	None
Body weights	None
Clinical pathology	Unremarkable
Organ weights	Unremarkable
Histopathology	No remarkable finding.
Adequate battery: Yes	

Source: Compiled by the reviewer

Abbreviations: (b) (4)

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

Four in vitro metabolism, two in vitro transporter, one in vitro plasma protein binding, one in vitro blood-to-plasma ratio, and five in vitro drug interaction study reports were submitted in current NDA.

14.1.1. In Vitro Metabolism Studies

In Study 10008691, the metabolic stability of palovarotene was evaluated in pooled liver microsomes from multiple species. Over a 60-minute incubation interval, the percent conversion of palovarotene was 89.1%, 68.5%, 50.4%, 40.6%, 25.5%, and 25.3%, respectively, in microsomes prepared from a human donor, Balb/c mouse, cynomolgus monkey, Hanover-Wistar rat, beagle dog, and CD-1 mouse. Five metabolites, M1 (6,7-dihydroxy), M2 (6-hydroxy), M3 (7-hydroxy), M4a (6-oxo), and M4b (7-oxo), were detected and characterized. Incubation of palovarotene with cryopreserved hepatocytes from human, dog, monkey, and Sprague-Dawley rat showed conversion of palovarotene to six metabolites, M1, M2, M3, M4a, M4b and one beta-glucuronide conjugate.

In Study 1008690, incubation of single human CYP450 isoforms with palovarotene demonstrated that CYP3A4, 2C8, and 2C19 oxidized palovarotene to metabolites. The major route of transformation was by CYP3A4, which converted palovarotene to M1, M2, M3, M4a and M4b. In human liver microsomal proteins (2 mg/mL), the V_{max} (the maximum initial velocity in the absence of inhibitor) of palovarotene was determined as 1.97 nmole/min/mg, the K_m (the Michaelis-Menten constant) was 59 μ M, and V_{max}/K_m (intrinsic clearance) was 0.033 mU/min/mg protein. The K_m values is much higher than the steady-state C_{max} (0.33 to 0.49 μ M) of palovarotene following 20 mg QD oral dosing. In human liver microsomes, ketoconazole, midazolam, and erythromycin appeared to be competitive inhibitors of palovarotene with K_i of 0.184 μ M, 37.5 μ M, and 64.6 μ M, respectively. Study CYP1933-04 investigated in vitro stability of palovarotene in an incubation with recombinant human CYP2B6 and no significant metabolism of palovarotene was observed.

In Study CYP1558R2A, palovarotene was incubated with recombinant UDP glucuronosyl transferases (UGT) enzymes. The half-life values of palovarotene in UGT1A1, UGT1A3, UGT1A9, UGT2B7 and UGT2B15 incubations were determined to be >240 minutes. The half-life values of palovarotene in UGT1A4 and UGT1A6 incubations were determined to be 183 and 142 minutes, respectively. However, due to the absence of phase I enzymes in the incubation, no conclusion could be drawn regarding the role of UGT enzymes in the metabolism of palovarotene.

14.1.2. In Vitro Transporter Studies

In Study CYP1933-01, bidirectional apparent permeability assays showed that palovarotene was not a substrate of P-gp or BCRP. Transporter-expressing HEK293 cell uptake assays showed that palovarotene was not a substrate of OATP1B1, OATP1B3, or OCT1. In Study CYP1933-02, palovarotene was determined to be an in vitro inhibitor of BCRP, OATP1B1, OATP1B3, OCT1, and bile salt export pump (BSEP) transporters with IC_{50} values of 9.69 μ M, 1.83 μ M, >3 μ M, >3 μ M, and 14.7 μ M, respectively. Palovarotene did not inhibit P-gp, OAT1, OAT3, OCT2, MATE1, or MATE2-K transporters in vitro.

Reviewer's comments: The steady-state C_{max} of palovarotene following 20 mg QD oral dosing was 0.33 μ M to 0.49 μ M. At the recommended maximum dose (20 mg QD), plasma palovarotene does not pose a clinically relevant risk with respect to the inhibition of OATP1B1, OATP1B3, OCT1, or BSEP transporters. Also, the Applicant measured the solubility of palovarotene in fed-state simulated intestinal fluid at 37°C and pH 5, which was 2.37±0.23 μ g/mL or 5.8 μ M. The ratio of I_{gut}/IC_{50} for intestinal BCRP transporter is 0.60 and the calculated palovarotene R value is 1.60, which is below the threshold value of 11. No BCRP-mediated DDI is expected for palovarotene at 20 mg QD.

14.1.3. Plasma Protein Binding and B/P Ratio

Study 1008422 showed that palovarotene was highly bound (ranging from 97.9% to 99.6%) to human plasma proteins over the concentration range of 6 to 1000 ng/mL. In Study 1008425, the in vitro mean whole blood-to-plasma ratios of palovarotene (100-1000 ng/mL) in male and female human subjects were determined as 0.62 and 0.61, respectively. Palovarotene did not partition into erythrocytes.

14.1.4. In Vitro Drug Interaction Studies

In Study 1008423, the potential of palovarotene to inhibit major CYP450 enzymes was assessed using cDNA-expressed enzymes. The showed that the IC₅₀ values of palovarotene on human CYP1A2, 2C8, 2C9, 2C19, and 2D6 were >100μM, 4.7μM, 8.1μM, 7.9μM, and >100μM, respectively. For CYP3A4, IC₅₀ values of palovarotene and its major metabolites were >100μM. Study CYP1933-05 showed that palovarotene inhibited CYP2B6 with an IC₅₀ value of 55.9μM. Study CYP1558 R2B showed that palovarotene reversibly inhibited multiple UGT enzymes. The IC₅₀ values of palovarotene against UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9 and UGT2B7 were 3.90μM, 21.3μM, 1.98μM, 21.8μM, 4.76μM, and 20.1μM, respectively. The steady-state C_{max} of palovarotene following 20 mg QD oral dosing is 0.33μM to 0.49μM. Therefore, at the recommended maximum dose, palovarotene is unlikely to inhibit major CYP450 or UGT enzymes.

In Study CYP1933-03, CYP450 enzyme induction potential of palovarotene was assessed in cryopreserved human hepatocytes from three separate human donors. Palovarotene at up to 1μM did not induce CYP1A2, CYP2C9, or CYP2C19 in any of the three donors. Using steady-state plasma palovarotene C_{max} of 0.49μM and f_{u,p} of 0.02, the maximal unbound plasma concentration of palovarotene in liver is estimated as 0.49 * 0.02 * 30=0.3μM. Palovarotene at 0.32μM induced mRNA expression of CYP2B6 by 1.8 – 2.4 fold compared to vehicle controls or 14% and 49% of the positive control in two donors, respectively but did not induce CYP2B6 in the third donor. Palovarotene at 0.32μM induced mRNA expression of CYP2C8 by 1.5 fold compared to vehicle controls or 55% of the positive control in one donor but did not induce CYP2C8 in the other two donors. Palovarotene at 0.32μM induced mRNA expression of CYP3A4 by 3.8 – 5.0 fold compared to vehicle controls or 1%, 1%, and 19% of the positive control in three donors.

Reviewer's comments: Based on the 2-fold induction and 20% of the positive control threshold, in vitro data suggest palovarotene may potentially induce CYP3A4 and 2B6 at the recommended maximum dose. At 20 mg QD dose, the potential of in vivo CYP2C8 induction is low. Further clinical assessment of CYP3A4 induction is needed. In clinical DDI study (Study PVO-1A-102), following co-administration of midazolam with palovarotene 20 mg QD for 14 days, palovarotene did not alter the PK of midazolam. Therefore, considering the smaller magnitude of in vitro induction of CYP2B6 compared to CYP3A4, a clinical DDI study for CYP2B6 induction assessment is not needed.

14.2. In Vivo Studies

A total of 22 clinical study reports and one clinical study synopsis (Study PVO-1A-203) were submitted in current NDA ([Table 94](#)). Study PVO-1A-203 was an open-label extension study in FOP patients and was terminated early. Studies NP17124, NA17098, NB18332, NA17598, and NB19751 were conducted in chronic obstructive pulmonary disorder (COPD) patients at doses of 0.2 – 5 mg QD. Study PVO-2A-201 was conducted in multiple osteochondromas (MO) patients at doses of 2.5 and 5.0 mg QD. Study NP17584 is a relative BA study conducted with two Roche's old formulations for COPD program. The formulations were not used in FOP patients. Study NP17055 is a clinical DDI study which assess the effect of palovarotene 1 mg QD on the PK of co-administered midazolam. The dose of palovarotene did not cover the recommended maximum dose for FOP indication (20 mg QD). Therefore, the five COPD studies, MO study,

Study PVO-1A-203, Study NP17584, and Study NP17055 were not reviewed. Only the 14 remaining clinical studies were reviewed in this section.

Table 94. Clinical Studies With Pharmacokinetic Data Submitted in Current Palovarotene NDA

Clinical Study	Protocol No.	Major Study Objective	Study Design
BA/PK	PVO-1A-102	Effect of food and of swallowing whole PVO capsule versus sprinkling on soft food; Effect of PVO on the PK of midazolam	FE/Mode of administration component: open-label, R, 3-sequence, 3-period, crossover study in healthy subjects: 20 mg (2×10 mg) capsules, fasted 20 mg (2×10 mg) capsules, fed 20 mg capsule contents sprinkled on 1 teaspoon apple sauce, fed
BE	NP17584	Assess relative bioavailability of 2 formulations of PVO (Roche's capsules versus tablets)	Open-label, single-dose, R, crossover in healthy subjects
PK	RB16328	Study of the PK of PVO versus placebo	Multiple ascending dose study: 4-week QD treatment 0.02 mg, 0.2 mg, 0.4 mg, 1.0 mg, 5.0 mg, 10 mg, and Placebo
QT	PVO-1A-103	To evaluate the effect of a therapeutic and supratherapeutic doses of PVO on the QTcF	Four single dose treatments in fed state: 50 mg (5×10 mg) 20 mg (2×10 mg) Placebo Moxifloxacin, 400 mg
PK	PVO-1A-104	To characterize the PK of PVO in plasma at steady state and concentrations in semen	open-label, single-period study in healthy subjects 5-day QD treatment, fed 20 mg (2×10 mg)
PK	NP17056	Mass balance study	Open-label, single-dose in healthy subjects, 1.0 mg
PK	NP17726	Assess the influence of age and gender on the PK of PVO and metabolites	Open-label, single-dose in healthy subjects, 1.0 mg
PK	PVO-1A-101	Assess the PK of PVO in healthy Japanese and matched non-Asian subject	Single-center, R, DB, crossover, single-dose in healthy subjects 5.0 mg 10 mg
PK	RB16327	Assess the safety, tolerability, and PK of single oral doses of up to 50 mg of PVO	Ascending, single-dose, R, DB study of PVO versus placebo in fed or fasted healthy subjects: 0.1 mg, 0.5 mg, 5.0 mg, 10 mg, 25 mg, and 50 mg
DDI	NP17040	Assess the effect of rifampicin on the PK of PVO	Open-label, sequential, crossover study in healthy subjects: 24-day QD treatment 1.0 mg
DDI	NP17041B	Ass the effect of ketoconazole on the PK of PVO	Open-label, sequential, crossover study in healthy subjects: 21-day QD treatment 1.0 mg
DDI	NP17055	Ass the effect of PVO on the PK of midazolam	Open-label, sequential, crossover study in healthy subjects: 7-day QD treatment 1.0 mg

Clinical Study	Protocol No.	Major Study Objective	Study Design
DDI	NP21025	Assess the effect of prednisone on the PK of PVO	Open-label, 1-sequence study in healthy subjects: 9-day QD treatment 5.0 mg
Dose-finding, phase 2	PVO-1A-201	Efficacy and Safety Study of PVO in FOP patients	Multicenter, R, DB, PC adaptive dose finding/POC: Cohort 1: oral QD 10 mg for 2 weeks, then 5.0 mg for 4 weeks, or placebo Cohort 2: oral QD 10 mg for 2 weeks, then 5.0 mg for 4 weeks; oral QD 5 mg for 2 weeks, then 2.5 mg for 4 weeks; or placebo
Dose-finding, phase 2	PVO-1A-202 (Parts A, B, C)	Efficacy and Safety Study of PVO in FOP patients	Multicenter, OLE study of PVO-1A-201: Part A: Oral QD 10 mg for 2 weeks, then 5 mg for 4 weeks for the next 2 subsequent flare-ups. Weight-based dosing for children 6+ years Part B: Adult Cohort (chronic/flare-up regimen): 5 mg QD for up to 24 months, with dose escalation for flare-up treatment to 20 mg QD for 4 weeks, then 10 mg QD for 8 weeks (total of 12 weeks or until flare-up resolution if treatment extended beyond 12 weeks). Pediatric Cohort (flare-up regimen only): same as flare-up dosing in the Adult Cohort except dosing is weight-adjusted. Part C: All subjects receive chronic/flare-up regimen from Part B (weight-adjusted for skeletally immature subjects). Part C is ongoing.
Efficacy/safety, phase 2	PVO-1A-203	Efficacy and Safety Study of PVO in FOP patients	Multicenter, OLE of PVO-1A-202: Oral QD 10 mg for 14 days followed by 5 mg for at least 28 days. Weight-based dosing according to 3 categories (20 to <40 kg, 40 to <60 kg, and ≥60 kg).
Efficacy/safety, pivotal phase 3	PVO-1A-301	Evaluating the efficacy and safety of PVO in decreasing HO in FOP patients versus untreated PVO patients in the NHS	Multicenter, open-label study: 5 mg QD for up to 48 months, with dose escalation for flare-up treatment to 20 mg QD for 4 weeks, then 10 mg QD for 8 weeks (total of 12 weeks; may be extended by 4-week intervals until flare-up resolves). Weight-based dosing according to 3 categories (20 to <40 kg, 40 to <60 kg, and ≥60 kg).

Protocol			
Clinical Study	No.	Major Study Objective	Study Design
Efficacy/safety, phase 2	PVO-2A-201	Evaluating the efficacy and safety of 2 regimens of PVO versus placebo in preventing the formation of new osteochondromas in MO patients	Multicenter, R, DB, PC study in MO patients: 24-month QD treatment 2.5 mg, 5.0 mg, and Placebo Weight-based dosing according to 3 categories (20 to <40 kg, 40 to <60 kg, and ≥60 kg).
PK/PD	NP17124	Study of multiple- dose PK and PD of PVO and metabolites in COPD patients	Multicenter, R, DB, PC in COPD patients: 14-day QD treatment, 0.2 mg, 0.5 mg, 1.0 mg, and Placebo
Efficacy/safety, phase 2a	NA17098	Study of the tolerability of PVO in COPD patients	Multicenter, R, DB, PC in COPD patients: 4-week QD treatment: 0.2 mg, 1.0 mg, and Placebo
PK	NB18332	Study of the safety and tolerability of PVO in COPD patients	Multicenter, R, DB, PC in COPD patients: 4-week QD treatment: 2.5 mg, 5.0 mg, and Placebo
Dose-finding, phase 2	NA17598	Study of the efficacy, safety, and tolerability of PVO in COPD patients	Multicenter, R, DB, PC, biphasic study in COPD patients: Tier 1: 12-month QD treatment with 1.0 mg or Placebo Tier 2: 12-month QD treatment with 5.0 mg or Placebo
Efficacy phase 2	NB19751	Study of the efficacy, safety, and tolerability PVO in COPD patients	Multicenter, R, DB, PC, parallel- group study in COPD patients: 24-month QD treatment with 5.0 mg or Placebo

Source: Summary of clinical pharmacology studies

Abbreviations: BA, bioavailability; BE, bioequivalence; COPD, chronic obstructive pulmonary disorder; DB, double-blind; DDI, drug-drug interaction; FE, Food effect; FOP, fibrodysplasia ossificans progressiva; HO, heterotopic ossification; MO, multiple osteochondromas; OLE, open-label extension; PC, placebo-controlled; PD, pharmacodynamics; PK, pharmacokinetics; POC, proof-of-concept; PVO, palovarotene; QD, once daily; QTcF, Corrected QT interval by Fredericia; R, randomized; NHS, natural history study

14.2.1. Study RB16327: Single Ascending Dose Study

Study Design

Study RB16327 was a single-center, ascending single-dose, randomized, double-blind, placebo-controlled study conducted in 40 healthy nonsmoking male subjects and eight healthy currently smoking male subjects aged 40 to 65 years. Six doses of palovarotene (oral solution or suspension) were studied. The number of subjects in each dose group is summarized in Table 95. A sequential food-effect study was performed with subjects in Group 5 to assess the influence of fasting on the PK of palovarotene. A washout period of approximately 3 weeks separated doses under fed (10 mg) and fasting conditions (5 mg) for Group 5 subjects. Except for subjects in the Group 5 fasted period, subjects were dosed approximately 10 minutes after consuming a standardized high-fat breakfast. Blood samples were drawn predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours postdose.

Table 95. Number of Subjects in Each Dose Group in Study RB16327

Group	Dosing Condition	Smoking Status	Dose Level (mg)	Number of Subjects	
				Palovarotene	Placebo
1	Fed	Nonsmokers	0.1	3	1
2	Fed	Nonsmokers	0.5	3	1
3	Fed	Nonsmokers	5	6	2
4	Fed	Nonsmokers	25	6	2
5	Fed	Nonsmokers	10	6	2
	Fasting	Nonsmokers	5	6	2
6	Fed	Nonsmokers	50	6	2
7	Fed	Smokers	5	6	2

Source: Clinical study report RB16327

PK Results: The mean $\pm$ SD PK parameters for palovarotene are presented in Table 96. The percent coefficient of variation (%CV) of the PK parameters was approximately 20% to 30%. The PK of palovarotene was linear and dose proportional from 0.1 to 50 mg in fed and nonsmoking subjects. The mean $AUC_{0-\infty}$ was 32% higher and the mean C_{max} was 62% higher in subjects who received palovarotene under fed conditions (Group 3) compared to fasted subjects (Group 5). The mean T_{max} was delayed by 1.1 hour under fed state. Smokers who received the 5 mg dose had a 22% higher mean $AUC_{0-\infty}$ and 32% higher mean C_{max} compared to the corresponding group of nonsmokers.

Table 96. Mean (SD) PK Parameters of Palovarotene After Single Doses

Parameter (Units)	0.1 mg Fed	0.5 mg Fed	5 mg Fed	25 mg Fed	50 mg Fed	5 mg Fed	5 mg Fed
	Nonsmoker	Nonsmoker	Nonsmoker	Nonsmoker	Nonsmoker	Fasted Nonsmoker	Smoker
AUC_{0-t} (ng•h/mL)	2.95 (1.07)	15.5 (4.4)	215 (31)	1121 (325)	1784 (651)	157 (60)	268 (74)
$AUC_{0-\infty}$ (ng•h/mL)	4.0 (0.8)	17.3 (5.0)	222 (29)	1135 (328)	1802 (652)	168 (63)	271 (75)
C_{max} (ng/mL)	0.99 (0.22)	3.46 (0.72)	30.1 (8.21)	176 (32.6)	309 (127)	18.6 (5.4)	39.7 (9.8)
T_{max} (h)	1.67 (0.58)	3.01 (1.00)	4.17 (0.98)	3.67 (0.52)	3.50 (0.55)	3.08 (0.92)	3.00 (0.89)
$t_{1/2}$ (h)	2.1 (0.3)	4.1 (0.6)	14.0 (7.8)	9.3 (4.7)	13.5 (8.9)	21.3 (7.2)	7.3 (2.5)
CL/F (L/h)	25.6 (4.8)	30.5 (8.6)	22.9 (3.3)	23.5 (6.3)	28.8 (19.0)	35.9 (21.0)	44.4 (59.6)
V/F (L)	75.7 (13.6)	177 (25.6)	472 (278)	321 (191)	617 (726)	1028 (476)	348 (319)

Source: Clinical study report RB16327

Abbreviations: AUC_{0-t} , area under the concentration versus time curve from time 0 to time t; $AUC_{0-\infty}$, area under the concentration versus time curve from time 0 to infinity; CL/F, oral clearance; C_{max} , maximum observed concentration; PK, pharmacokinetics; SD, standard deviation; $t_{1/2}$, half-time; T_{max} , time to maximum observed concentration; V/F, volume of distribution

Reviewer's comments: Compared to nonsmokers, smokers showed a 22% increase in mean AUC (271 ± 75 ng•h/mL versus 222 ± 29 ng•h/mL) and 32% increase in mean C_{max} (39.7 ± 9.83 ng/mL versus 30.1 ± 8.21 ng/mL). The small samples size ($N=6$) may affect PK comparison between smokers and nonsmokers. Population PK analysis based on the PK data of 66 smokers and 370 nonsmokers did not detect smoking status as a significant covariate on the PK of palovarotene. The review team agree with the Applicant that no dose adjustment is needed for smokers.

14.2.2. Study RB16328: Multiple Ascending Dose Study

Study Design

Study RB16328 was a single-center, ascending multiple-dose, randomized, double-blind, placebo-controlled study conducted in 40 healthy, male and female nonsmokers between 40 and 65 years of age and 24 healthy male and female smokers ≥ 60 years of age. Palovarotene oral solution or suspension was administered once daily under fed conditions at ascending doses of 0.02, 0.2, 0.4, 1, 5, and 10 mg for 28 days. Blood samples were collected for PK analysis on Day 1 predose and 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose and on Day 28 predose and 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours after the last dose. In addition, morning trough samples were collected predose on Days 3, 7, 11, 14, 18, 21, and 24.

PK Results

The mean $\pm$ SD PK parameters for palovarotene on Day 1 and Day 28 are summarized in Table 97.

Table 97. Mean $\pm$ SD PK Parameters of Palovarotene After Single and Multiple Oral Doses (Day 1 and Day 28)

Dose	0.02 mg QD Smokers (N=9)	0.2 mg QD Smokers (N=9)	0.4 mg QD Nonsmokers (N=9)*	1 mg QD Nonsmokers (N=6)	5 mg QD Nonsmokers (N=6)	10 mg QD Nonsmokers (N=9)*
Day 1						
AUC _{0-τ} (ng•h/mL)	0.75 (0.26)	6.75 (2.23)	14.9 (4.0)	44.3 (16.0)	182 (83.5)	336 (69.4)
C _{max} (ng/mL)	0.13 (0.05)	1.7 (0.6)	2.1 (1.0)	7.1 (2.4)	24.0 (11.7)	49.1 (14.0)
T _{max} (h)	4.0 (2.5)	3.8 (1.8)	5.9 (2.5)	5.2 (1.8)	7.3 (5.5)	4.3 (2.4)
Day 28						
AUC _{0-τ} (ng•h/mL)	0.68 (0.22)	6.4 (2.0)	14.1 (4.9)	46.3 (11.9)	212 (84.9)	385 (73.3)
AUC _{0-∞} (ng•h/mL)	0.77 (0.20)	7.6 (1.6)	14.2 (4.5)	51.2 (15.8)	256 (109)	482 (139.4)
C _{max,ss} (ng/mL)	0.11 (0.04)	1.5 (0.5)	2.8 (1.4)	7.1 (1.8)	27.8 (11.1)	52.2 (12.7)
T _{max} (h)	4.0 (2.5)	3.8 (1.8)	5.9 (2.5)	5.2 (1.8)	7.3 (5.5)	4.3 (2.4)
t _{1/2} (h)	3.7 (1.4)	2.8 (1.2)	3.2 (0.9)	7.0 (2.7)	11.1 (3.6)	21.2 (19.3)
CL/F (L/h)	27.4 (7.4)	27.1 (4.4)	31.2 (11.4)	21.0 (5.7)	25.2 (18.0)	22.3 (6.3)
V/F (L)	148 (87.5)	110 (49.7)	136 (39.8)	199 (44.9)	362 (162)	574 (386)
Rc	0.90	0.95	0.95	1.04	1.16	1.14

Source: Clinical study report RB16328

*N=9 on Day 1 and N=8 on Day 28

Abbreviations: AUC_{0- τ} , area under the concentration versus time curve from time 0 to time τ ; AUC_{0- ∞} , area under the concentration versus time curve from time 0 to infinity; CL/F, oral clearance; C_{max}, maximum observed concentration; C_{max,ss}, maximum observed concentration, steady state; PK, pharmacokinetics; Rc, accumulation ratio; t_{1/2}, half-time; T_{max}, time to maximum observed concentration; V/F, volume of distribution

Following once daily dosing, PK parameters of palovarotene were linear over the range of 0.02 to 10 mg based on AUC and C_{max} . Based on trough palovarotene plasma concentrations, steady state PK was attained by Day 3. Mean T_{max} ranged from 3.8 to 7.3 hours postdose on Day 1 and from 2.7 to 5.7 hours postdose on Day 28 across the six dose levels. No obvious accumulation of palovarotene was observed across the six dose levels after 28 days of once-daily dosing. The accumulation ratio (R_c) was between 0.9 and 1.16.

14.2.3. Study NP17056: Mass Balance Study

Study Design

Study NP17056 was a phase 1, single-center, nonrandomized, open-label, single oral dose study of [^{14}C]-radiolabeled palovarotene absorption, distribution, metabolism, and excretion in six healthy male subjects aged 45 to 64 years. Enrolled subjects received 1.0 mg of [^{14}C]-radiolabeled palovarotene under fed conditions on Day 1. Blood, urine, and feces samples were collected daily until the limits of radioactivity recovery were met (Day 10 for five subjects and Day 14 for one subject). The formulation used in Study NP17056 was a hard gelatin capsule containing a solution. Measurement of the plasma concentrations of palovarotene and its major metabolites M2, M3, M4a, and M4b was determined using a validated LC-MS/MS method. Liquid scintillation spectrometry was used for plasma and urine samples.

PK Results

The mean plasma concentration versus time profile of palovarotene was characterized by a moderate absorption rate (T_{max} of approximately 4 hours) followed by a biphasic decline with a mean $t_{1/2}$ of approximately 8 hours. In plasma samples, based on $AUC_{0-\infty}$, palovarotene accounted for approximately 14% of the mean radioactivity over the complete sample collection period. The four major metabolites, M3, M4b, M2, and M4a accounted for 10%, 7%, 5%, and 4% of the mean total radioactivity, respectively. The pharmacological activity of two active metabolites M3 and M4b was 1.7% and 4.2% of that of palovarotene based on in vitro RAR γ transactivation assay.

The whole blood to plasma radioactivity ratio ranged from 0.44 to 0.83 with a mean value of 0.61. The radioactivity in blood cells ranged from 1% to 33% with a mean value of 12%, indicating that most of the radioactivity was in plasma (88%).

For mass balance, the combined mean (SD) accumulative dose recovered in urine and feces was 97.0% (5.6%) over 168 hours postdose (7 days) and 100% (2.7%) over 312 hours postdose (13 days). Overall, 97.1% of the dose was recovered in the feces and 3.2% in the urine over 13 days postdose. Palovarotene and its four known major metabolites accounted for 67.2% of the dose (M4a and M4b 32.2%, M2 20.2%, M3 12.4%, and palovarotene 2.4%) in feces while six other unidentified metabolites accounted for 28.4% of the dose in feces. Metabolites were unsuccessfully profiled from the urine samples.

14.2.4. Study NP17726: Effect of Age and Sex

Study Design

Study NP17726 was an open-label, parallel-group, nonrandomized study to investigate the influence of age and sex on the PK of palovarotene in healthy young adult male and healthy elderly male and female subjects. Twelve healthy subjects in each of the following three groups were recruited: Group 1 (young male group)—males aged 18 to 45 years; Group 2 (elderly male group)—males aged 65 to 74 years; Group 3 (elderly female group)—females aged 65 to 74 years. Enrolled subjects received a single 1.0-mg dose (2×0.5 -mg soft gelatin capsules) of palovarotene on Day 1, within 30 minutes of completing a standardized breakfast. Blood samples were collected for PK analysis before and 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours after study drug administration.

PK Results

As shown in [Table 98](#), the PK parameters of palovarotene were similar in elderly males and young adult males. However, the geometric mean $C_{\max}$ and AUC_{0-t} in elderly females 36% and 20% higher than that in elderly males. Both CL/F and V/F were lower in elderly females compared with elderly males. However, when CL/F was adjusted for body surface area (BSA) and V/F was adjusted for body weight, no obvious differences in these PK parameters between elderly males and elderly females were observed. The differences in palovarotene exposure between elderly males and elderly females can be explained by differences in body size.

Table 98. Mean Palovarotene PK Parameters After Single Oral 1 mg Dose

Parameter (Units)	Study Group	N	Mean (SD)	Geometric Mean
AUC_{0-t} (ng•h/mL)	Young males	12	47.3 (8.86)	46.6
	Elderly males	12	50.9 (9.02)	50.0
	Elderly females	12	60.8 (10.7)	59.9
$C_{\max}$ (ng/mL)	Young males	12	9.78 (1.91)	9.62
	Elderly males	12	9.78 (2.48)	9.47
	Elderly females	12	13.1 (2.95)	12.8
$T_{\max}$ (h)	Young males	12	2.92 (1.17)	2.63
	Elderly males	12	3.59 (1.45)	3.32
	Elderly females	12	2.91 (1.56)	2.48
$t_{1/2}$ (h)	Young males	12	11.9 (2.70)	11.6
	Elderly males	12	10.0 (2.57)	9.71
	Elderly females	12	9.26 (1.93)	9.07
CL/F (L/h)	Young males	12	21.7 (4.11)	21.4
	Elderly males	12	20.3 (4.42)	19.9
	Elderly females	12	17.0 (3.64)	16.6
V/F (L)	Young males	12	377 (146)	356
	Elderly males	12	287 (82)	278
	Elderly females	12	221 (39)	218

Source: Clinical study report NP17726

Abbreviations: AUC_{0-t} , area under the concentration versus time curve from time 0 to time t; CL/F, oral clearance; $C_{\max}$, maximum observed concentration; PK, pharmacokinetics; $t_{1/2}$, half-time; $T_{\max}$, time to maximum observed concentration; V/F, volume of distribution

14.2.5. Study PVO-1A-101: Effect of Race

Study Design

Study PVO-1A-101 was a single-center, double-blind, randomized, crossover, single-dose study comparing the PK profile of palovarotene in 10 healthy Japanese and 8 non-Asian subjects (two African American, five White and one other) aged 18 to 55 years. Of the 18 subjects, there were eight matched pairs of non-Asian and Japanese subjects matched by age, gender, and BMI. In Period 1, subjects were randomly assigned to receive either 5-mg or 10-mg palovarotene hard gelatin capsules under fed state. In Period 2, they received the alternate dose under fed state. A washout interval of 5 days separated the two doses. Blood samples were obtained predose and 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, and 72 hours postdose.

PK Results

The PK parameters of palovarotene are summarized in [Table 99](#). The PK parameters of palovarotene were similar between Japanese and non-Asian groups at both dose levels. C_{max} and AUC values appear dose-proportional between doses in each racial group. Mean total body clearance (CL/F) values ranged from 22.7 to 24.2 L/h across doses and racial group confirming dose proportionality and similar PK between racial groups.

Table 99. Summary of PK Parameters by Palovarotene by Dose and Race

Parameter	Palovarotene 5 mg		Palovarotene 10 mg	
	Japanese Subjects (N=10)	Non-Asian Subjects (N=8)	Japanese Subjects (N=10)	Non-Asian Subjects (N=8)
AUC _{0-∞} (ng•h/mL)				
Mean (SD)	223 (63.5)	260 (101)	442 (103)	485 (189)
AUC _{0-t} (ng•h/mL)				
Mean (SD)	222 (62.5)	259 (101)	440 (103)	483 (190)
C _{max} (ng/mL)				
Mean (SD)	41.2 (17.4)	41.9 (14.1)	77.2 (21.9)	81.0 (23.5)
T _{max} (h)				
Mean (SD)	4.1 (1.1)	4.0 (1.4)	4.5 (1.7)	4.0 (1.4)
t _{1/2} (h)				
Mean (SD)	10.9 (3.3)	11.4 (1.7)	9.7 (4.6)	13.0 (6.3)
CL/F (L/h)				
Mean (SD)	24.2 (7.1)	22.7 (10.4)	24.1 (7.1)	24.0 (10.4)

Source: Clinical study report PVO-1A-101

Abbreviations: AUC_{0-t}, area under the concentration versus time curve from time 0 to time t; AUC_{0-∞}, area under the concentration versus time curve from time 0 to infinity; CL/F, oral clearance; C_{max}, maximum observed concentration; PK, pharmacokinetics; t_{1/2}, half-time; T_{max}, time to maximum observed concentration

14.2.6. Study PVO-1A-103: Thorough QT Study

Study Design

Study PVO-1A-103 was a single-center, randomized, partially double-blind, placebo- and positive-controlled, four-way crossover study to evaluate the effect of a therapeutic and a supratherapeutic dose of palovarotene on the QT interval in 32 healthy adult subjects aged 18 to 55 years. Subjects received the following single-dose treatments in random order under fed state:

palovarotene 50 mg, palovarotene 20 mg, placebo, and moxifloxacin 400 mg. A minimum washout interval of 5 days separated each dose. Blood samples were obtained 1.25, 1, and 0.75 hours predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours postdose. The 12-lead electrocardiograms (ECGs) were extracted from a continuous Holter recording by a central ECG laboratory at the following time points on Day 1 in each period: 1.25, 1 and 0.75 hours predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours postdose.

PK Results

As shown in Table 100, the plasma PK of palovarotene was dose proportional from 20 to 50 mg in the fed state following a single dose.

In the concentration-QTc analysis, a linear model with an intercept was fitted for the palovarotene plasma concentrations, which represented the data in an acceptable way. The estimated slope of palovarotene plasma concentration in the concentration-QTc relationship was shallow and not statistically significant (-0.000087 ms per ng/mL [90% CI: -0.0058 , 0.0056]) with a positive and not statistically significant intercept of 1.0 ms. The predicted QT effects ($\Delta\Delta\text{QTcF}$) using this model were 0.97 ms (90% CI: -0.80 , 2.74) and 0.95 ms (90% CI: -0.98 , 2.89) for palovarotene 20 mg (geometric mean C_{max} = 134 ng/mL) and palovarotene 50 mg (geometric mean C_{max} = 314 ng/mL), respectively. Based on this concentration-QTc analysis, an effect on $\Delta\Delta\text{QTcF}$ exceeding 10 ms can be excluded within the range of observed palovarotene plasma concentrations up to ~500 ng/mL. There were no subjects with $\text{QTcF} > 450$ ms and no subjects with $\Delta\text{QTcF} > 30$ ms. There were no treatment-emergent T-wave morphology changes or U-waves.

Table 100. Summary of Pharmacokinetic Parameters by Palovarotene Dose

PK Parameter	Palovarotene 20 mg N=31	Palovarotene 50 mg N=31
$\text{AUC}_{0-\infty}$ (ng•h/mL)		
n	30	29
Mean (SD)	969 (306)	2370 (662)
AUC_{0-t} (ng•h/mL)		
n	31	31
Mean (SD)	943 (302)	2320 (665)
C_{max} (ng/mL)		
n	31	31
Mean (SD)	145 (60.2)	328 (92.2)
T_{max} (h)		
n	31	31
Median (min, max)	4.1 (1.1, 12.1)	4.1 (2.1, 10.1)
$t_{1/2}$ (h)		
n	30	29
Mean (SD)	3.70 (0.84)	3.33 (0.55)

Source: Clinical study report PVO-1A-103

Abbreviations: AUC_{0-t} , area under the concentration versus time curve from time 0 to time t; $\text{AUC}_{0-\infty}$, area under the concentration versus time curve from time 0 to infinity; CL/F, oral clearance; C_{max} , maximum observed concentration; PK, pharmacokinetics; $t_{1/2}$, half-time; T_{max} , time to maximum observed concentration

Reviewer's comment: Palovarotene exhibits a linear PK at a dose ≤ 50 mg. The mean C_{max} following a single dose of palovarotene 50 mg (328 ± 92 ng/mL) is 2-fold higher than the mean steady state C_{max} (165 ± 72.7 ng/mL) in FOP patients receiving 20 mg QD dose in Study PVO-1A-301. The palovarotene exposure - QTc model and predicted QT effects are reviewed by OND QT-IRT team. Refer to QT-IRT consult review for more information.

14.2.7. Study PVO-1A-104: Exposure in Seminal Fluid

Study Design

Study PVO-1A-104 was a single-center, randomized, open-label, single-period study to assess the relationship between oral doses of palovarotene and the transfer of palovarotene into seminal fluid following multiple oral doses in 24 healthy adult male subjects aged 18 to 55 years. Subjects were randomized to one of three postdose semen sampling times (3, 24, or 72 hours postdose on Day 5). Single doses of 20 mg (two 10-mg capsules) were taken orally, once daily, 30 minutes following a standardized high-fat, high-calorie breakfast for 5 days. Blood samples were obtained predose on Days 1 and 5 and at 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours after palovarotene administration on Day 5.

PK Results

The geometric means of plasma C_{max} and AUC_{0- τ} were 120 ng/mL and 876 ng•h/mL, respectively, on Day 5 following daily doses of 20-mg palovarotene for 5 days. The mean $t_{1/2}$ of palovarotene was 11 hours. The median T_{max} of palovarotene was approximately 4 hours and ranged from 1 to 8 hours postdose. Palovarotene levels in all seminal fluid samples collected at 24 hour and 72 hours postdose were below the limit of quantitation (5 pg/mL). In the eight subjects randomized to the 3-hour collection time point, the mean amount of palovarotene in ejaculate was 8.84 ng, which accounted for 0.0000442% of the dose. The time-matched ratio of semen to plasma concentration was 0.0273.

14.2.8. Study PVO-1A-102: Food Effects and CYP3A4 Induction by Palovarotene

Study Design

Study PVO-1A-102 was conducted in two components. The DDI component was an open-label single sequence component to assess the induction potential of the highest proposed clinical dose of palovarotene (20 mg) on the PK of midazolam as a CYP3A4 substrate. The PK of palovarotene after single and multiple 20-mg doses was also evaluated as part of this DDI component. In addition, the food effect component evaluated the effect of food and the effect of swallowing the intact capsule versus sprinkling the contents on apple sauce on the PK/BA of palovarotene.

In the DDI component, in the morning of Day 1, 24 subjects received a single oral dose of 2-mg midazolam 30 minutes after the start of a standardized breakfast. On Day 2 through Day 15, subjects received oral QD dose of 20 mg palovarotene capsule in the morning, 30 minutes after the start of a standardized breakfast. A second dose of 2 mg midazolam was administered on Day 15 in the morning (immediately following the palovarotene dose). PK samples for midazolam and its metabolite 1-hydroxymidazolam were obtained at the following time points on Days 1

and 15: predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after midazolam administration. PK samples for palovarotene were obtained at the following time points on Days 2 and 15: predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after palovarotene administration. An additional blood sample was collected at 48 hours after the palovarotene dose on Day 15.

The food effect component was an open-label, single-dose, randomized, 3-treatment, 3-period, crossover study design. A total of 24 healthy subjects were randomized 1:1:1 to one of three treatment sequences (n=8/sequence): Sequence A-B-C, Sequence B-C-A, or Sequence C-A-B. All subjects received three single oral doses of 20 mg palovarotene on Days 1, 6, and 11, separated by 5-day washout periods.

- Treatment A: 20 mg palovarotene whole capsule administered under fasting conditions
- Treatment B: 20 mg palovarotene whole capsule administered under fed conditions
- Treatment C: 20 mg palovarotene sprinkled on apple sauce, administered under fed conditions

PK samples for palovarotene in the food effect component were obtained at the following time points:

- Days 1, 6, and 11 at predose (Hour 0), and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 16 hours postdose
- Days 2, 7, and 12 at 24 hours postdose
- Days 3, 8, and 13 at 48 hours postdose

PK Results

As shown in Table 101, co-administration of palovarotene 20 mg QD for 14 days reduced the AUC and C_{max} of midazolam by 14% and 10% respectively. The AUC and C_{max} of 1-hydroxymidazolam decreased by 8% and 9%, respectively.

Table 101. Statistical Analysis to Assess Potential Effect of Palovarotene on the PK of Midazolam

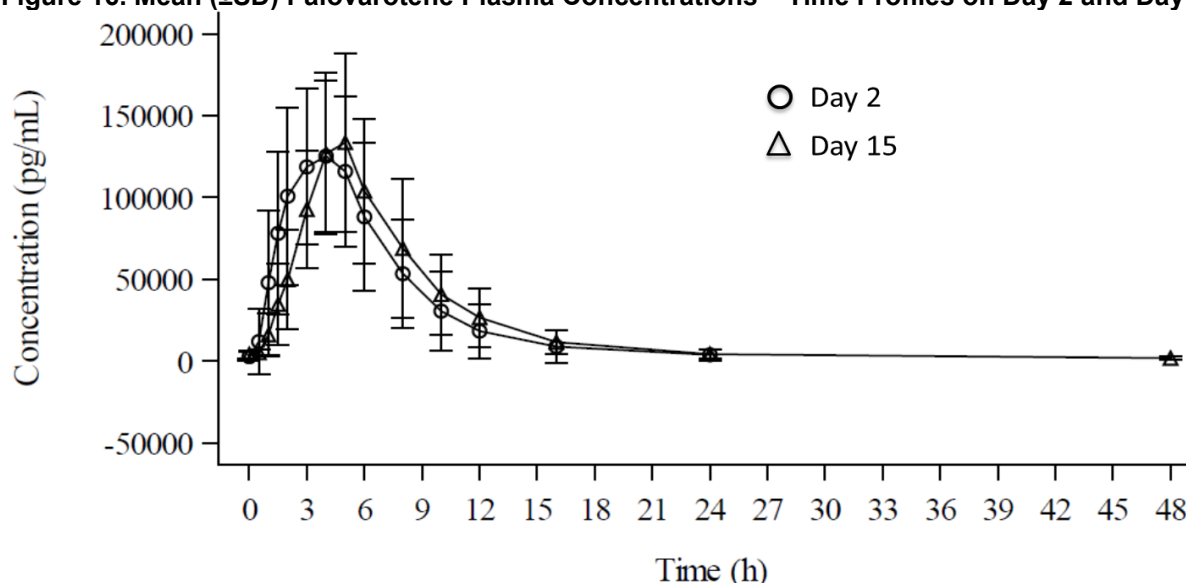
Test/ Reference	Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CIs)
		Test	Reference	
Day 15/Day 1 Midazolam	AUC _{0-inf} (ng•h/mL)	28.38	32.81	86.48 (79.66 – 93.88)
	AUC _{0-t} (ng•h/mL)	27.38	31.70	86.37 (79.78 – 93.50)
	C _{max} (ng/mL)	5.10	5.67	89.94 (83.33 – 97.07)
Day 15/Day 1 1-Hydroxymidazolam	AUC _{0-t} (ng•h/mL)	11.72	12.69	92.35 (85.63 – 99.61)
	C _{max} (ng/mL)	2.09	2.29	91.42 (83.08 – 100.60)

Source: Clinical pharmacology reviewer's analysis

Abbreviations: AUC_{0-t}, area under the concentration versus time curve from time 0 to time t; AUC_{0-inf}, area under the concentration versus time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum observed concentration; PK, pharmacokinetics

As shown in [Figure 16](#) and [Table 102](#), in the DDI component, when palovarotene was administered under fed conditions, palovarotene PK profiles on Day 2 (single-dose) and Day 15 (multiple-dose) were comparable. No obvious accumulation of palovarotene was observed following 20 mg QD for 14 days.

Figure 16. Mean ($\pm$ SD) Palovarotene Plasma Concentrations – Time Profiles on Day 2 and Day 15



Source: Clinical study PVO-1A-102 report Figure 5.
Abbreviations: h, hour; SD, standard deviation

Table 102. Summary of Palovarotene Plasma PK Parameters on Day 2 and Day 15

Day	Parameter (units)	Summary Statistic	Overall (N=23)
2	C _{max} (ng/mL)	GeoMean (CV%)	139 (30.4)
	T _{max} (h)	Median (min, max)	4 (1.5, 8)
	AUC ₀₋₂₄ (ng•h/mL)	GeoMean (CV%)	857 (35.8)
15	C _{max,ss} (ng/mL)	GeoMean (CV%)	133 (37.8)
	T _{max,ss} (h)	Median (min, max)	5 (3, 6)
	C _{min,ss} (ng/mL)	GeoMean (CV%)	3.08 (59.5)
	AUC _{0-τ} (ng•h/mL)	GeoMean (CV%)	892 (38.4)
	t _{1/2} (h)	Mean (SD)	8.68 (2.39)*
	CL _{ss} /F (L/h)	GeoMean (CV%)	22.4 (28.4)
	Vd _{ss} /F (L)	GeoMean (CV%)	319 (63.7)
	Rac	GeoMean	1.04 (17.3)

Source: Clinical Pharmacology Summary Table 18

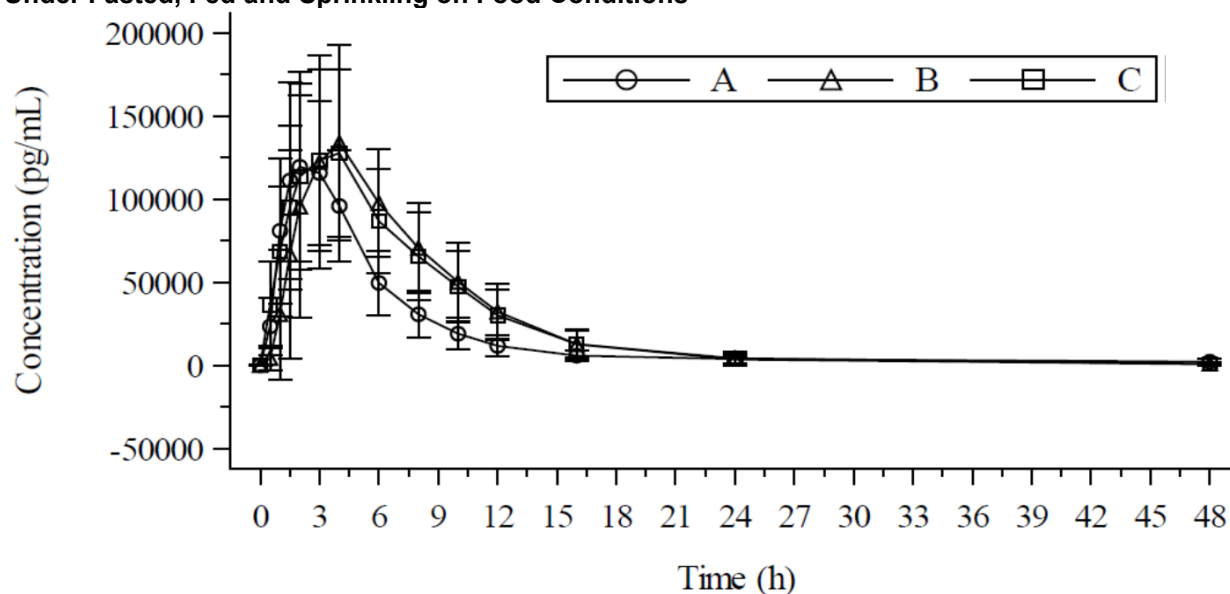
*Based on data of 13 subjects

Abbreviations: AUC_{0-τ}, area under the concentration versus time curve from time 0 to time τ; AUC₀₋₂₄, area under the concentration versus time curve from time 0 to 24 hours; CL/F, oral clearance; C_{max}, maximum observed concentration; C_{min}, minimum observed concentration; CV, cardiovascular; PK, pharmacokinetics; Rac, accumulation ratio; SD, standard deviation; ss, steady state; t_{1/2}, half-time; T_{max}, time to maximum observed concentration; V/F, volume of distribution

For the food effect component, mean ($\pm$ SD) plasma palovarotene concentration-time profiles are presented in Figure 17. Statistical analyses of BA of palovarotene under fed and fasted conditions and administered as sprinkled food under fed conditions are summarized in Table 103. Following administration of the palovarotene capsules by swallowing whole after a high-fat, high-caloric breakfast, there was a 39% increase in AUC_{0-inf} and a 15% increase in C_{max}

compared with administration under fasted conditions. Oral administration by sprinkling the contents onto apple sauce did not affect palovarotene exposure compared to administration as whole capsules.

Figure 17. Mean ($\pm$ SD) Palovarotene Plasma Concentrations – Time Profiles When Administered Under Fasted, Fed and Sprinkling on Food Conditions



Source: Clinical study PVO-1A-102 report Figure 2.

Treatment A: whole capsule under fasting conditions; Treatment B: 20 mg whole capsule under fed conditions; Treatment C: sprinkled on apple sauce under fed conditions

Abbreviations: h, hour; SD, standard deviation

Table 103. Statistical Analysis of Bioavailability of Palovarotene Under Fed and Fasted Conditions

Test/ Reference	Pharmacokinetic Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CIs)
		Test	Reference	
Fed/Fasted	AUC _{0-inf} (ng•h/mL)	1071.0	770.2	139.1 (128.5 – 150.5)
	AUC _{0-t} (ng•h/mL)	1059.8	751.4	141.0 (132.5 – 150.1)
	C _{max} (ng/mL)	139.4	121.0	115.2 (100.5 – 132.1)
Sprinkling/ Capsules	AUC _{0-inf} (ng•h/mL)	1052.3	1071.0	98.26 (91.09 – 106.0)
	AUC _{0-t} (ng•h/mL)	1042.1	1059.8	98.33 (92.38 – 104.7)
	C _{max} (ng/mL)	131.9	139.4	94.66 (82.57 – 108.5)

Source: Clinical pharmacology reviewer's analysis

Abbreviations: AUC_{0-t}, area under the concentration versus time curve from time 0 to time t; AUC_{0-inf}, area under the concentration versus time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum observed concentration

14.2.9. Study NP17041: CYP3A4 Inhibition by Ketoconazole

Study Design

Study NP17041 was an open-label study conducted to investigate the effect of ketoconazole on the PK of palovarotene in 18 healthy male subjects aged 18 to 64 years. Palovarotene 1 mg (2×0.5 mg soft gelatin capsules) was administered once daily for 21 days, within 30 minutes after completing a standardized breakfast. Palovarotene was co-administered with 400-mg ketoconazole once daily on Day 15 through Day 21. Blood samples for PK analysis were collected on Day 14 (palovarotene alone at steady state) and Day 21 (palovarotene + ketoconazole) predose and 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose.

PK Results

As shown in [Table 104](#), co-administration of ketoconazole increased the AUC_{0-t} and C_{max} of palovarotene by 3.1 fold and 2.2 fold, respectively, relative to treatment with palovarotene alone. The AUC_{0-inf} of palovarotene on Day 14 could not be calculated because palovarotene was administered from Day 1 through Day 21. Statistical analysis was conducted with AUC_{0-t} and C_{max} only.

Table 104. Statistical Analysis of the Effect of Ketoconazole on of the PK Parameters of Co-administered Palovarotene

Test/Reference	Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CIs)
		Test	Reference	
With Ketoconazole / Palovarotene alone	AUC_{0-t} (ng•h/mL)	157.64	50.63	311.34 (296.46 – 326.97)
	C_{max} (ng/mL)	22.069	10.048	219.64 (197.91 – 243.75)

Source: Clinical pharmacology reviewer's analysis

Abbreviations: AUC_{0-t} , area under the concentration versus time curve from time 0 to time t; CI, confidence interval; C_{max} , maximum observed concentration

14.2.10. Study NP17040: CYP3A4 Induction by Rifampin

Study Design

Study NP17040 (Module 5.3.3.4 Report 1010704/NP17040) is open-label study was conducted to investigate the effect of rifampicin (a CYP3A4 inducer) on the PK of palovarotene in 18 healthy male subjects aged 18 to 64 years. Palovarotene 1 mg (2×0.5 -mg soft gelatin capsules) was administered once daily for 24 days, within 30 minutes after completing breakfast, co-administered with rifampicin (600 mg orally) on the last 10 days. Blood samples for PK analysis were taken predose and 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose on Days 14 and 24.

PK Results

As shown in [Table 105](#), co-administration of rifampin decreased the AUC_{0-t} and C_{max} of palovarotene by 89% and 81%, respectively, relative to treatment with palovarotene alone. The AUC_{0-inf} of palovarotene on Day 14 could not be calculated because palovarotene was

administered from Day 1 through Day 24. Statistical analysis was conducted with AUC_{0-t} and C_{max} only

Table 105. Statistical Analysis of the Effect of Rifampin on the PK Parameters of Co-administered Palovarotene

Test/ Reference	Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CIs)
		Test	Reference	
With Rifampin / Palovarotene alone	AUC _{0-t} (ng•h/mL)	4.480	39.91	11.22 (10.02 – 12.58)
	C _{max} (ng/mL)	1.544	7.969	19.37 (16.47 – 22.78)

Source: Clinical pharmacology reviewer's analysis

Abbreviations: AUC_{0-t}, area under the concentration versus time curve from time 0 to time t; CI, confidence interval; C_{max}, maximum observed concentration

14.2.11. Study NP21025: Drug Interaction with Prednisone

Study Design

Study NP21025 was an open-label, single sequence study to investigate the effect of prednisone, a weak CYP3A4 inducer, on the PK of palovarotene in 22 healthy male subjects aged 18 to 64 years. Within 30 minutes after completing a standardized breakfast, 5-mg palovarotene (2 × 2.5-mg soft gelatin capsules) was administered once daily on Days 2 through 9 and a single 40-mg dose of prednisone was administered once daily on Days 1 and 9. On Days 1, 8, and 9, blood samples for the PK assessment of palovarotene and its metabolites and prednisone/prednisolone were taken before and 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after study drug administration. The effect of prednisone on palovarotene PK and the effect of palovarotene on prednisone PK were assessed.

PK Results

As shown in [Table 106](#), co-administration of a single dose of prednisone 40 mg decreased the AUC and C_{max} of palovarotene by 13%, relative to treatment with palovarotene alone. On the other hand, co-administration of palovarotene 5 mg QD for 8 days did not change the AUC or C_{max} of prednisone.

Table 106. Statistical Analysis of the Drug Interactions Between Palovarotene and Prednisone

Test/Reference	Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CIs)
		Test	Reference	
Day 9/Day 8	AUC _{0-t} (ng•h/mL)	246.49	284.61	86.61 (76.06 – 98.62)
Palovarotene	C _{max} (ng/mL)	35.53	40.82	87.03 (72.10 – 105.04)
Day 9/Day 1	AUC _{0-t} (ng•h/mL)	380.85	374.45	101.71 (98.40 – 105.13)
Prednisone	C _{max} (ng/mL)	47.88	47.10	101.65 (96.52 – 107.05)

Source: Clinical study report NP21025

Abbreviations: AUC_{0-t}, area under the concentration versus time curve from time 0 to time t; CI, confidence interval; C_{max}, maximum observed concentration

Reviewer's comment: Complete induction of CYP3A4 was unlikely to reach with a single dose of prednisone. The results from Study NP21025 cannot be used to justify that co-administration of multiple-dose prednisone does not affect the PK of palovarotene. However, population PK analysis of the PK data of 59 subjects concomitantly taking prednisone did not detect concomitant use of prednisone as a significant covariate on the PK of palovarotene. The review team agrees that no dose adjustment is needed for palovarotene in patients who concomitantly use prednisone. Also, the palovarotene dose (5 mg QD) used in Study NP21025 did not cover flare-up doses (10 mg and 20 mg QD).

14.2.12. Study PVO-1A-201: Phase 2 Study in FOP Patients

Study Design

Study PVO-1A-201 was a multicenter, randomized, double-blind (investigator and subject), Applicant-unblinded, placebo-controlled phase 2 study to evaluate the efficacy and safety of episodic treatment with palovarotene at the time of a flare-up in adult and pediatric subjects with FOP. Overall, 21 subjects received 10-mg palovarotene hard gelatin capsules once daily for 14 days followed by 5-mg once daily for 28 days (10/5-mg regimen), nine subjects received 5-mg palovarotene hard gelatin capsules once daily for 14 days followed by 2.5-mg once daily for 28 days (5/2.5-mg regimen), and 10 subjects received placebo for 24 days. To achieve daily drug exposures equivalent to 10, 5, and 2.5 mg, pediatric subjects received weight-adjusted doses according to three weight categories (20 to <40 kg, 40 to <60 kg, and ≥60 kg). Weight-adjusted doses of palovarotene estimated to achieve exposures equivalent to 10, 5, and 2.5 mg are shown in Table 107. The actual weight adjusted doses received by 10 pediatric patients are summarized in Table 108. Blood samples for PK analysis were collected before dosing and 3, 6, 10, and 24 hours postdose on Day 14 and Days 28 or 42.

Table 107. Weight-Adjusted Palovarotene Doses Equivalent to 10, 5, and 2.5 mg

Weight Range Category	10-mg Equivalent	5-mg Equivalent	2.5-mg Equivalent
20 to <40 kg	6 mg	3 mg	1.5 mg
40 to <60 kg	8 mg	4 mg	2 mg
≥60 kg	10 mg	5 mg	2.5 mg

Source: Clinical study report PVO-1A-201

Table 108. Actual Weight-Adjusted Doses Received by Subjects

Subject	Baseline Weight (kg)	PVO 5/2.5 mg N=9	PVO 10/5 mg N=21
n (%)		5 (55.6)	5 (23.8)
(b) (6)	27.5		PVO 6/3 mg
	50.1	PVO 4/2 mg	
	54.4		PVO 8/4 mg
	25.8	PVO 3/1.5 mg	
	23.4	PVO 3/1.5 mg	
	19.6	PVO 3/1.5 mg	
	50.1		PVO 8/4 mg
	33.2		PVO 6/3 mg
	28.0		PVO 6/3 mg
	58.2	PVO 4/2 mg	

Source: Clinical study report PVO-1A-201

Abbreviations: N, number of subjects, n, number of subjects with the given weight-adjusted dose; PVO, palovarotene

PK Results

Plasma palovarotene PK parameters at steady state are summarized in Table 109. Increases in C_{max} and AUC values with increasing dosage suggest dose-proportionality. The mean CL/F values ranged from 12.8 ± 4.1 L/h to 19.5 ± 10.7 L/h, also supporting a linear PK. The mean half-life values across groups receiving different doses were 4.4 to 4.9 hours. The plasma palovarotene exposures were compared by the status of new HO. As shown in Table 110, the mean AUC_{0-24h} values at Week 4/Week 6 were similar for subjects (N=4) who had new HO at Week 6 compared to subjects (N=20) who had no new HO at Week 6.

Table 109. Plasma Palovarotene PK Parameters (Study PVO-1A-201)

Parameters	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-T} (ng·h/mL)	CL/F (L/h)
Palovarotene 5/2.5 mg						
Week 2, 5 mg						
N	5	5	5	4	4	4
Mean (SD)	35.6 (19.9)	1.74 (0.96)	3.3 (1.5)	4.9 (1.2)	350 (182)	12.8 (4.1)
Week 4/Week 6, 2.5 mg						
N	7	7	7	4	7	7
Mean (SD)	19.0 (9.24)	0.614 (0.290)	3.9 (1.5)	4.5 (0.5)	143 (84.8)	19.5 (10.7)
Palovarotene 10/5 mg						
Week 2, 10 mg						
N	15	15	15	11	13	13
Mean (SD)	95.6 (30.3)	3.13 (2.36)	3.6 (1.3)	4.6 (1.1)	686 (247)	15.6 (7.0)
Week 4/Week 6, 5 mg						
N	17	17	17	16	17	17
Mean (SD)	45.5 (17.1)	3.88 (7.04)	3.2 (0.7)	4.4 (0.7)	311 (129)	17.7 (7.4)

Source: Clinical study report PVO-1A-201

Abbreviations: AUC_{0-T} , area under the concentration versus time curve from time 0 to time T; CL/F, oral clearance; C_{max} , maximum observed concentration; C_{min} , minimum observed concentration; PK, pharmacokinetics; PVO, palovarotene; SD, standard deviation, $T_{1/2}$, half-time; T_{max} , time to maximum observed concentration

Table 110. Week 4/Week 6 Plasma Palovarotene Pharmacokinetic Parameters by With or Without New HO

Category	Statistic	C _{max} (pg/mL)	C _{min} (pg/mL)	AUC _{0-24h} (h*pg/mL)
New HO at Week 6	N	4	4	4
	Mean ± SD	38550±20349	3803±5939	269963±127156
No new HO at Week 6	N	20	20	20
	Mean ± SD	37605±19760	2752±6230	260389±145018

Source: Clinical study report PVO-1A-201

Abbreviations: AUC_{0-24h}, area under the concentration versus time curve from time 0 to 24 hours; C_{max}, maximum observed concentration; C_{min}, minimum observed concentration; HO, heterotopic ossification; N, number of subjects; SD, standard deviation

Reviewer's comments: The elimination half-life of palovarotene observed in FOP patients (4.4 to 4.9 hours) was shorter than that (approximately 8 to 12 hours) observed in healthy adults in multiple phase 1 studies. In Study PVO-1A-201, plasma PK samples were collected from FOP patients at five time points only and the last time point was at 24 hours postdose. In contrast, more intense PK sampling was conducted in studies conducted in healthy subjects and the last sampling time point was at 48 hours or 72 hours post dose. The half-life of palovarotene in FOP patients may not be accurately characterized.

14.2.13. Study PVO-1A-202: Phase 2 Study in FOP Patients

Study Design

Study PVO-1A-202 is an open-label extension of Study PVO-1A-201, comprising three parts: Parts A, B, and C. In Part A, all subjects received the 10/5-mg palovarotene regimen at the time of a subsequent eligible flare-up (weight adjusted for skeletally immature pediatric subjects). No PK sampling was performed in Part A. Part B included 18 new adult subjects who did not participate in Study PVO-1A-201 or Study PVO-1A-202/Part A. Adult and skeletally mature pediatric subjects (i.e., those with at least 90% skeletal maturity) received 5-mg palovarotene hard gelatin capsules daily for up to 24 months (chronic treatment). When a flare-up occurred, subjects received 20-mg palovarotene hard gelatin capsules daily for 4 weeks followed by 10-mg hard gelatin capsules daily for 8 weeks (20/10-mg regimen). This flare-up regimen was extended if the flare-up had not resolved after 12 weeks. Eight skeletally immature pediatric subjects received only flare-up treatment with weight adjusted-equivalents (Table 111) of the 20/10-mg regimen (i.e., no 5-mg chronic treatment).

The steady-state PK of palovarotene was assessed 7 days after treatment initiation and at the end of treatment for the first treated flare-up only. In Part C, all subjects received 5-mg palovarotene daily for up to 24 months, with dose escalation for flare-up treatment to 20-mg palovarotene for 4 weeks followed by 10-mg palovarotene for 8 weeks (20/10-mg regimen). This flare-up regimen was extended if the flare-up had not resolved after 12 weeks. Doses were weight-adjusted in skeletally immature subjects. In Parts B and C, blood samples for PK analysis were obtained once during chronic palovarotene treatment and twice during flare-up-based treatment: once during the 20-mg regimen and once during the 10 mg regimen. Blood samples were collected predose and 3, 6, 10, and 24 hours postdose.

Table 111. Weight-Based Equivalent Doses Received by Subjects During Flare-ups

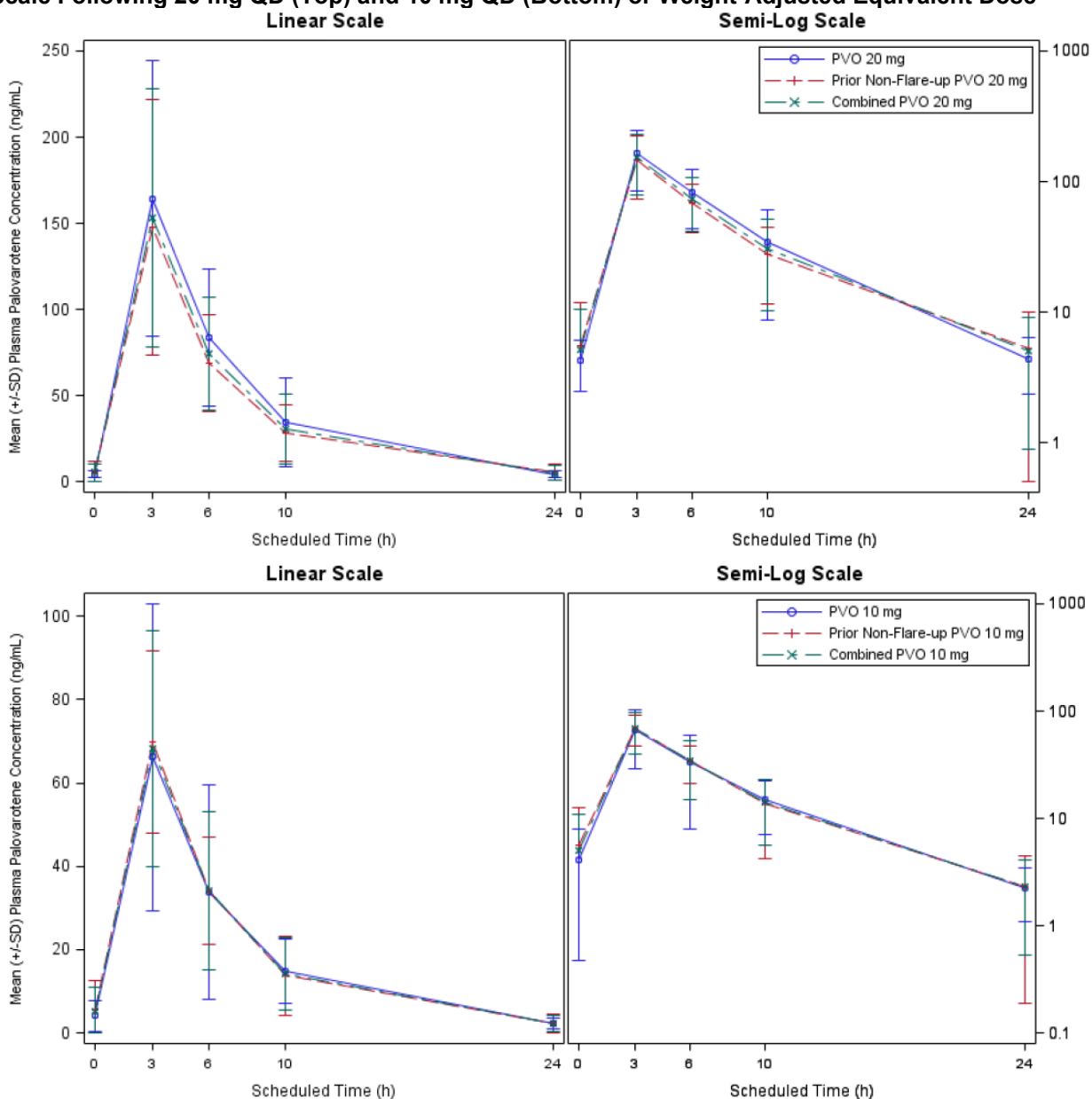
Subject	Baseline Weight (kg)	PVO 20 mg N=8	PVO 10 mg N=8
(b) (6)	29.7	PVO 12.5 mg	PVO 6 mg
	29.8	PVO 12.5 mg	PVO 6 mg
	30.0	PVO 12.5 mg	PVO 6 mg
	23.3	PVO 12.5 mg	PVO 6 mg
	27.4	PVO 12.5 mg	PVO 6 mg
	45.6	PVO 15 mg	PVO 7.5 mg
	35.0	PVO 12.5 mg	PVO 6 mg
	29.0	PVO 12.5 mg	PVO 6 mg

Source: Clinical study report PVO-1A-202
Abbreviations: N, number of subjects; PVO, palovarotene

PK Results From Part B

The mean plasma palovarotene concentration versus time profiles for the PVO 20/10 mg group, chronic/flare-up 20/10 mg group and combined groups are shown in [Figure 18](#) for the 20-mg or weight-based equivalent dose and the 10-mg or weight-based equivalent dose, respectively.

Figure 18. Mean (SD) Plasma Palovarotene Concentration Time Profiles in Linear and Semi-Log Scale Following 20 mg QD (Top) and 10 mg QD (Bottom) or Weight-Adjusted Equivalent Dose



Source: Clinical study report PVO-1A-202

Abbreviations: h, hour; PVO, palovarotene; QD, once daily; SD, standard deviation

A summary of plasma palovarotene PK parameters at steady state during flare-up treatment for subjects with no prior chronic treatment, with prior chronic treatment, and combined is presented in [Table 112](#) and [Table 113](#) for the 20-mg or weight-based equivalent dose and the 10-mg or weight-based equivalent dose, respectively. Overall, the $C_{\max,ss}$ and $AUC_{0-\tau}$ for combined group increased approximately proportionally with dose from 10 mg to 20 mg. The mean CL/F values across different groups ranged from 14.0 ± 5.34 L/h to 23.7 ± 6.28 L/h.

Table 112. Plasma Palovarotene PK Parameters for 20 mg QD Dose or Weight-Adjusted Equivalent (Study PVO-1A-202/Part B)

Parameters	$C_{\max,ss}$ (ng/mL)	$C_{\min,ss}$ (ng/mL)	$T_{\max}$ (h)	$t_{1/2}$ (h)	AUC_{0-T} (ng•h/mL)	CL/F (L/h)
Palovarotene 20/10 mg						
N	8	8	8	7	7	7
Mean (SD)	176 (64.6)	3.34 (0.93)	3.36 (1.10)	4.85 (1.78)	1201 (332)	14.0 (5.34)
Chronic/flare-up PVO 20/10 mg						
N	12	12	12	11	11	11
Mean (SD)	138 (43.3)	3.09 (2.08)	3.17 (0.90)	5.24 (1.86)	886 (266)	23.7 (6.28)
Combined Palovarotene 20/10 mg						
N	20	20	20	18	18	18
Mean (SD)	153 (54.6)	3.19 (1.68)	3.24 (0.96)	5.09 (1.78)	1008 (325)	19.9 (7.53)

Source: Clinical study report PVO-1A-202

Abbreviations: AUC_{0-T} , area under the concentration versus time curve from time 0 to time T; CL/F, oral clearance; $C_{\max,ss}$, maximum observed concentration, steady state; $C_{\min,ss}$, minimum observed concentration, steady state; N, number of subjects; PK, pharmacokinetics; PVO, palovarotene; SD, standard deviation, $T_{1/2}$, half-time; $T_{\max}$, time to maximum observed concentration

Table 113. Plasma Palovarotene PK Parameters for 10 mg QD Dose or Weight-Adjusted Equivalent (Study PVO-1A-202/Part B)

Parameters	$C_{\max,ss}$ (ng/mL)	$C_{\min,ss}$ (ng/mL)	$T_{\max}$ (h)	$t_{1/2}$ (h)	AUC_{0-T} (ng•h/mL)	CL/F (L/h)
Palovarotene 20/10 mg						
N	8	8	8	7	8	8
Mean (SD)	67.6 (36.6)	2.15 (1.14)	3.38 (1.06)	6.02 (3.76)	459 (235)	20.7 (16.6)
Chronic/flare-up PVO 20/10 mg						
N	10	10	10	9	9	9
Mean (SD)	73.6 (18.5)	1.89 (2.06)	3.10 (0.70)	4.82 (1.18)	474 (164)	22.0 (5.30)
Combined Palovarotene 20/10 mg						
N	18	18	18	16	17	17
Mean (SD)	70.9 (27.2)	2.00 (1.67)	3.22 (0.86)	5.34 (2.60)	467 (194)	21.4 (11.6)

Source: Clinical study report PVO-1A-202

Abbreviations: AUC_{0-T} , area under the concentration versus time curve from time 0 to time T; CL/F, oral clearance; $C_{\max,ss}$, maximum observed concentration, steady state; $C_{\min,ss}$, minimum observed concentration, steady state; N, number of subjects; PK, pharmacokinetics; PVO, palovarotene; SD, standard deviation, $T_{1/2}$, half-time; $T_{\max}$, time to maximum observed concentration

PK Results From Part C

A summary of plasma palovarotene PK parameters at steady state during flare-up treatment and chronic treatment is presented in Table 114. The $C_{\max,ss}$ and $AUC_{0-\tau}$ increased approximately proportionally with dose from 5 mg to 10 mg. The mean values of CL/F ranged from 14.8 L/h to 20.5 L/h.

Table 114. Plasma Palovarotene PK Parameters for 5 mg, 10 mg, or 20 mg QD Doses or Weight-Adjusted Equivalent (Study PVO-1A-202/Part C)

Parameters	C _{max,ss} (ng/mL)	C _{min,ss} (ng/mL)	T _{max} (h)	t _½ (h)	AUC _{0-T} (ng•h/mL)	CL/F (L/h)
Palovarotene 5 mg						
N	7	7	7	7	7	7
Mean (SD)	57.1 (23.1)	0.97 (0.37)	3.00 (0.25)	4.49 (1.34)	341 (111)	14.8 (4.6)
Palovarotene 10 mg						
N	5	5	5	4	5	5
Mean (SD)	104 (52.0)	1.82 (0.78)	3.09 (0.17)	4.02 (0.63)	651 (258)	16.3 (8.9)
Palovarotene 20 mg						
N	1	1	1	1	1	1
Mean	166	3.00	2.83	4.07	978	20.5

Source: Clinical study report PVO-1A-202

Abbreviations: AUC_{0-T}, area under the concentration versus time curve from time 0 to time T; CL/F, oral clearance; C_{max,ss}, maximum observed concentration, steady state; C_{min,ss}, minimum observed concentration, steady state; N, number of subjects; PK, pharmacokinetics; PVO, palovarotene; SD, standard deviation, T_½, half-time; T_{max}, time to maximum observed concentration

14.2.14. Study PVO-1A-301: Pivotal Phase 3 in FOP Patients

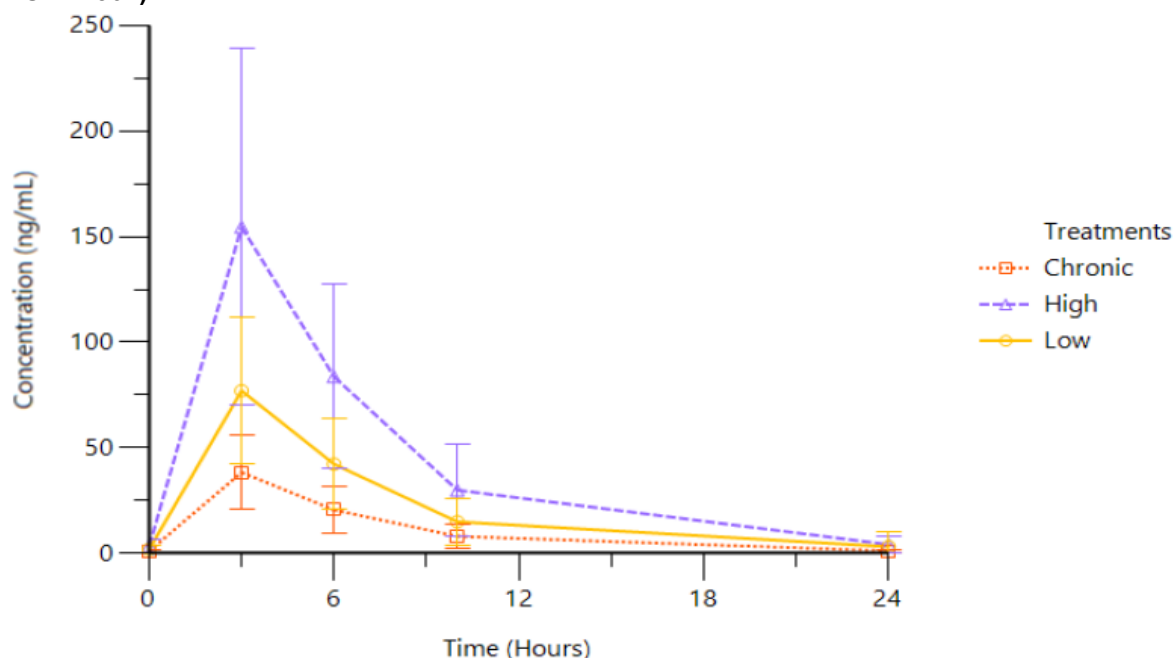
Study Design

Study PVO-1A-301 is a phase 3, multicenter, open-label study to evaluate the efficacy and safety of palovarotene in adult and pediatric subjects with FOP. Subjects receive chronic dosing with 5-mg palovarotene hard gelatin capsules or weight-adjusted dose for up to 24 months with dose escalation to 20-mg palovarotene hard gelatin capsules or weight-adjusted dose for 4 weeks followed by 10-mg palovarotene hard gelatin capsules or weight-adjusted dose for 8 weeks (20/10-mg regimen) if the subjects experience a flare-up or a high-risk traumatic event likely to lead to a flare-up. This flare-up regimen is extended if the flare-up has not resolved after 12 weeks. Doses are weight-adjusted in skeletally immature subjects. Blood samples for PK analysis are obtained once during chronic palovarotene treatment and twice during flare-up-based treatment: once during the 20-mg regimen and once during the 10-mg regimen. Blood samples are collected pre-dose and 3, 6, 10, and 24 hours post-dose.

PK Results

Mean (±SD) plasma concentrations of palovarotene versus time by treatment are presented in Figure 19. The overall shape of the mean plasma concentration versus time profile for palovarotene was similar across the treatment groups of 5 mg, 10 mg and 20 mg QD or weight-adjusted equivalent doses. As shown in Table 115, following chronic (5 mg or weight-adjusted) and flare-up (high dose 20 mg and low dose 10 mg or weight-adjusted) treatments, the mean steady-state palovarotene C_{max} and AUC_{0-24h} proportionally increased with dose. Across the dose cohorts, mean T_{1/2} of palovarotene was approximately between 4 to 5 hours. The mean CL/F values of palovarotene ranged from 16.5 to 17.8 L/h, across all the doses tested.

Figure 19. Mean ($\pm$ SD) Plasma Concentrations of Palovarotene Versus Time by Treatment (Study PVO-1A-301)



Source: Clinical study report PVO-1A-301
Abbreviations: SD, standard deviation

Table 115. Palovarotene Plasma Pharmacokinetic Parameters Following 5, 10, 20 mg or Weight-Adjusted Palovarotene (Study PVO-1A-301)

Parameters	$C_{max,ss}$ (ng/mL)	$C_{min,ss}$ (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-T} (ng·h/mL)	CL/F (L/h)
Palovarotene Chronic 5 mg						
N*	70	70	70	55	64	64
Mean (SD)	40.6 (16.2)	1.03 (0.71)	NC	4.87 (1.42)	264 (98.4)	17.8 (8.64)
Median	39.0	0.80	3.00	4.53	262	15.6
Min, max	9.51, 102	0.28, 4.06	2.67, 6.07	3.41, 12.2	91.7, 565	6.71, 54.5
Palovarotene Flare-up 10 mg						
N**	48	48	48	35	41	41
Mean (SD)	78.4 (33.3)	1.86 (1.59)	NC	4.25 (0.73)	540 (226)	17.0 (7.80)
Median	73.7	1.41	3.00	4.15	459	15.3
Min, max	28.7, 214	0.37, 8.67	2.75, 10.0	2.90, 5.87	204, 1110	6.47, 49.0
Palovarotene Flare-up 20 mg						
N***	53	53	53	43	47	47
Mean (SD)	165 (72.7)	3.11 (2.47)	NC	4.42 (1.20)	1060 (449)	16.5 (7.43)
Median	151	2.37	3.00	3.98	992	15.0
Min, max	45.1, 400	0.00, 14.8	2.83, 10.0	3.17, 9.78	370, 2720	7.26, 47.2

Source: Clinical study report PVO-1A-301

* 29 subjects received weight-based dosing

** 22 subjects received weight-based dosing

*** 29 subjects received weight-based dosing

Abbreviations: AUC_{0-T} , area under the concentration versus time curve from time 0 to time T; CL/F, oral clearance; $C_{max,ss}$, maximum observed concentration, steady state; $C_{min,ss}$, minimum observed concentration, steady state; N, number of subjects; PK, pharmacokinetics; PVO, palovarotene; SD, standard deviation, $T_{1/2}$, half-time; T_{max} , time to maximum observed concentration

14.3. Pharmacometrics Review

An NDA (NDA 215559, SDN 1) for palovarotene was previously submitted to the FDA on March 31, 2021, including a population PK report (pvo-popPK-001) based on phase 1-3 data and an exposure-response analyses report (pvo-fop-er-001) based on phase 2 data. The Applicant withdraw the original application on August 12, 2021, after discussions between the FDA to allow further adequate verification of data and integration of data updates into the NDA. On April 29, 2022, the Applicant resubmitted the NDA application (NDA 215559, SDN 29) with additional efficacy data from subjects with confirmed anatomy whole-body CT scan. An additional population PK report (pvo-poppk-003) exploring the effect of renal and hepatic status on palovarotene exposure, and an updated exposure-response analyses report (pvo-fop-er-002) based on both phase 2 and phase 3 data were provided in this resubmission. These reports were used to support palovarotene dose selection in general patient population and specific populations (e.g., pediatrics, patients with renal, and hepatic impairment).

In general, the Applicant's population PK and exposure-response (ER) analyses are considered acceptable in describing the observed palovarotene concentrations in healthy subjects and patients. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined (Table 116).

Table 116. Pharmacometrics Review and Summary

Utility of the Final Model		
Recommendation	Statement	Reviewer's Comments
Support the labeling statement for intrinsic factor of body weight	Section 12.3 "Body weight was found to have a significant effect on the pharmacokinetics of palovarotene resulting in increasing exposure with decreasing weight at the same dose."	The statement is acceptable. The covariate analysis demonstrates that the clearance of palovarotene was affected by weight, resulting in increasing exposure with decreasing weight at the same dose. Instead, age was not found to be a significant covariate affecting palovarotene exposure. Therefore, the reviewer determined that 14 years of age is not an appropriate age cut-off for determining weight-based dosing regimen. Instead, we recommend following the same dosing instructions in phase 3 study that weight based-dosing regimen be used in skeletally immature (<90%) patients under 18 years, while patients ≥18 years of age used flat dose of 5 mg QD, with dose escalation for flare-up at 20 mg/10 mg.

Utility of the Final Model		
Recommendation	Statement	Reviewer's Comments
Support the labeling statement for intrinsic factor of hepatic impairment	Section 8.7 The effect of moderate or severe hepatic impairment on the pharmacokinetics of palovarotene has not been evaluated. (b) (4) No dose adjustment is recommended in patients with mild (Child-Pugh A) hepatic impairment. Use of palovarotene in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment is not recommended Section 12.3 There were no clinically significant differences in the pharmacokinetics of palovarotene based on mild hepatic impairment. The effect of moderate to severe hepatic impairment on the pharmacokinetics of palovarotene is unknown.	(b) (4) there is a limited number of subjects with moderate hepatic impairment in the dataset, and therefore the conclusion regarding the impact of moderate hepatic impairment is inconclusive.
Support the labeling statement for intrinsic factor of renal impairment	Section 8.6 The effect of renal impairment on the pharmacokinetics of palovarotene has not been evaluated. Given that palovarotene is hepatically eliminated, no dose adjustment of palovarotene is recommended in patients with mild (CL_{cr} 60 to 89 mL/min) or moderate (CL_{cr} 30 to 59 mL/min) renal impairment. Use of palovarotene in patients with severe (CL_{cr} 15 to 29 mL/min) renal impairment is not recommended Section 12.3 There were no clinically significant differences in the pharmacokinetics of palovarotene based on mild to moderate renal impairment. The effect of severe renal impairment on the pharmacokinetics of palovarotene is unknown.	The statement is acceptable.
Derive exposure metrics for exposure-response analyses	PK model was used to predict C_{min}, C_{max}, AUC. The dose/exposure-safety analyses suggested that dose adjustment will not fully reduce the PPC risk in pediatric patients ≥ 8 years of age.	The Applicant's final model is generally acceptable for generating exposure metrics. No association was observed between palovarotene exposure and PPC risk.

Source: Pharmacometrics reviewer's summary.

Abbreviations: AUC, area under the concentration versus time curve; CL_{cr} , creatinine clearance; C_{max} , maximum observed concentration; C_{min} , minimum observed concentration; PPC, premature physeal closure; QD, once daily

14.3.1. Population PK Analyses

14.3.1.1. Applicant's Population PK Analyses

The population PK (popPK) analyses was based on PK data from 16 studies: nine studies in healthy volunteers (RB16327, NP17584, NP17726, PVO-1A-101, RB16328, NP17055, NP21025, PVO-1A-102 and PVO-1A-103), three studies (NA17598 [Tier 2], NP17124 and NB18332) in patients with symptomatic emphysema secondary to chronic obstructive pulmonary disease (COPD), three studies (PVO-1A-201, PVO-1A-202 B and C and PVO-1A-301) in patients with FOP and one study (PVO-2A-201) in patients with multiple osteochondromas (MO).

Palovarotene was administered orally as a single or multiple once daily dosing either as a powder-filled hard gelatin capsule (to be marketed formulation), solution-filled hard gelatin capsule, soft gelatin capsule, or tablet formulation.

The analyses dataset included 9088 quantifiable concentration records from 701 subjects. Concentrations that were below the limit of quantification (BLQ) were excluded from the analysis (n=673). The majority of BLQ values (n=594) came from the two studies (RB16327 and RB16328) which had higher lower limit of quantification (LLOQ) (0.02 and/or 0.2 ng/mL) compared to all other studies (LLOQ of 0.01 or 0.0005 ng/mL). The impact of including the postdose BLQ concentrations was assessed during interim analyses by implementing the M3 method. However, these BLQ concentrations had no impact on parameter estimates or model predictions. Palovarotene PK samples following the administration of ketoconazole (study RB16328 [group 6]) were not included in the PopPK analyses. The planned timing of PK samples for palovarotene are presented in [Table 117](#).

The summary statistics for the continuous and categorical covariates are presented in Table 118.

Table 117. Summary of Studies with PK Sampling Included in Population PK Analyses

Protocol # & Study Design	Study Description & PK Sampling Time	Number of Subjects in PopPK Analyses, Subject Type	Dose(s) [mg]
RB16327 (Phase 1)	SAD, fed/fasted PK Sampling: 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 h after study drug administration	36 healthy male subjects Age 40-65 years	0.1 mg, 0.5 mg, 5 mg, 10 mg, 25 mg, 50 mg
NP17584 (Phase 1)	Bioequivalence PK Sampling: 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after study drug administration	12 healthy male subjects Age 18-64 years	1-mg (2 × 0.5 mg) capsule, 1-mg tablet
NP17726 (Phase 1)	Age/sex PK Sampling: 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 h after study drug administration	36 healthy subjects; 12 males age 18-45 years; 12 males and 12 females ≥65 years	1.0 mg
PVO-1A-101 (Phase 1)	Bridging Study in Asian Subjects PK Sampling: Predose (0 hour), 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, and 72 h postdrug administration	18 healthy Japanese and non-Asian subjects age 18-55 years	5 mg, 10 mg

Protocol # & Study Design	Study Description & PK Sampling Time	Number of Subjects in PopPK Analyses, Subject Type	Dose(s) [mg]
RB16328 (Phase 1)	Multiple ascending dose Groups 1-4 (Healthy nonsmoking subjects): Predose, 1h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 16h, 24h, Days 3, 7, 11, 14, 18 Group 5-6 (elderly smoking subjects): predose, 2h, 3h, 6h, 8h, 10h, 12h, 16 h, Days 2, 7, 14, 18	48 healthy male and female subjects age 40-65 years and elderly male and female smokers age >60 years	4-week QD treatment 0.02 mg 0.2 mg 0.4 mg 1.0 mg 5.0 mg 10 mg
NP17055 (Phase 1)	DDI midazolam PK Sampling: before midazolam administration, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 24 h postdose	18 healthy male subjects age 18-64 years	7-day QD treatment 1.0 mg palovarotene (Days 1 to 7) 15 mg midazolam (Day 1 and Day 14)
NP21025 (Phase 1)	DDI prednisone Day 1: 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h after dose administration. Days 8: predose, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h after dose administration, Day 9: Predose and 24 h, Day 10: one pharmacokinetic sample in the morning	22 healthy male subjects age 18-64 years	9-day QD treatment 5.0 mg palovarotene (Days 2 to 9) 40 mg prednisone (Day 1 and 9)
PVO-1A-102 (Phase 1)	Fed/fasted intact/sprinkle PK Sampling: before dosing and 3-, 6-, 10-, and 24-hour postdose on Day 14 and Days 28 or 42	48 healthy male and female subjects age 18-55 years	20-mg (fasted, fed, sprinkled on soft food)
PVO-1A-103 (Phase 1)	Thorough QT PK Sampling: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24 h postdose.	31 healthy male and female subjects age 18-55 years	20 mg 50 mg
NA17598 (Phase 2- Tier 2)	Double-blind, placebo-controlled efficacy/safety/ tolerability PK Sampling: spares PK sample at baseline and at Weeks 4, 12, 28, 40, and 52	125 male and female subjects with COPD	12-month QD treatment 5.0 mg (129) Placebo (133)
NP17124 (Phase 1)	MAD PK Sampling: Baseline (between Days -7 and -4) Day 14: before and 1, 2, 3, 4, 6, 8, 10, 12, and 16 h postdose.	29 male and female subjects with COPD age ≥40 years	14-day QD treatment 0.2 mg 0.5 mg 1.0 mg
NB18332 (Phase 1)	MAD Predose, and 1, 2, 4-, 6-, 8-, and 10-h postdose.	44 male and female subjects with COPD age ≥50 years	4-week QD treatment 2.5 mg 5 mg

Protocol # & Study Design	Study Description & PK Sampling Time	Number of Subjects in PopPK Analyses, Subject Type	Dose(s) [mg]
PVO-1A-201 (Phase 2)	Double-blind, placebo-controlled safety/efficacy/ PK A sparse sampling strategy was used to obtain palovarotene PK data in this study. Blood samples for PK analyses were collected predose and 3-, 6-, 10-, and 24-h postdose.	Cohort 1: FOP subjects with active flare-ups; aged ≥15 years Cohort 2: FOP subjects with active flare-ups; aged ≥6 years A total of 40 subjects; 18 subjects <18 years of age; <u>28 subjects were included in the PK Population</u>	Cohort 1: 2-week QD 10 mg, then 4-week QD 5 mg Placebo Cohort 2: 2-week QD 10 mg, then 4-week QD 5 mg or 2-week QD 5 mg, then 4-week QD 2.5 mg Placebo Weight-based dosing in Cohort 2 when children aged ≥6 years enrolled
PVO-1A-202 (Phase 2)	Open-Label Extension of PVO-1A-201 Parts B and C: Blood samples for PK analyses were obtained once during chronic palovarotene treatment and twice during flare-up-based treatment: once during the 20-mg regimen and once during the 10-mg regimen. Blood samples were collected predose and 3-, 6-, 10-, and 24-h postdose.	Part B: 54 subjects including 18 new Adult Cohort subjects and 19 subjects <18 years of age; <u>30 subjects were included in the PK Population</u> Part C: 48 subjects including 14 subjects <18 years of age; <u>14 subjects were included in the PK Population</u>	Part A: 2-week QD 10 mg, then 4-week QD 5 mg for next 2 flare-ups Part B: Up to 24 months QD 5 mg 4-week QD 20 mg, then 10 mg for 8 weeks Part C: Up to 24 months QD 5 mg with dose escalation for flare-up treatment to QD 20 mg for 4 weeks, then 10 mg for 8 weeks (12 weeks total or until flare-up resolution if treatment is extended beyond 12 weeks)
PVO-1A-301 (Phase 3)	Open-label safety/efficacy/PK Blood samples for PK analyses are obtained once during chronic palovarotene treatment and twice during flare-up-based treatment: once during the 20-mg regimen and once during the 10-mg regimen. Blood samples are collected predose and 3-, 6-, 10-, and 24-h postdose	107 FOP subjects aged ≥4 years of which <u>88 contributed PK data</u>	Chronic/flare-up dosing regimen: oral QD administration 5 mg for up to 24 months, with dose escalation for flare-up treatment to oral QD 20 mg for 4 weeks, then 10 mg for 8 weeks (12 weeks total or until flare-up resolution if treatment extended beyond 12 weeks) Dosing is weight-adjusted in skeletally immature subjects.
PVO-2A-201 (Phase 2)	Double-blind, placebo-controlled safety/efficacy/PK PK Sampling: Blood samples for PK analyses were collected predose and 3-, 6-, 10-, and 24-h postdose	131 MO subjects aged 2 to 14 years of which <u>101 contributed PK data</u>	2.5 mg (or weight-adjusted equivalent) 5.0 mg (or weight-adjusted equivalent)

Source: Reviewer's summary based on individual study reports.

Abbreviations: COPD, chronic obstructive pulmonary disease; DDI, drug-drug interaction; FOP, fibrodysplasia ossificans progressiva; h, hours; MAD, multiple ascending dose; MO, multiple osteochondromas; PK, pharmacokinetics; popPK, population pharmacokinetics; PVO, palovarotene; QD, once daily; SAD, single ascending dose

Table 118. Summary of Demographic Characteristics

Covariate	Statistic	Overall
	Number of Subjects	701
Age (yrs)	Median (Min-Max)	42.0 (2.00-85.0)
Weight (kg)	Median (Min-Max)	68.2 (12.5-149)
Albumin (g/dL)	Median (Min-Max)	4.50 (3.34-5.50)
ALP (U/L)	Median (Min-Max)	77.0 (22.0-878)
ALT (U/L)	Median (Min-Max)	17.0 (5.00-90.0)
AST (U/L)	Median (Min-Max)	21.0 (6.00-76.0)
Bilirubin (mg/dL)	Median (Min-Max)	0.468 (0.0994-2.07)
Creatinine (mg/dL)	Median (Min-Max)	0.800 (0.200-1.60)
Gender, N (%)	Female	251 (36)
	Male	450 (64)
Race, N (%)	Asian	28 (4)
	Black	41 (6)
	White	583 (83)
	Other	24 (3)
	Unknown	25 (4)
Health Status, N (%)	COPD	198 (28)
	FOP	133 (19)
	HV	269 (38)
	MO	101 (14)
Smoking Status, N (%)	Unknown	151 (22)
	No	484 (69)
	Yes	66 (9)
Administration Method ^{a, b} , N (%)	Sprinkled on food	125 (18)
	Swallowed whole	597 (85)
	Sprinkled on food & Swallowed whole	2 (0)
	Unknown	6 (1)
Prednisone Flag ^d , N (%)	No	693 (99)
	Yes	62 (9)
Fed ^e , N (%)	No	41 (6)
	Yes	689 (98)
Formulation ^c , N (%)	Powder-filled hard gelatin capsule	331 (47)
	Solution-filled hard gelatin capsule	84 (12)
	Soft gelatin capsule	286 (41)
	Tablet	12 (2)

ALP = Alkaline Phosphatase, ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, HV = healthy volunteer, COPD=chronic obstructive pulmonary disease, FOP=fibrodysplasia ossificans progressiva, MO=multiple osteochondromas

^a The same subject may have had more than one method of administration.

^b Tablet, solution filled hard-gelatin capsule and soft gelatin capsule studies are flagged as swallowed whole.

^c Subjects in study NP17584 received both tablet and soft gelatin capsule formulations

^d The same subject may have had prednisone administered for not all PK concentrations so in both no and yes groups.

^e The same subject may have had palovarotene administered in both fasted and fed conditions.

Source: Reviewer's Summary from the Population PK datasets.

Abbreviations: N, number of subjects

Base PK Model

The pharmacokinetics of palovarotene was described by a 2-compartment distribution model, with first-order absorption from an absorption compartment, six transit compartments to describe the delay in absorption, and first-order elimination. The PK model was parameterized in terms of apparent clearance (CL/F), apparent central and peripheral volumes of distribution (Vc/F and Vp/F respectively), apparent intercompartmental clearance (Q/F), absorption rate constant (Ka) and mean transit time (MTT), and relative BA (F) between fed and fasted status. Between-subject variability or interindividual variability (IIV) was estimated on all parameters, except the parameter F. A full variance-covariance matrix for random effects was included in the model. Between-occasion variability or interoccasion variability (IOV) was estimated on Ka and MTT. The residual error model consisted of a proportional error model.

Covariates Analysis

Covariate selection was based on plots of inter-individual variability (ETA) of different PK parameters versus covariates, univariate covariate analysis, and physiological rationale or clinical interest. Age, body weight, gender, race, smoking status, health status, administration with food, formulation, method of administration, administration of prednisone, albumin, ALT, AST, ALP, creatinine, and bilirubin were selected to be evaluated. The full covariate model with backwards deletion approach (at a significance level of 0.001) was utilized for covariate modeling.

The following covariates were included in the final model:

- Baseline weight on CL/F, Vc/F, Q/F and Vp/F, using a power model centered at 70 kg.
- Fasted conditions on MTT and F.
- Method of administration on MTT, when the content of the capsule was sprinkled on food.

Final Model

The parameter estimates from the final popPK model for palovarotene are listed in [Table 119](#). CL/F, Vc/F, Q/F and Vp/F increased with body weight. For the range of weights in the analysis population (13-149 kg), CL/F ranged from 8.59-29.0 L/h (i.e., 57% lower to 46% higher compared to a 70-kg subject), Q/F ranged from 0.688-9.36 L/h (83% lower to 124% higher compared to a 70-kg subject), Vc/F ranged from 7.97-71.4 L (78% lower to 97% higher compared to a 70-kg subject), and Vp/F ranged from 19.7-143 L (75% lower to 85% higher compared to a 70-kg subject).

Under fasted state, the MTT was 64% shorter indicating that the appearance of palovarotene is expected to be quicker in the fasted state, and the relative BA was 23% lower compared to the fed state. The MTT was also 73% shorter when palovarotene powder-filled hard-gelatin capsule were sprinkled on food compared to capsule swallowed whole, suggesting a quicker appearance of palovarotene in the systemic circulation, but there was no difference on F, and thus in the overall exposure.

Table 119. Parameter Estimates From the Final Population PK Model

CL/F = 19.9 x (WT/70)^{0.499}
Q/F = 4.17 x (WT/70)^{1.07}
Vc/F = 36.2 x (WT/70)^{0.899}
Vp/F = 77.3 x (WT/70)^{0.812}
Ka = 0.396
MTT = 1.12 x 0.357^{fasted} x 0.267^{sprinkled}
F = 1 x 0.768^{fasted}

Parameter	Units	NONMEM Estimates					MCMC BAYES Estimates ^e
		Estimate ^a	%RSE ^b	95% CI ^a	IIV CV% ^c (%RSE)	IOV CV% (%RSE)	Median [95% CI]
CL/F	L/hr	19.9	1.51	19.3-20.5	34.1 (6.49)	-	19.8 [19.3 to 20.4]
Vc/F	L	36.2	6.52	31.9-41.2	90.1 (12.4)	-	37.7 [32.1 to 43.3]
Q/F	L/hr	4.17	4.69	3.80-4.57	106 (9.65)	-	4.17 [3.82 to 4.60]
Vp/F	L	77.3	4.59	70.7-84.6	89.0 (9.23)	-	76.7 [70.2 to 84.2]
Ka	hr ⁻¹	0.396	3.31	0.371-0.423	19.9 (49.7)	43.7 (13.3)	0.414 [0.385 to 0.448]
MTT	hr	1.12	4.45	1.02-1.22	84.2 (9.61)	44.6 (16.4)	1.10 [0.999 to 1.21]
F~fasted	unitless	0.768	2.68	0.727-0.808	-	-	0.782 [0.739 to 0.824]
MTT~fasted	unitless	0.357	13.3	0.264-0.450	-	-	0.361 [0.269 to 0.457]
CL/F~weight	unitless	0.499	6.82	0.432-0.565	-	-	0.522 [0.445 to 0.589]
Vc/F~weight	unitless	0.899	11.3	0.700-1.10	-	-	1.10 [0.891 to 1.33]
Q/F~weight	unitless	1.07	9.00	0.883-1.26	-	-	0.866 [0.678 to 1.06]
Vp/F~weight	unitless	0.812	13.3	0.601-1.02	-	-	0.780 [0.578 to 0.970]
MTT~sprinkled	unitless	0.267	15.7	0.185-0.349	-	-	0.192 [0.138 to 0.297]
σ ² _{prop} TAD > 4 hr HV	unitless	0.0851	3.02	0.0800-0.0901	29.2% ^d	-	0.0850 [0.0801 to 0.0904]
σ ² _{prop} TAD ≤ 4 hr HV	unitless	0.164	3.79	0.152-0.176	40.5% ^d	-	0.164 [0.152 to 0.177]
σ ² _{prop} Patients	unitless	0.166	3.18	0.156-0.176	40.8% ^d	-	0.166 [0.156 to 0.177]

^a Back-transformed from natural log scale (except for σ², F~fasted, MTT~fasted, CL/F~weight, Vc/F~weight, Q/F~weight, Vp/F~weight, MTT~sprinkled)

^b RSE=SE/100 (except for σ², F~fasted, MTT~fasted, CL/F~weight, Vc/F~weight, Q/F~weight, Vp/F~weight, MTT~sprinkled). RSE for σ², F~fasted, MTT~fasted, CL/F~weight, Vc/F~weight, Q/F~weight, Vp/F~weight, MTT~sprinkled = SE(θ)/θ · 100

^c CV for IIV calculated as $CV_{IIV} = \sqrt{e^{\omega_p^2} - 1} \cdot 100$ if $\omega_p^2 \leq 0.15$, else $CV_{IIV} = \sqrt{e^{\omega_p^2} - 1} \cdot 100$

^d Proportional residual error expressed as CV.

^e From 1,000 iterations in which every 10th iteration from a total of 10,000 was sampled.

Abbreviations: CL/F = apparent total clearance, Vc/F = apparent volume of central compartment, Vp/F = apparent volume of peripheral compartment, Q/F = inter compartment clearance between central and peripheral compartments, Ka=first order absorption, MTT=mean transit time, F=bioavailability, IIV = inter-subject variability, CI=confidence interval, RSE=relative standard error, CV=coefficient of variation, σ²_{prop} = proportional residual error, TAD=time after dose, HV=healthy volunteers

The reference population is a 70 kg subject administered palovarotene in the fed state and swallowed whole.

Source: 082.cnv/ext, 082mcmcbay.csv

Source: Applicant's Population PK Report (Addendum2, July22,2020), Table 8-10, page 83.

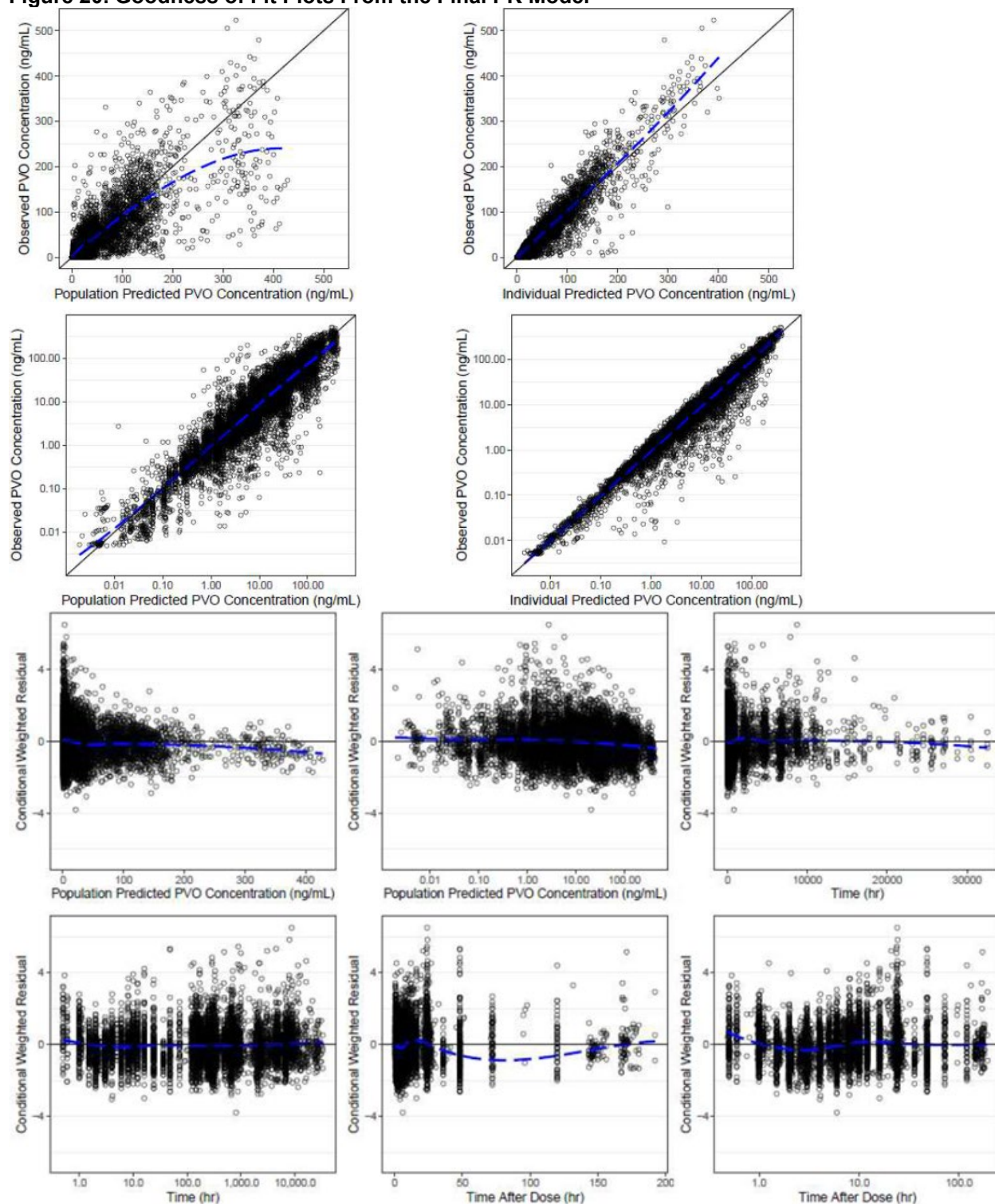
The ETA shrinkages from the final popPK model were estimated as 8% for CL/F, 25% for Vc/F, 18% for Q/F, 22% for Vp/F, 39% for Ka and 27% for MTT.

The goodness-of-fit (GOF) plots from the final PopPK model, are shown in [Figure 20](#).

The plots of the observed concentrations versus population predicted as well as the individual predicted concentrations show random normal scatter around the identity lines, indicating absence of systematic bias except for very few large concentrations ($>100 \mu\text{g/mL}$) showing underprediction of these observations by the PK model.

The population conditional and individual weighted residuals versus time after dose or versus population predicted concentrations also show random normal scatter around zero with no specific trend, indicating any model misspecifications.

Figure 20. Goodness of Fit Plots From the Final PK Model



Source: Applicant's Population PK Report (Addendum2, July22,2020), Figure 5-9 and Figure 5-10, page 52 to 53.
Abbreviations: PK, pharmacokinetics; PVO, palovarotene

14.3.1.2. Reviewer's Assessment on the Population PK Analyses

14.3.1.2.1. Adequacy of the Model in Describing the Data

The Applicant's PK model adequately describes the observed concentrations from palovarotene clinical studies and can be used for predicting exposure metrics and performing simulations.

14.3.1.2.2. Impact of Hepatic and Renal Impairment on Palovarotene PK

Applicant's Analyses

Data

The final updated PopPK dataset (pk16stv2.xpt).

Methods

The effect of both renal and hepatic status on palovarotene PK was explored based on AST, bilirubin, and creatinine clearance (CRCL) levels as continuous variables, and the corresponding derived hepatic and renal status for each subject as categorical variables. Estimated CRCL was calculated based on the Cockcroft-Gault equation with both baseline and time-varying age, weight, and creatinine. Both baseline and time-changing renal status was derived based on the following criteria:

Table 120. Renal Function Groups

Group	Description	CRCL (mL/min)
1	Normal renal function	≥ 90
2	Mildly decreased renal function	60- <90
3	Moderately decrease renal function	30- <60
4	Severely decreased renal function	<30
5	End stage renal disease (ESRD)	<15

Source: Applicant's Report pvo-poppk-003.pdf.

Abbreviations: CRCL, creatinine clearance; ESRD, end-stage renal disease

Hepatic status was derived from both baseline and time-changing bilirubin and AST based on the criteria shown in the tables and figures below.

Table 121. Hepatic Function Groups

Category	Bilirubin	AST
Normal	$\leq$ ULN	$\leq$ ULN
Mild	1. $\leq$ ULN 2. >1-1.5xULN	1. >ULN 2. Any
Moderate	>1.5-3xULN	Any
Severe	>3xULN	Any

Source: Applicant's Report pvo-poppk-003.pdf.

Abbreviations: ULN, upper limit of normal

The impact of hepatic and renal impairment on palovarotene PK was explored by investigating the relationship of the interindividual random effect (ETA) versus these additional covariate

relationships, and conditional weighted residuals (CWRES) versus time-changing CRCL and hepatic and renal status based on the final model (Run 082).

Results

Covariate distributions: The distribution of CRCL, and renal and hepatic status is presented below.

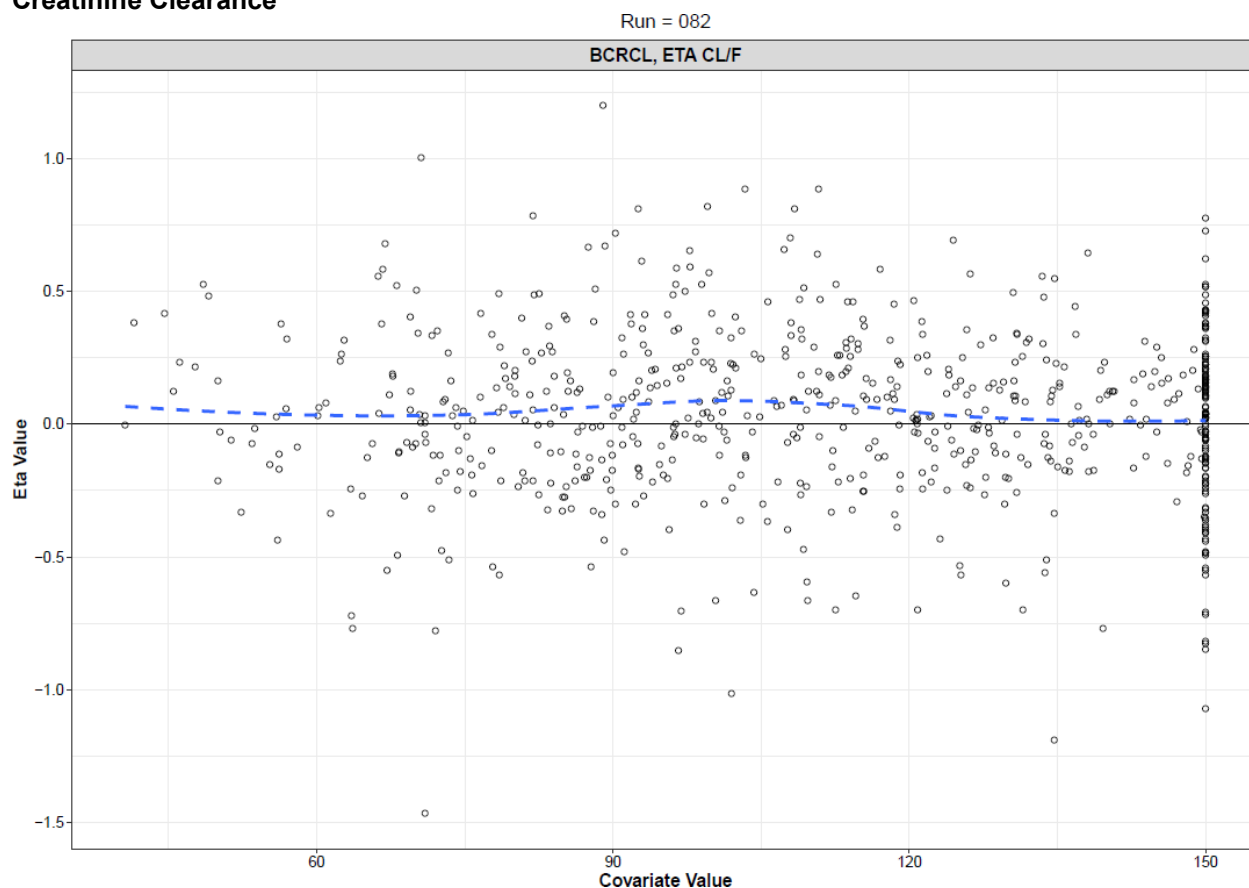
Table 122. Covariate Distributions

Covariate	Statistic	Overall
	Number of Subjects	701
Baseline Creatinine Clearance (mL/min)	Median (Min-Max)	113 (40.6-150)
Creatinine Clearance (mL/min)	Median (Min-Max)	105 (6.43-150)
Baseline Renal Status, N (%)	Normal	519 (74)
	Mild	158 (23)
	Moderate	24 (3)
Renal Status ^a , N (%)	Normal	537 (77)
	Mild	181 (26)
	Moderate	26 (4)
	Severe	1 (0)
	ESRD	1 (0)
Baseline Hepatic Status, N (%)	Normal	652 (93)
	Mild	47 (7)
	Moderate	2 (0)
Hepatic Status ^a , N (%)	Normal	667 (95)
	Mild	66 (9)
	Moderate	5 (1)

Source: Applicant's Report pvo-popk-003.pdf.

Abbreviations: ESRD, end-stage renal disease; N, number of subjects; ULN, upper limit of normal

Figure 21. Interindividual Random Effect (ETA CL/F) Versus Baseline Creatinine Clearance, Renal and Hepatic Status Plots for the Final PopPK Model (Run 082): ETA (CL/F) Versus Baseline Creatinine Clearance

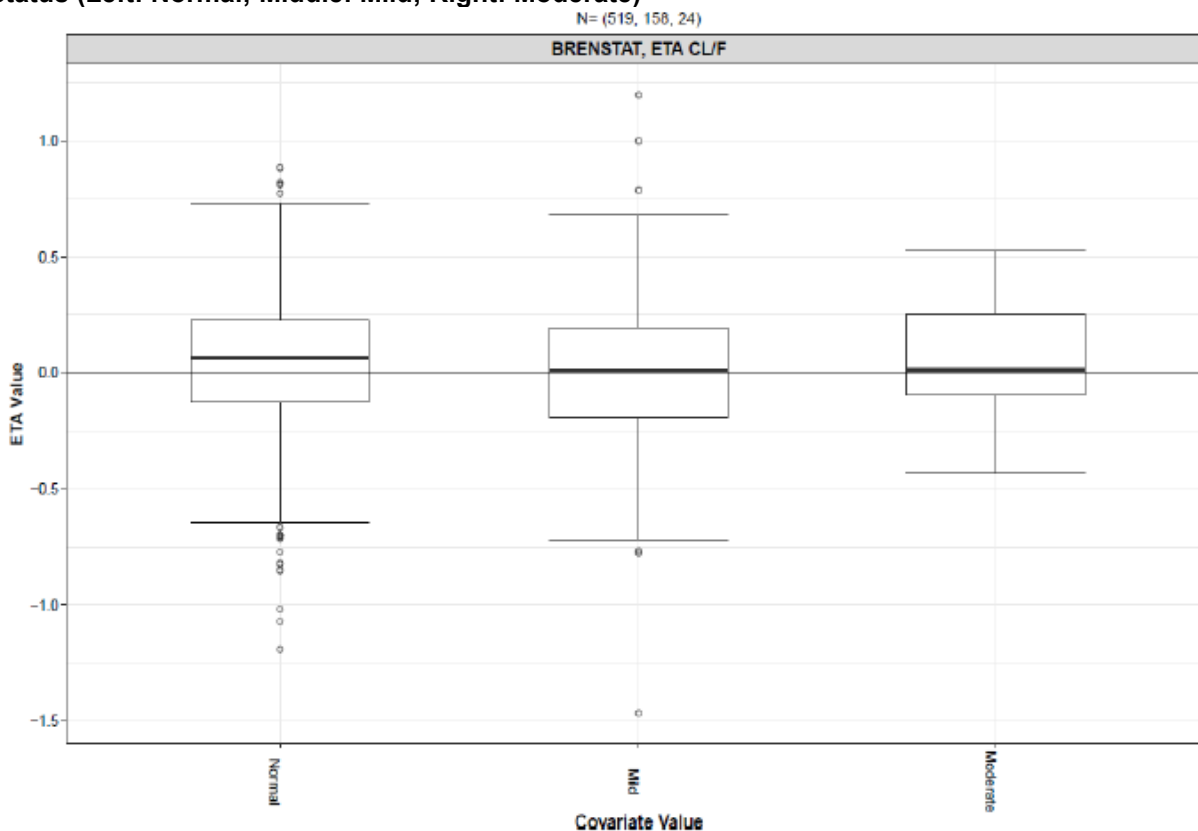


Source: Applicant's Report pvo-poppk-003.pdf. Figure 8-4.

Note: Upper figure: blue dashed line: Local regression (Loess) smoothing line

Abbreviations: ESRD, end-stage renal disease; ETA, interindividual random effect; N, number of subjects; ULN, upper limit of normal

Figure 22. Interindividual Random Effect (ETA CL/F) Versus Baseline Creatinine Clearance, Renal and Hepatic Status Plots for the Final PopPK Model (Run 082): ETA (CL/F) Versus Baseline Renal Status (Left: Normal; Middle: Mild; Right: Moderate)

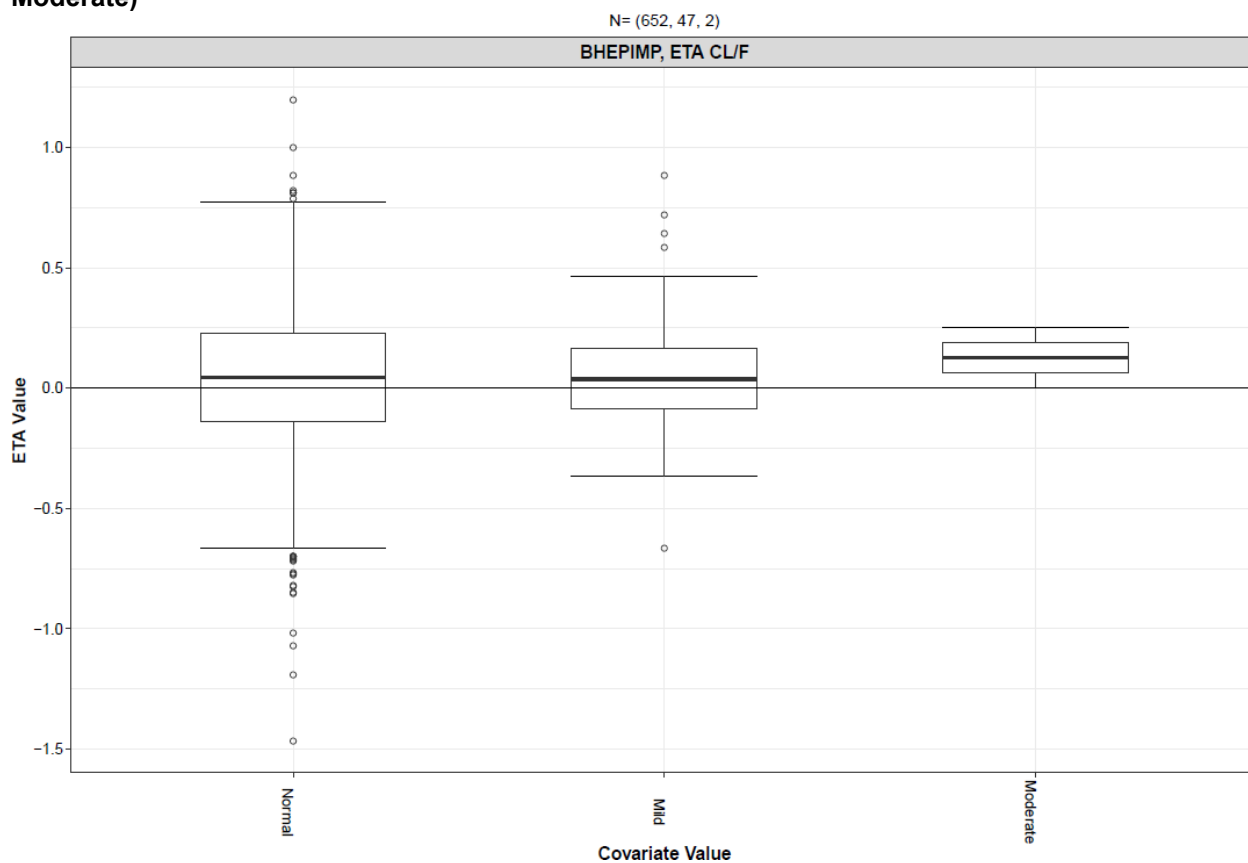


Source: Applicant's Report pvo-poppk-003.pdf. Figure 8-4.

Note: black center line represents median, top and base of the box represent first and third quartiles (interquartile range [IQR]). Whiskers represent 1.5*IQR. Outliers beyond upper or lower 1.5*IQR are represented by open circles

Abbreviations: BRESTAT, baseline renal status; CL/F, oral clearance; ETA, interindividual random effect; PopPK, population pharmacokinetics

Figure 23. ETA (CL/F) Versus Baseline Hepatic Status (Left: Normal; Middle: Mild; Right: Moderate)



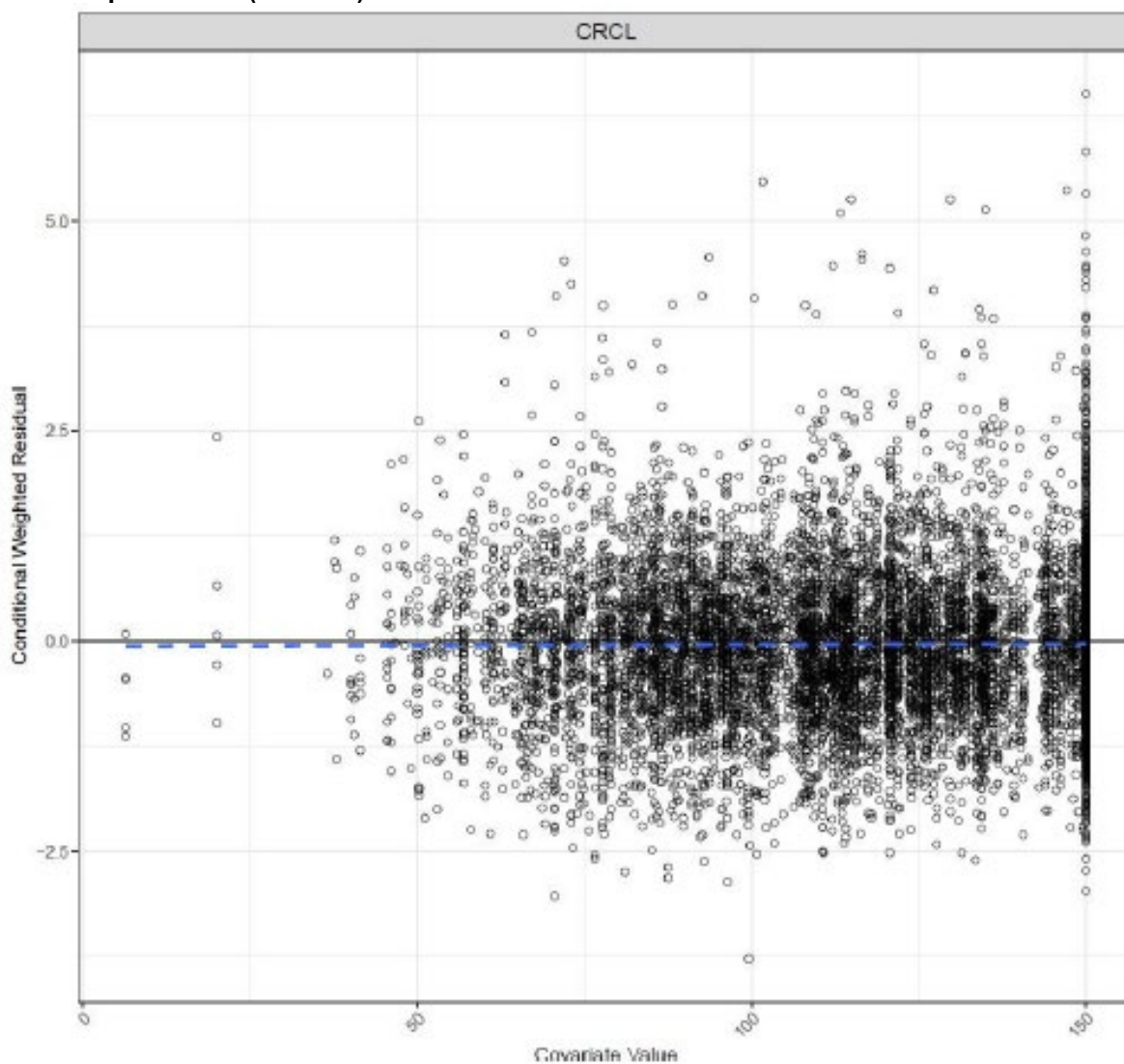
Source: Applicant's Report pvo-poppk-003.pdf. Figure 8-4.

Note: black center line represents median, top and base of the box represent first and third quartiles (interquartile range [IQR]).

Whiskers represent 1.5*IQR. Outliers beyond upper or lower 1.5*IQR are represented by open circles

Abbreviations: BCRCL, baseline creatinine clearance; BHEPIMP, baseline hepatic status; CL/F, oral clearance; ETA, interindividual random effect

Figure 24. CWRES Versus Time Changing Creatinine Clearance, and Renal and Hepatic Status for the Final PopPK Model (Run 082): CWRES Versus Creatinine Clearance

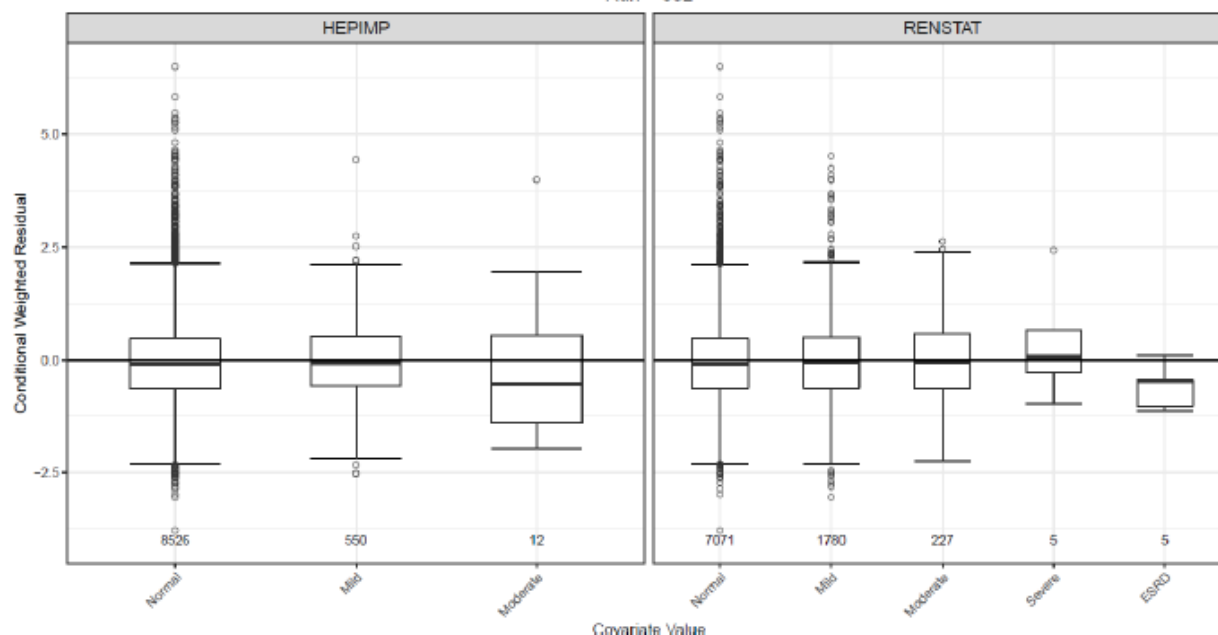


Source: Applicant's Report pvo-poppk-003.pdf.

Note: Blue dashed line: Local regression (Loess) smoothing line

Abbreviations: CRCL, creatinine clearance; CWRES, conditional weighted residuals

Figure 25. CWRES Versus Time Changing Creatinine Clearance, and Renal and Hepatic Status for the Final PopPK Model (Run 082): CWRES Versus Hepatic (Left) and Renal Status (Right)



Source: Applicant's Report pvo-popk-003.pdf.

Note: Black center line represents median, top and base of the box represent first and third quartiles (interquartile range [IQR]). Whiskers represent 1.5*IQR. Outliers beyond upper or lower 1.5*IQR are represented by open circles

Abbreviations: CRCL, creatinine clearance; CWRES, conditional weighted residuals; HEPIMP, hepatic status; RENSTAT, renal status

The Applicant concluded that there is no relationship between palovarotene clearance and CRCL/hepatic status/renal status. No additional modelling to assess the impact of hepatic or renal status on palovarotene PK was undertaken.

Reviewer's comments: The Applicant proposed that no dose adjustment is recommended in patients with mild or moderate renal impairment. This conclusion is based on the above analysis showing no impact of mild or moderate renal status on ETA (CL/F) or CWRES based on the final PopPK model. A total of 181 subjects with mild renal impairment and 26 subjects with moderate renal impairment were included in this analysis. This sample size is considered sufficient to inform no impact of these covariate on major palovarotene pharmacometrics parameters in the PopPK model, and the model also appears to be unbiased without these covariates. Therefore, the Applicant's analyses regarding impact of renal impairment on palovarotene PK are acceptable.

Table 123. Statistical Summary of Baseline Characteristics for Major Covariates

Covariate	Statistic	Overall
	Number of Subjects	701
Baseline Creatinine Clearance (mL/min)	Median (Min-Max)	113 (40.6-150)
Creatinine Clearance (mL/min)	Median (Min-Max)	105 (6.43-150)
Baseline Renal Status, N (%)	Normal	519 (74)
	Mild	158 (23)
	Moderate	24 (3)
Renal Status ^a , N (%)	Normal	537 (77)
	Mild	181 (26)
	Moderate	26 (4)
	Severe	1 (0)
	ESRD	1 (0)
Baseline Hepatic Status, N (%)	Normal	652 (93)
	Mild	47 (7)
	Moderate	2 (0)
Hepatic Status ^a , N (%)	Normal	667 (95)
	Mild	66 (9)
	Moderate	5 (1)

Source: Applicant's Report pvo-popk-003.pdf.

Abbreviations: N, number of subjects with specific covariate

Due to limited number of subjects with moderate hepatic impairment (< five subjects), the effect of moderate (Child-Pugh B) hepatic impairment on the PK of palovarotene is not conclusive based on population PK analyses. The effect of severe (Child-Pugh C) hepatic impairment on the PK of palovarotene has not been evaluated. The use of palovarotene in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment is not recommended.

14.3.1.2.3. Palovarotene Exposures by Weight-based Dosing Regimen by Age Groups

Applicant's Proposed Dosing Regimen

The Applicant proposed that for patients ≥ 14 years of age, the recommended dosing is 5 mg once daily (chronic treatment), with an increase in dose at the time of a flare-up to 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks for a total of 12 weeks (20/10 mg flare-up treatment), even if symptoms resolve earlier. For patients who are under 14 years of age, the Applicant's weight-adjusted dosage is proposed as shown in [Figure 26](#).

Figure 26. Weight-Adjusted Dosage for Children <14 Years

Weight	Chronic Dosing	Flare-up (Weeks 1 to 4)	Flare-up (Weeks 5 to 12)
≥ 60 kg ¹	5 mg	20 mg	10 mg
$40 \leq 60$ kg	4 mg	15 mg	7.5 mg
$20 \leq 40$ kg	3 mg	12.5 mg	6 mg
$10 \leq 20$ kg	2.5 mg	10 mg	5 mg

¹ All children ≥ 14 years of age and adults will receive the dose in the ≥ 60 kg weight category.

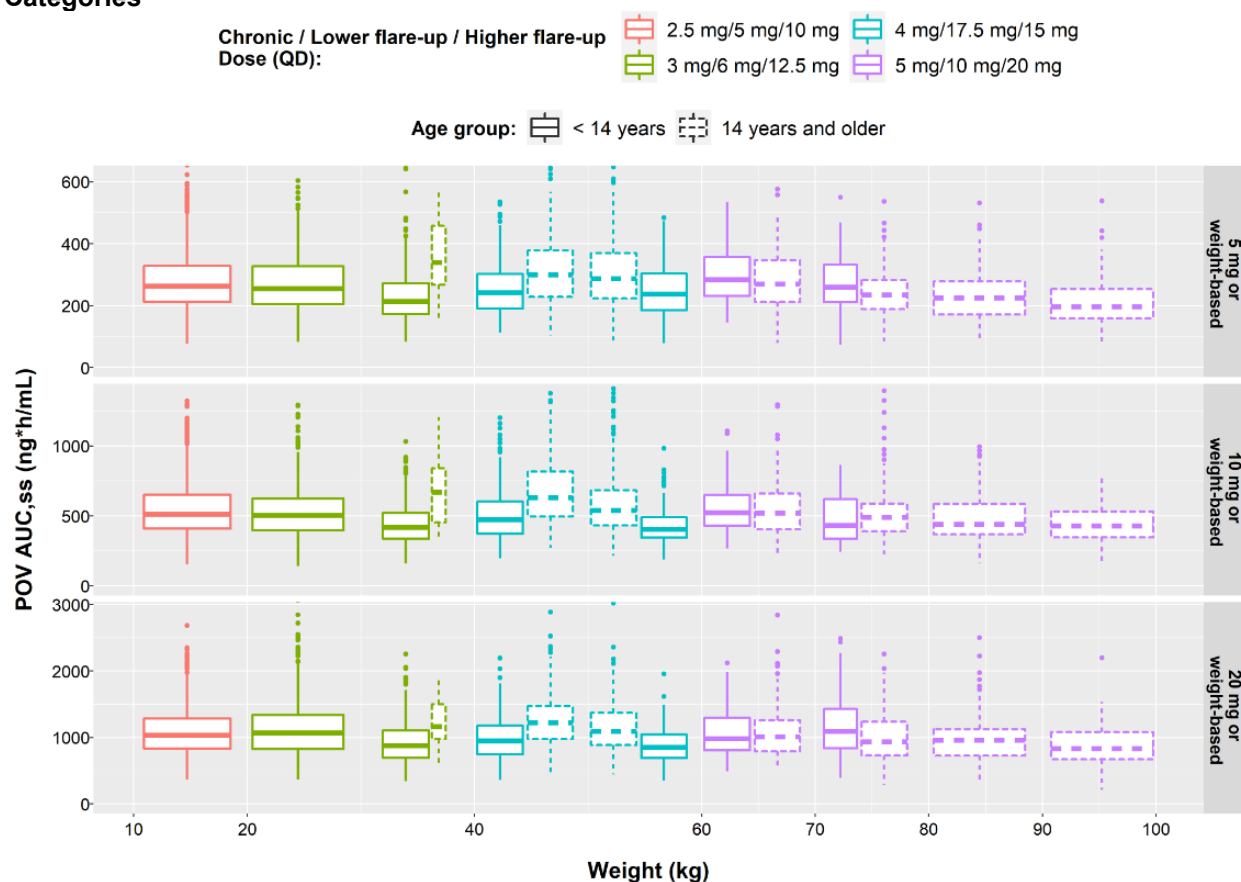
(b) (4)

Reviewer's Analyses

PopPK analyses suggested that body weight has a significant effect on the exposure of palovarotene, whereas age was not included as a significant covariate in the model. Therefore, it is not clear why an age cut-off (i.e., 14 years) is needed for determining the use of weight-based dosing regimen.

In order to assess the impact of age cut-off for the proposed weight-based dosing regimen, the distribution of palovarotene AUC was simulated at different dose levels and body weight groups for patients both <14 years of age and ≥ 14 years of age ([Figure 27](#)).

Figure 27. Simulated Palovarotene AUC at Steady-state (AUC_{ss}) by Different Body Weight and Age Categories



Source: Reviewer's analyses

Abbreviations: AUC, area under the concentration versus time curve; POV, palovarotene; QD, once daily; ss, steady state

The results show that the proposed weight-based dosing (<14 years old) provides comparable AUC_{ss} across body weight range from 10 kg to 100 kg. In addition, it is also noticed that subjects ≥ 14 years of age had higher exposure as compared to subjects <14 years of age in the same body weight categories (i.e., 30 kg – 40 kg, 40 kg – 50 kg, and 50 kg – 60 kg). This suggest that patients ≥ 14 years old & weight <60 kg may also benefit from weight-based dose adjustment regardless of age.

In addition, in phase 3 clinical studies, patients greater or equal than 18 years of age received orally administered 5-mg palovarotene once daily and 20 mg/10 mg dose at flare-up, whereas weight-adjusted dose was used for skeletally immature subjects under 18 years of age.

As a result, we determined that 14 years of age is not appropriate to be used as the cut-off age for determining weight-based dosing regimen. Instead, we recommend following the same dosing regimen as studied in phase 3 trials with age cut-off at 18 years of age.

14.3.2. Dose/Exposure-Response Analyses

14.3.2.1. PK/PD Relationships for Efficacy

The primary endpoint for the palovarotene in this submission is the change from baseline [CFB] in HO volume. The objective of the dose/exposure-response analysis is to investigate the

relationship between palovarotene dose or exposures and its efficacy. This analysis was used to support the proposed dosing regimen for palovarotene in both pediatric and adult patients, specifically whether weight-based dosing regimen is acceptable for pediatrics and/or adults.

Applicant's Analyses

Data

Phase 2 trials: PVO-1A-001, PVO-1A-201, and PVO-1A-202

Phase 3 trial: (PVO-1A-301)

Methods

At phase 2 trials, several dosing regimens for palovarotene was explored as following:

- Palovarotene 5 mg once daily for 2 weeks followed by 2.5 mg once daily for 4 weeks (5/2.5 mg flare-up only regimen) within 7 days of flare-up initiation.
- Palovarotene 10 mg once daily for 2 weeks followed by 5 mg once daily for 4 weeks (10/5 mg flare-up only regimen) within 7 days of flare-up initiation.
- Palovarotene 20 mg once daily for 4 weeks followed by 10 mg once daily for 8 weeks (20/10 mg) within 7 days of flare-up initiation, with treatment extension in 4 week increments for persistent symptoms.
- Palovarotene 5 mg daily with increased dosing at the time of a flare-up to palovarotene 20 mg once daily for 4 weeks followed by 10 mg once daily for 8 weeks (chronic/flareup regimen) within 7 days of flare-up initiation, with treatment extension in 4-week increments for persistent symptoms.
- Weight-based dosing to achieve daily drug exposures equivalent to adult subjects were selected for skeletally immature children according to three weight categories (20 to <40 kg, 40 to <60 kg, and ≥ 60 kg).

For Study PVO-1A-301, subjects received chronic dosing with 5-mg palovarotene hard gelatin capsules or weight-adjusted dose for up to 24 months with dose escalation to 20-mg palovarotene hard gelatin capsules or weight-adjusted dose for 4 weeks followed by 10-mg palovarotene hard gelatin capsules or weight-adjusted dose for 8 weeks (20/10-mg regimen) if the subjects experience a flare-up or a high-risk traumatic event likely to lead to a flare-up. This flare-up regimen is extended if the flare-up has not resolved after 12 weeks.

HO volume and relative change from baseline in HO volume versus exposure metrics (average daily dose, cumulative dose of palovarotene, average AUC and cumulative AUC of palovarotene) was assessed based on phase 2 (Day 84) and phase 3 clinical data (Month 12). Empirical Bayes estimates (EBEs) of individual pharmacokinetic (PK) parameters for individual subjects were obtained from the final palovarotene PopPK Model 082.

Results

Reassessment of phase 2 ER trends

Table 124. Linear Regression Parameters for HOVcfb and HOV%cfb at Day 84 Versus Exposure Metrics Based on Phase 2 Data

Parameter	Estimate	Std.Error	t.value	Pr.t	Response	Exposure	N.Obs	Day
Intercept	5635.299	2156.972	2.612598	0.009831	HO Volume (CFB)	CUMDOSE	164	Day 84
Slope	-0.56029	3.856306	-0.14529	0.884661	HO Volume (CFB)	CUMDOSE	164	Day 84
Intercept	5779.118	2155.362	2.681275	0.008093	HO Volume (CFB)	DAYDOSE	164	Day 84
Slope	-80.1409	324.4385	-0.24701	0.80521	HO Volume (CFB)	DAYDOSE	164	Day 84
Intercept	6189.612	2119.874	2.919802	0.004012	HO Volume (CFB)	AUC	161	Day 84
Slope	-2272.37	4576.109	-0.49657	0.620177	HO Volume (CFB)	AUC	161	Day 84
Intercept	6052.809	2116.469	2.859862	0.004808	HO Volume (CFB)	CUMAUC	161	Day 84
Slope	-21.3635	54.03865	-0.39534	0.693124	HO Volume (CFB)	CUMAUC	161	Day 84

Parameter	Estimate	Std.Error	t.value	Pr.t	Response	Exposure	N.Obs	Day
Intercept	79.98789	53.01382	1.508812	0.134597	HO Volume (%CFB)	CUMDOSE	99	Day 84
Slope	0.072156	0.09102	0.792747	0.42986	HO Volume (%CFB)	CUMDOSE	99	Day 84
Intercept	80.94179	52.96751	1.52814	0.129732	HO Volume (%CFB)	DAYDOSE	99	Day 84
Slope	5.870737	7.647247	0.767693	0.444534	HO Volume (%CFB)	DAYDOSE	99	Day 84
Intercept	62.44379	52.92096	1.179944	0.240969	HO Volume (%CFB)	AUC	97	Day 84
Slope	171.1792	124.5439	1.374449	0.172536	HO Volume (%CFB)	AUC	97	Day 84
Intercept	60.72734	52.98379	1.146149	0.254612	HO Volume (%CFB)	CUMAUC	97	Day 84
Slope	2.11317	1.48971	1.418511	0.159314	HO Volume (%CFB)	CUMAUC	97	Day 84

Source: Applicant's ER report pvo-fop-er-002.pdf. Table 6.1

Abbreviations: AUC, average daily area under the curve (h*mg/L); CFB, change from baseline; CUMAUC, cumulative area under the curve from the first dose to Day 84 (h*mg/L); CUMDOSE, cumulative palovarotene dose to Day 84 (mg); DAYDOSE, average daily palovarotene dose (mg); HOV, HO Volume; N.Obs, number of observations; Pr.t, probability of a greater student's t-statistic for test that parameter =0; Std.Error, standard error; t.value, student's t-statistic for test that parameter =0

No significant linear relationship was identified between different palovarotene exposure parameters (average daily dose, cumulative dose of palovarotene, average AUC and cumulative AUC of palovarotene) and HO volume or relative change from baseline in HO volume at Day 84 based on phase 2 data, indicating no exposure-response relationship.

Assessment of ER trends in Study PVO-1A-301

Table 125. Linear Regression Parameters for HOVcfb and HOV%cfb at Month 12 Versus Exposure Metrics in Study PVO-1A-301

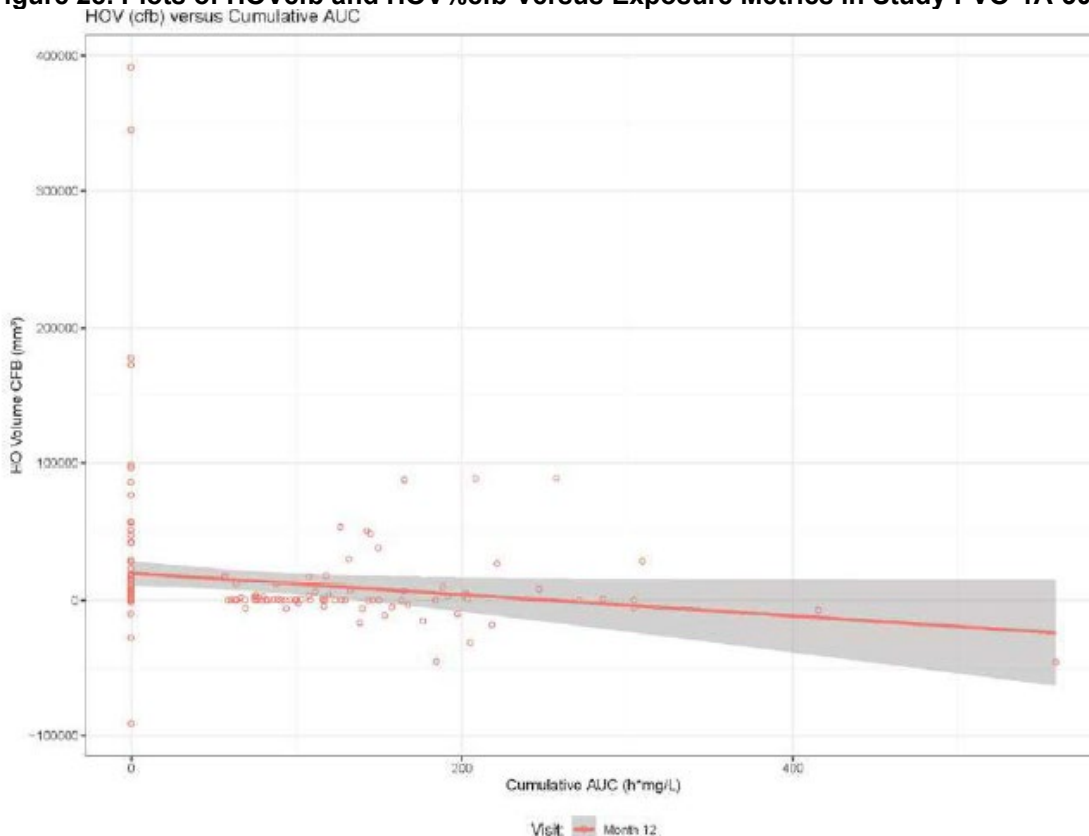
Parameter	Estimate	Std.Error	t.value	Pr.t	Response	Exposure	n
Intercept	17856.19	4599.602	3.882115	0.000145	HOV cfb	avgDose	183
Slope	-1405.18	986.0464	-1.42506	0.155861	HOV cfb	avgDose	183
Intercept	19694.02	4535.189	4.342492	2.39E-05	HOV cfb	avgAUC	175
Slope	-28085.5	14285.34	-1.96604	0.050894	HOV cfb	avgAUC	175
Intercept	17880.5	4600.199	3.886896	0.000142	HOV cfb	cumDose	183
Slope	-3.8938	2.717969	-1.43262	0.153693	HOV cfb	cumDose	183
Intercept	19710.06	4530.788	4.350251	2.32E-05	HOV cfb	cumAUC	175
Slope	-77.687	39.30034	-1.97675	0.049659	HOV cfb	cumAUC	175
Intercept	56.48192	32.73676	1.725336	0.086212	HOV %cfb	avgDose	179
Slope	-3.99458	6.961376	-0.57382	0.566817	HOV %cfb	avgDose	179
Intercept	62.35812	32.38835	1.925326	0.055858	HOV %cfb	avgAUC	172
Slope	-83.7604	101.2152	-0.82755	0.409087	HOV %cfb	avgAUC	172
Parameter	Estimate	Std.Error	t.value	Pr.t	Response	Exposure	n
Intercept	57.32845	32.7397	1.751038	0.081672	HOV %cfb	cumDose	179
Slope	-0.01176	0.019185	-0.61315	0.540567	HOV %cfb	cumDose	179
Intercept	62.64241	32.35522	1.936084	0.054516	HOV %cfb	cumAUC	172
Slope	-0.23508	0.278454	-0.84425	0.399716	HOV %cfb	cumAUC	172

Source: Applicant's ER report pvo-fop-er-002.pdf. Table 6.2

Abbreviations: avgAUC, average daily area under the curve (h*mg/L); avgDOSE, average daily palovarotene dose (mg); CFB, change from baseline; cumAUC, cumulative area under the curve over 12 months (h*mg/L); cumDOSE, cumulative palovarotene dose over 12 months (mg); HOV, HO Volume; n, number of observations; Pr.t, probability of a greater student's t-statistic for test that parameter =0; Std.Error, standard error; t.value, student's t-statistic for test that parameter =0

Plots and regression analyses show a trend to decrease change from baseline or relative change from baseline in HO volume versus the assessed exposure metrics (cumulative dose, average daily dose, average daily AUC, and cumulative AUC). Furthermore, a statistically significant relationship (linear regression analysis) was observed between change from baseline in HO volume at Month 12 and cumulative AUC (p=0.0497).

Figure 28. Plots of HOVcfb and HOV%cfb Versus Exposure Metrics in Study PVO-1A-301



Source: Applicant's ER report pvo-fop-er-002.pdf. Figure 6.2

Abbreviations: AUC, area under the concentration versus time curve; CFB, change from baseline; HO, heterotopic ossification; HOV, HO Volume

Reviewer's comments: In general, the Applicant's ER analyses between the change from baseline [CFB] in HO volume versus different palovarotene dose/exposure parameters. No significant ER relationship was observed based on phase 2 data for the change from baseline [CFB] in HO volume at Day 84, while there is a trend of decreasing change from baseline or relative change from baseline in HO volume with increasing assessed exposure metrics (cumulative dose, average daily dose, average daily AUC, and cumulative AUC), suggesting higher dose/exposure level might have better efficacy as measured by annualized change in new HO volume.

The results for ER analyses are different between phase 2 and phase 3 trials, possibility due to longer duration of new HO volume measurement in phase 3 study (12 months) and phase 2 trials (84 days). However, we should also consider that this ER analyses based on phase 3 trials have some limitations due to the study design as only one dosing regimen or placebo was tested in Study PVO-1A-301: (1) Patients with annualized change in new HO volume data were either treated with one dosing regimen (chronic 5 mg, flare-up 20/10 mg) or not treated with palovarotene; (2) patients with flare-ups were treated with high doses (20/10 mg QD) and patients without flare-ups were treated with the low dose (5 mg QD). In addition, we also noticed that placebo response mainly obtained from Study PVO-1A-001 has a large variability, in which HO volume change from baseline could range from -91300 mm to 391730 mm by Month 12 for the placebo group. This large variability limited the precision we interpreted for the placebo

response, and therefore we have less confidence for the detected ER relationship as shown in [Figure 28](#). In general, flare-up doses for controlling new HO formation seems to be appropriate.

In summary, the exposure-response analyses in FOP patients support the effectiveness of the proposed chronic 5 mg and flare-up 20/10 mg dosing regimen. The primary support for the efficacy of the palovarotene chronic and flare-up dosing regimen is the clinical data of annualized new HO data generated in Studies PVO-1A-301 and the NHS.

14.3.2.2. PK/PD Relationships for Safety

Applicant's Analyses

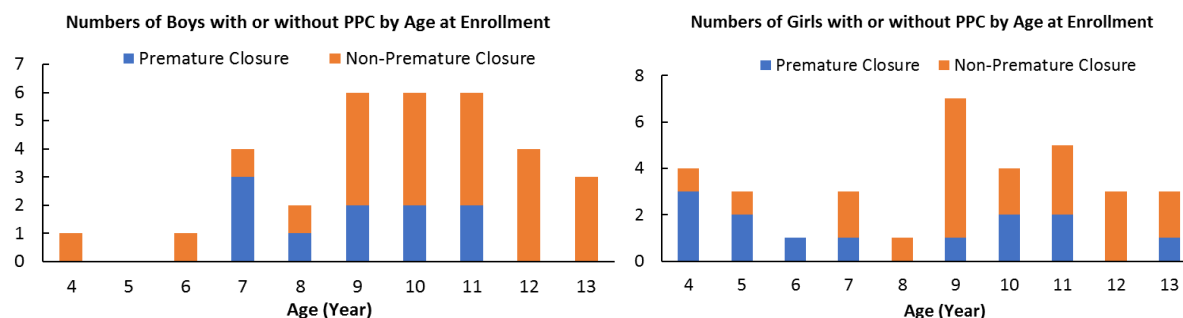
No PK/PD (pharmacokinetic/pharmacodynamic) relationship for safety was performed.

Reviewer's Analyses

The main adverse effects reported for palovarotene is premature physeal closure (PPC). By June 25, 2020, a total of 24 events of PPC were reported in 96 pediatric subjects aged <17 years at enrollment. To mitigate the risk of PPC, the Applicant proposed to limit target population to females ≥ 8 years and males ≥ 10 years (" $\geq 8/10$ population"). In order to further assess the impact of age on PPC, additional analyses were performed.

[Figure 29](#) shows the number of pediatric subjects (boys or girls) with or without PPC by age at enrollment. PPC occurs in ~30% of patients $\geq 8/10$ years to 11 years of age, with 4 of 12 (33%) boys aged 10 to 11 years and 5 of 17 (29%) girls aged 8 to 11 years. The prevalence of PPC is higher with increasing palovarotene AUC_{ss} ([Figure 30](#)). However, this result is likely to be driven by patients <8 years old. When excluding subjects younger than 8 years of age, there is absence of relationship between proportion of PPC and AUC in patients 8/10 to 13 years old ([Figure 31](#)).

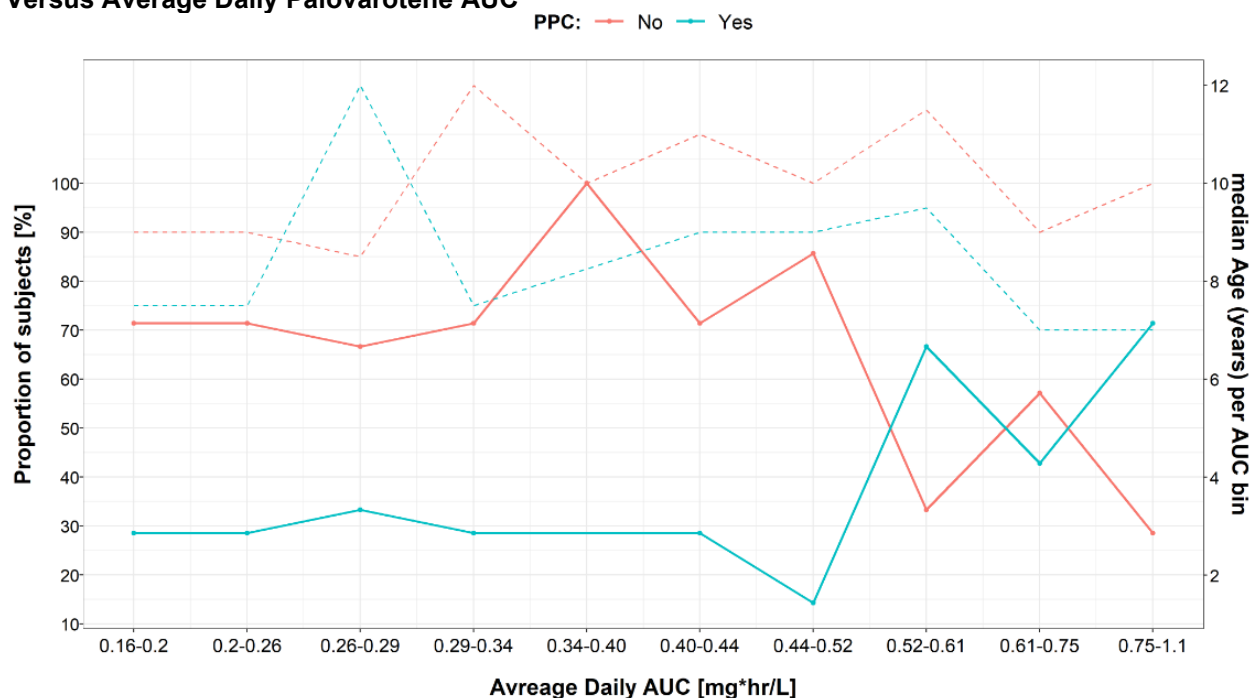
Figure 29. The Number of Pediatric Boys (Left) or Girls (Right) With or Without PPC by Age at Enrollment



Source: Clinical pharmacology reviewer's analyses
Abbreviations: PPC, premature physeal closure

In addition, there is a higher proportion of PPC with increased average daily AUC of palovarotene.

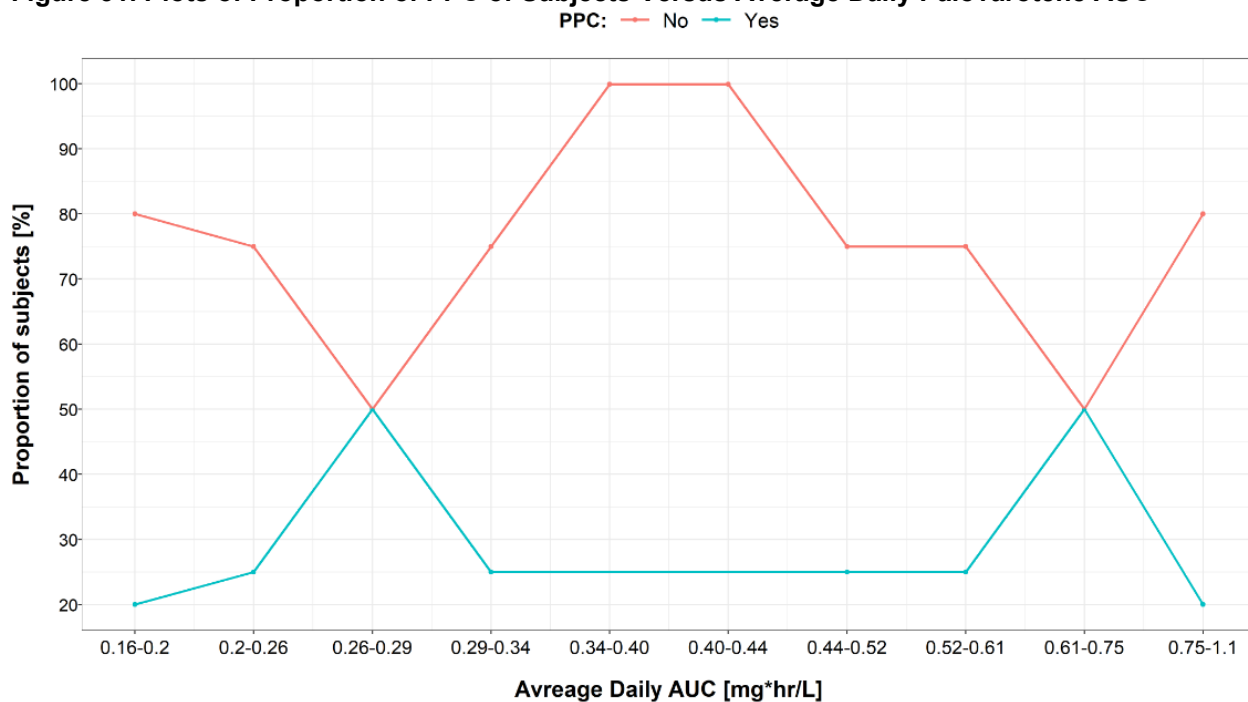
Figure 30. Plots of 1) Proportion of PPC (Solid Line) and 2) Median Age (Dashed Line) of Subjects Versus Average Daily Palovarotene AUC



Source: Clinical pharmacology reviewer's analyses.

Abbreviations: AUC, area under the concentration versus time curve; PPC, premature physeal closure

Figure 31. Plots of Proportion of PPC of Subjects Versus Average Daily Palovarotene AUC



Source: Clinical pharmacology reviewer's analyses.

Abbreviations: AUC, area under the concentration versus time curve; PPC, premature physeal closure

In general, no ER relationship could be detected for palovarotene exposure and proportion of patients with PPC events for subjects greater than 8/10 years of age. Lowering dose of palovarotene dose for subjects younger than 12 years of age is not predicted to reduce risks of PPC for pediatrics. The reviewer acknowledged that this conclusion is limited by the small number of reported PPC events in the clinical studies.

14.4. Physiological Based Pharmacokinetic (PBPK) Review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses to:

- evaluate the drug-drug interaction (DDI) potentials of palovarotene as a victim of moderate CYP3A inhibitors or inducers, strong CYP2C8 inhibitors, and strong CYP2C19 inhibitors.
- predict the PK of palovarotene in subjects with hepatic or renal impairment

The Division of Pharmacometrics has reviewed the PBPK analyses report (IPN-3B), the response to FDA's information request (rtq-fda-10june2022) submitted on July 8th (seq 0034), and the modeling supporting files to conclude that:

- The PBPK analyses are adequate to evaluate the effects of the moderate CYP3A inhibitor erythromycin on the PK of palovarotene. Drug interactions of palovarotene with erythromycin was approximately 2.5-fold increase in AUC, which is similar to the observed effect of the strong CYP3A inhibitor ketoconazole.
- Because the metabolic pathways of palovarotene have not been well characterized, the PBPK analyses are inadequate
 - to evaluate the effects of strong CYP2C19 inhibitors, strong CYP2C8 inhibitors and moderate CYP3A inducer efavirenz
 - to evaluate the effects of organ impairment

Background

Palovarotene (also known as IPN60120, CLM-001, or RO3300074) is a retinoic acid receptor gamma (RAR γ) selective agonist currently being developed for prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with FOP. The available dose strengths are 1 mg, 1.5 mg, 2.5 mg, 5 mg, 10 mg. Recommended dosages are 5 mg once daily for chronic treatment, with an increase in dose at the time of a flare-up to 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks for a total of 12 weeks (20/10 mg flare-up treatment). The tablets should be taken with food preferably at same time each day.

Following oral administration of single- and multiple-dose of palovarotene, its C_{max} and AUC increased dose proportionally across the dose range of 0.02- to 50-mg after single doses and 0.4 to 20 mg after once daily dosing (QD) in healthy adult subjects, and no accumulation of palovarotene was observed (NP17726, RB16327, PVO-1A-102, POV-1A-301 and RB16328).

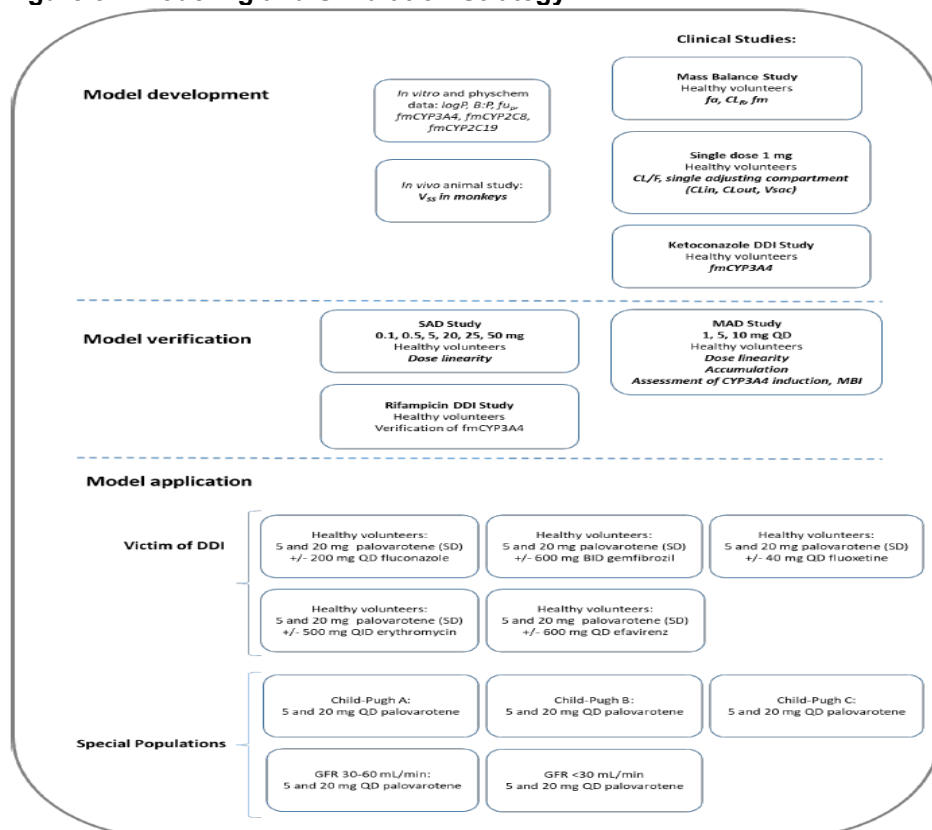
Steady state was reached by Day 3 (Report 1006914/RB16328). After a standardized FDA high-fat meal, the $C_{\max}$ and AUC of palovarotene increased 16% and 40%, and $T_{\max}$ delayed by approximately 2h, compared to the fasted state, following a single 20-mg dose.

Palovarotene has high permeability and low solubility (Quality Report 2.3.S.1.3). It is well-absorbed and is extensively metabolized primarily through CYP3A4 with minor contribution of CYP2C8 and CYP2C19 (study 1008690). In the human ADME study, approximately 3.2% and 97% of radioactivity dose were recovered in the urine (negligible amount of unchanged parent) and the feces (2.31% unchanged parent), respectively. Palovarotene is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, or OCT1 (CYP1933_01). Palovarotene is determined in vitro to be a competitive inhibitor of CYP2C8, 2C9 and 2C19 with K_i values of 4.7, 8.1, and 7.9 μM , respectively (1008423). Whether palovarotene is a time-dependent inhibitor of CYP enzymes has not been investigated. Palovarotene is an inducer of CYP2B6 and CYP3A4 in vitro; whether palovarotene is also an inducer of CYP2C9 and CYP2C19 is inconclusive based on the in vitro study because the response of the positive controls was less than 2-fold (CYP1933_03). Palovarotene inhibited probe substrate transport mediated by BCRP, OATP1B1, OATP1B3, OCT1 and BSEP, with IC_{50} values of 9.69 μM , 1.83 μM , >3 μM , >3 μM , and 14.7 μM in vitro, respectively (CYP1933_02). Palovarotene is not an inhibitor of probe substrate transport mediated via P-gp, OAT1, OAT3, OCT2, MATE1 and MATE2-K (CYP1933_02). The Applicant conducted clinical DDI studies with ketoconazole, rifampin, and midazolam to evaluate some of the in vitro findings. Refer to the Clinical Pharmacology review section for detailed information on palovarotene regarding ADME properties, in vitro and clinical studies used in the PBPK modeling analysis.

Methods

Simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Versions 19 and 21, Certara, Sheffield, UK). Schemes of the PBPK modeling and simulation strategy are shown in [Figure 32](#), which summarizes the studies used for palovarotene model development and verification, and model applications in predicting DDI and effects of organ impairment. The final model input parameters were summarized in [Table 126](#). The palovarotene PBPK model consists of a first-order absorption model, a minimal PBPK model with a single adjustable compartment for distribution and an enzyme kinetics model for elimination. The Simcyp library files sim-ketoconazole-400 mg QD, SV-rifampin-MD, SV-Efavirenz, SV-Erythromycin_EC, SV-Fluconazole, and SV-Fluoxetine were used for DDI simulations without any modification unless otherwise noted. Simcyp population models of sim-Cirrhosis CP-A, -B and -C in Version 21 were used to simulate effects of organ impairment on palovarotene exposure. All other simulations were performed using Version 19.

Figure 32. Modeling and Simulation Strategy



Source: Figure 1 in the PBPK report -ipn-3B

Table 126. Final Input Parameters in the Palovarotene Model

Parameter	Value	Reference	Parameter	Value	Reference
Physicochemical and binding parameters			Elimination parameters		
Molecular Weight (g/mol)	414.55	Simcyp checklist	CL/F (L/h)	21.7	Report 1016632 (Study NP17726); healthy young males (n = 12)
log P	6.80	Simcyp checklist	$f_{mCYP3A4}$	70%	Optimised using ketoconazole DDI data from Report 1010705 (Study NP17041B)
Compound type	Ampholyte	Simcyp checklist	$f_{mCYP2C8}$		(b) (4)
pKa 1 (acidic)	4.3	Simcyp checklist	$f_{mCYP2C19}$		
pKa 2 (basic)	2	Simcyp checklist	CYP3A4 CL_{int} (μ L/min/pmol)	2.99	(b) (4)
B:P	0.62	Report 1008425	CYP2C8 CL_{int} (μ L/min/pmol)		
f_u	0.01	Report 1008422	CYP2C19 CL_{int} (μ L/min/pmol)		
Main binding protein	Serum Albumin	Assumed	CL _R (L/h)	0	Report 1016529 (Study NP17056; mass balance); only 3% of the radioactive dose recovered in urine
Absorption model – First Order					
PSA ($\text{\AA}^2$)	55.12	Drugbank (ChemAxon)			
HBD	1	Drugbank (ChemAxon)			
$P_{eff,max}$ ($\times 10^{-4}$ cm/s)	3.71	Predicted			
Q_{gut} (L/h)	13.6	Predicted			
f_{ugut}	0.01	Assumed equilibrium			
k_a (h^{-1})	0.369	PopPK report (b) (4) project No. 3998-008; interim final model			
f_a	1	Report 1016529 (Study NP17056; mass balance); 97% of the radioactive dose recovered in faeces, with only 2.38% represented by parent			
t_{lag} (h)	0.795	PopPK report (b) (4) project No. 3998-008; interim final model			
F_0	1	Assumed			
Distribution model – Minimal PBPK model					
V_{ss} (L/kg)	1.39	Monkey V_{ss} corrected by f_u			
CL_{in} (1/h)	3.90	Estimated using parameter estimation, with residual errors weighted by $\frac{1}{y^2}$			
CL_{out} (1/h)	5.26				
V_{SAC} (L/kg)	1.11				

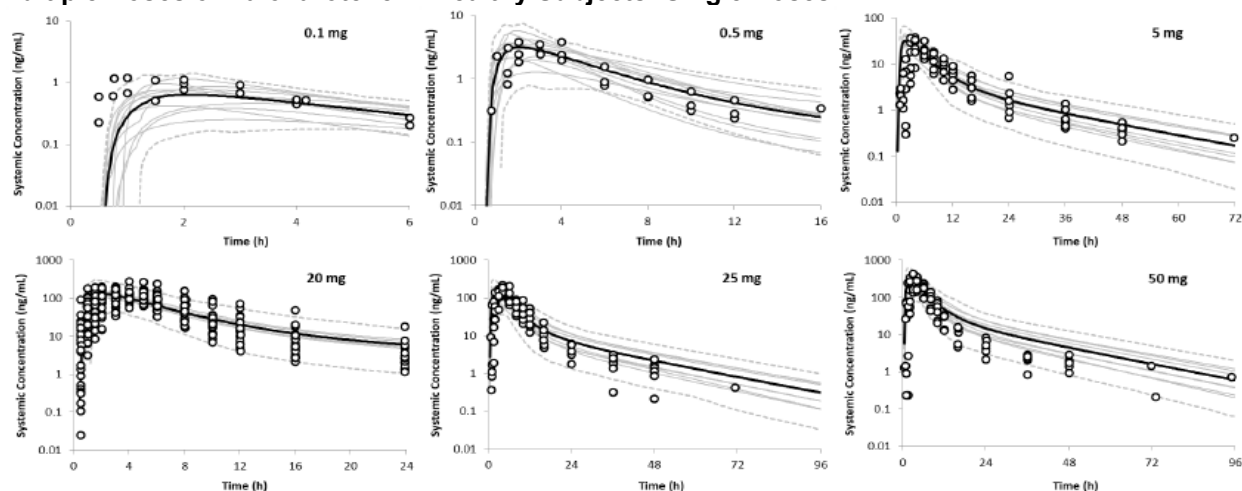
Source: Table 6 in the PBPK report -ipn-3B

Results

Can the PBPK model adequately describe the PK profiles of palovarotene?

Yes. The palovarotene PBPK model could reasonably well describe palovarotene PK following administration of single and multiple doses of palovarotene ([Figure 33](#) and Table 127).

Figure 33. Simulated and Observed PK Profiles Following Oral Administration of Single and Multiple Doses of Palovarotene in Healthy Subjects: Single Doses

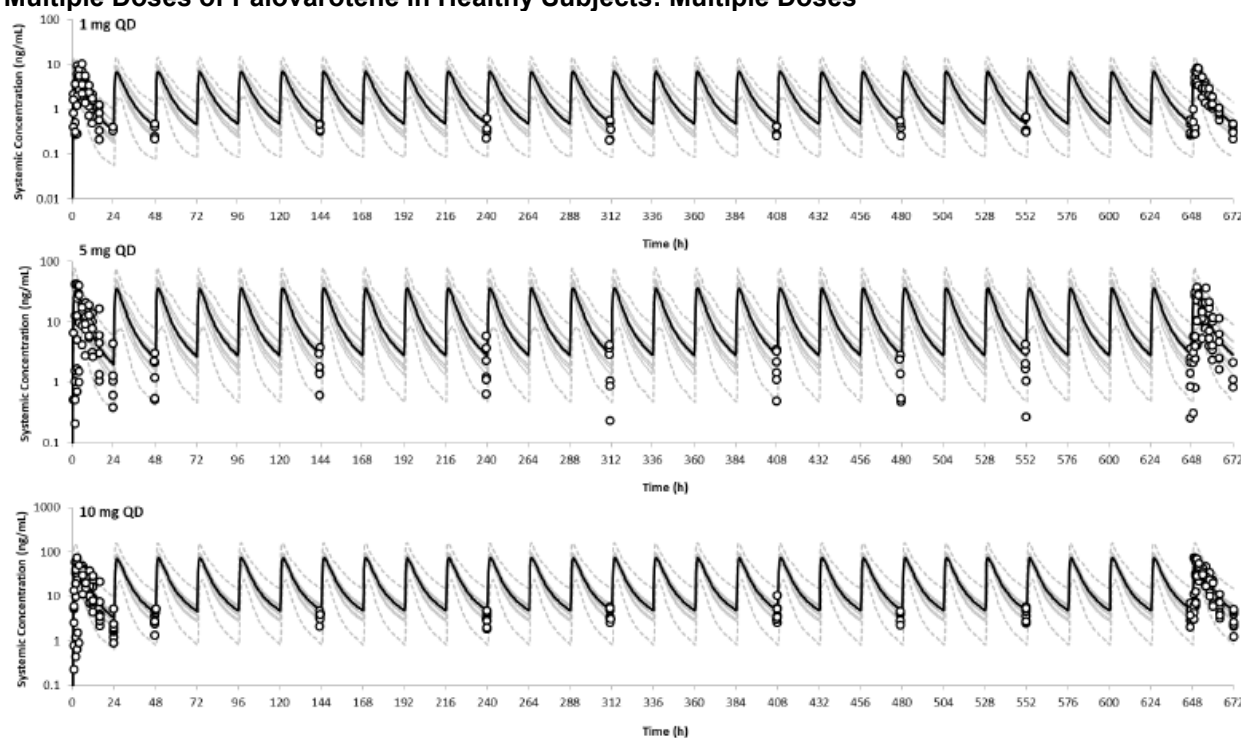


Source: Figures 5B and 6B in the PBPK report (PBPK_report-ipn-3b)

Depicted are simulated (lines) and observed data (circles, Clinical Studies RB16327 and PVO-1A-102 Cohort 2). The grey solid lines represent mean values of simulated individual trials, the black lines represent the mean data of the simulated population (n=30, 30, 60, 230, 60, and 60), and the grey dashed lines represent 5% and 95% percentiles.

Abbreviations: h, hour; PK, pharmacokinetics; PVO, palovarotene

Figure 34. Simulated and Observed PK Profiles Following Oral Administration of Single and Multiple Doses of Palovarotene in Healthy Subjects: Multiple Doses



Source: Figures 5B and 6B in the PBPK report (PBPK_report-ipn-3b).
Depicted are simulated (lines) and observed data (circles, Clinical Study RB16328). The grey solid lines represent mean values of simulated individual trials, the black lines portray the mean data of the simulated population (n=60, 60, and 90), and the grey dashed lines represent 5% and 95% percentiles.
Abbreviations: h, hour; PK, pharmacokinetics; PVO, palovarotene

Table 127. Simulated and Observed PK Parameters Following Oral Administration of Single and Multiple Doses of Palovarotene in Healthy Subjects: Single Doses

Study	n	Dose mg		AUC _{0-last} ng·h/mL (CV%)	C _{max} ng/mL (CV%)
RB16327	3	0.1	Simulated	2.47 (50.3)	0.73 (60.3)
			Observed	2.95 (36.3)	0.986 (22.2)
			S/O	0.839	0.739
RB16327	3	0.5	Simulated	18.1 (44.9)	3.60 (63.9)
			Observed	15.5 (28.4)	3.46 (20.8)
			S/O	1.17	1.04
RB16327	6	5	Simulated	246 (44.3)	37.2 (57.6)
			Observed	215 (14.4)	30.1 (27.3)
			S/O	1.14	1.24
PVO-1A-102 Cohort 2	23	20	Simulated	870 (53.2)	151 (59.2)
			Observed	902 (35.8)	145 (30.4)
			S/O	0.964	1.04
RB16327	6	25	Simulated	1124 (45.7)	170 (58.0)
			Observed	1121 (29.0)	176 (18.5)
			S/O	1.00	0.97
RB16327	6	50	Simulated	2305 (46.6)	347 (57.7)
			Observed	1784 (36.5)	309 (41.0)
			S/O	1.29	1.12

Source: Tables 9 and 10 in the PBPK report (PBPK_report-ipn-3b)

Abbreviations: CV, Coefficient of Variation; S/O, Simulated/Observed

Figure 35. Simulated and Observed PK Parameters Following Oral Administration of Single and Multiple Doses of Palovarotene in Healthy Subjects: Multiple Doses

Study	n	Dose mg		Day1 AUC _{0-tau} ng·h/mL (CV%)	Day28 AUC _{0-tau} ng/mL (CV%)	R _{ac}	Day1 C _{max} ng/mL (CV%)	Day28 C _{max} ng/mL (CV%)
RB16328	6	1 (QD)	Simulated	44.4 (46.5)	51.1 (50.1)	1.13	7.59 (57.4)	7.99 (55.2)
			Observed	44.3 (36.1)	46.3 (25.7)	1.04	7.10 (33.8)	7.10 (25.4)
			S/O	1.00	1.10	1.09	1.07	1.12
RB16328	6	5 (QD)	Simulated	240 (48.9)	279 (52.9)	1.15	39.9 (58.4)	42.2 (55.8)
			Observed	182 (45.9)	212 (40.05)	1.16	24.0 (48.8)	27.8 (39.9)
			S/O	1.32	1.31	0.99	1.66	1.52
RB16328	9	10 (QD)	Simulated	463 (54.3)	530 (57.7)	1.13	80.7 (62.2)	84.8 (60.8)
			Observed	336 (20.7)	385 (19.04)	1.14	49.1 (28.5)	52.2 (24.3)
			S/O	1.38	1.38	0.99	1.64	1.62

Source: Tables 9 and 10 in the PBPK report (PBPK_report-ipn-3b)

Abbreviations: CV, Coefficient of Variation; R_{ac}, Accumulation Ratio calculated as Day28 AUC_{0-tau} / Day1 AUC_{0-tau}; S/O, Simulated/Observed

Can PBPK Analyses Predict the Effects of CYP Inhibitors and Inducers on the PK of Palovarotene?

No. The palovarotene PBPK model could not be used to predict the effects of CYP inhibitors and inducers, except for the moderate CYP3A inhibitor erythromycin for reasons discussed below.

Effect of the Moderate CYP3A Inhibitor Erythromycin

The relative contributions of CYP3A4, CYP2C8, and CYP2C19 in the hepatic metabolism ($f_{m,CYP}$) were initially estimated to be (b) (4) (Report 1008690). However, when these values were applied to the palovarotene PBPK model, the model overpredicted the effect of the strong CYP3A inhibitor ketoconazole on palovarotene PK. The $f_{m,CYP3A}$ value in the palovarotene PBPK model was optimized to be 0.7 in order to reproduce the observed inhibitory effect of ketoconazole on palovarotene PK (Study NP17041B). In the human ADME study, metabolites formed by CYP3A represent for approximately 65% of the recovered dose, which is similar to the $f_{m,CYP3A}$ value estimated from the ketoconazole DDI study. Therefore, the $f_{m,CYP3A}$ value is considered verified and the predicted effects of erythromycin on palovarotene are considered adequate. Palovarotene AUC and C_{max} were predicted to increase 2.54- and 1.64- fold, respectively, following co-administration of a single 5- or 20-mg dose of palovarotene with 500 mg erythromycin QID (4 times a day).

Effects of Strong CYP2C8 or CYP2C19 Inhibitors

The predicted effects of strong CYP2C8 or CYP2C19 inhibitors are considered inadequate due to the uncertainty about the contribution of CYP2C8 and CYP2C19 in the metabolism of palovarotene. As mentioned above, the $f_{m,CYP3A}$ value in the palovarotene PBPK model was optimized to be 0.7 based on the ketoconazole DDI study. The Applicant assigned (b) (4) to CYP2C8 and CYP2C19 (b) (4). However, there is no reason to believe that this assignment appropriately reflects the contribution of CYP2C8 and CYP2C19 in palovarotene elimination since the $f_{m,CYP3A}$ value estimated from the same recombinant CYP enzyme study could not reproduce the effect of ketoconazole. Furthermore, approximately 30% of the administered dose recovered in the human ADME study were metabolites whose chemical structure had not been identified; thus, there is uncertainty about the enzymes involved in their catalysis. Therefore, due to the uncertainty about the contribution of CYP2C8 and CYP2C19, the predicted effects of gemfibrozil (strong CYP2C8 inhibitor), fluoxetine (strong CYP2C19 inhibitor) and fluconazole (moderate CYP3A inhibitor and strong CYP2C19 inhibitor) are considered inadequate.

Effect of the Moderate CYP3A Inducer Efavirenz

The predicted effect of efavirenz on palovarotene PK is considered inadequate for the following reasons: 1) Although the palovarotene PBPK model could recover the effect of ketoconazole, the model underpredicted the effect of rifampin on AUC and C_{max} of palovarotene (b) (4) when the default model of rifampin was used. The reason for the underprediction is unclear; thus, the ability of the palovarotene model to predict the effect of other inducers is in question. 2) A clinical DDI study showed that efavirenz reduced the AUC of CYP2C19 sensitive substrate omeprazole by 46% . Currently, there are no validated induction parameters of

CYP2C19 in the efavirenz PBPK model. 3) As mentioned above, there is uncertainty about the contribution of CYP2C19 in the disposition of palovarotene.

Can PBPK Analyses Predict the effects of Organ Impairment on the PK of Palovarotene?

No. Besides uncertainty about the contribution of CYP2C8 and CYP2C19 in the disposition of palovarotene, approximately 30% of the administered dose recovered in the human ADME study were metabolites whose chemical structure and enzyme involved in their formation had not been identified. Due to the uncertainty about elimination pathways of palovarotene, it is inadequate to predict the effects of hepatic or renal impairment using the PBPK approach. Furthermore, the verification of the population models submitted by the Applicant is insufficient to support the use of the organ impairment models to predict the effects of renal impairment on palovarotene and inform dose recommendation.

Conclusions

- The PBPK analyses are adequate to evaluate the effects of the moderate CYP3A inhibitor erythromycin on the PK of palovarotene. Drug interactions of palovarotene with erythromycin was approximately 2.5-fold increase in AUC, which is similar to the observed effect of ketoconazole.
- Because the metabolic pathways of palovarotene have not been well characterized, the PBPK analyses are inadequate
 - to evaluate the effects of strong CYP2C19 inhibitors, strong CYP2C8 inhibitors and moderate CYP3A inducer efavirenz
 - to evaluate the effects of organ impairment

14.5. Bioanalytical Method Validation and Performance

In clinical PK studies conducted by Roche, three liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods (Method A, Method B and Method 1012543) were developed and validated for the determination of palovarotene and four major metabolites in human plasma.

14.5.1. LC-MS/MS Method for Study RB16327 (Method A) and Study RB16328 (Method B)

Quantitative analysis of palovarotene in human plasma in Study RB16327 and Study RB16328 was performed using two validated LC-MS/MS methods (Method A and Method B). The method validation parameters are summarized in Table 128.

Table 128. Bioanalytical Method Specifications and Validation Parameters for Methods A and B

(b) (4) Validation Report No. 017-01007V: An LC/MS/MS Method for the Determination of Ro330-0074/000 in Human Lithium Heparin Plasma Samples	
Validation Report	
Matrix	Human plasma
Anticoagulant	Lithium heparin
Method description	LC/MS/MS. For Method A, the HPLC mobile phase eluent was 0.3 mL acetonitrile with 0.2 mL of 0.2% formic acid. For Method B, the HPLC mobile phase eluent was methanol:acetonitrile 1:1 v:v and 0.15 mL of 0.2% formic acid.
Injection volume (µL)	10 (Method A) 20 (Method B)
Sample storage temperature	-20°C
Analyte	Palovarotene
Internal standard (IS)	[¹³ C ² H ₄] Palovarotene
Regression, weighting	1/x (Methods A and B)
Sensitivity (accuracy at the LLOQ)	102% (Method A); 99.5% (Method B)
Average recovery of drug	92.4% to 112% (Method A); 71.6% to 127% (Method B)
Average recovery of IS	93.8% to 108% (Method A); 68.2% to 125% (Method B)
Standard curve concentrations (ng/mL)	0.200, 0.400, 1.00, 2.00, 10.0, 40.0, 100 (Method A) 0.0200, 0.0500, 0.100, 0.500, 2.00, 5.00 (Method B)
QC concentrations (ng/mL)	0.200, 0.400, 10.0, 80.0 (Method A) 0.0200, 0.0500, 0.500, 4.00 (Method B)
Intra-assay precision (%CV)	1.21% to 5.03% (Method A); 1.43% to 8.53% (Method B)
Interassay precision (%CV)	1.09% to 4.59% (Method A); 2.13% to 3.63% (Method B)
Accuracy (%)	97.4% to 98.6% (Method A); 101% to 102% (Method B)
Thawed matrix stability (room temperature and refrigerator) (h)	4 (Methods A and B)
Solution stability (room temperature; plasma extracts) (days)	8 (Method A); 3 (Method B)
Freeze-thaw stability (cycles)	3
Frozen matrix storage stability (-20°C) (days)	46 (Method A); 50 (Method B)
Selectivity	No interference

Source: Summary of biopharmaceutical studies and associated analytical methods

Abbreviations: C, Celsius; CV, coefficient of variation; HPLC, high performance liquid chromatography; IS, internal standard; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control

14.5.2. LC-MS/MS Method for Studies NP17040, NP17041, NP17055, NP17056, NA17098, NA17598 NP17584, NP21025, and NB18332 (Method 1012543)

LC-MS/MS Method 1012543 was used to quantify palovarotene and four major metabolites in nine studies conducted by Roche. Method specifications and validation parameters are summarized in [Table 129](#).

Table 129. Bioanalytical Method Specifications and Validation Parameters for Method 1012543

Validation Report	Validation Report for Analysis of RO3300074-000 and Metabolites in Human Plasma ((b) (4) Study 02349)				
Matrix	Human plasma				
Anticoagulant	Lithium heparin				
Method description	Solid-phase extraction followed by turbo ion spray LC-MS/MS in positive ion mode using selected reaction monitoring. For RO3304835 and RO3305210, the HPLC mobile phase eluent was 43% acetonitrile in water with 0.025% formic acid and 0.0001% oxalic acid at a flow rate of 325 µL/min. For RO3300074, RO3304974, and RO3305659, the mobile phase eluent was 70% acetonitrile in water with 0.025% formic acid and 0.0001% oxalic acid at a flow rate of 200 µL/min.				
Injection volume (µL)	50				
Sample storage temperature	-70°C				
Analytes	Palovarotene	M2	M4a	M3	M4b
Regression, weighting	1/x ²	1/x ²	1/x ²	1/x ²	1/x ²
Sensitivity (accuracy at the LLOQ)	111.6%	110.7%	91.9%	94.0%	102.5%
Average recovery of drug	51.7%	45.1%	81.1%	45.4%	72.3%
Average recovery of IS	52.1%	42.7%	85.7%	47.0%	75.5%
Standard curve concentrations (ng/mL)	0.01- 2	0.01 - 2	0.01 - 2	0.01 - 2	0.01 - 2
QC concentrations (ng/mL)	0.03, 1.0, 1.5	0.03, 1.0, 1.5	0.03, 1.0, 1.5	0.03, 1.0, 1.5	0.03, 1.0, 1.5
Intra-assay and interassay precision	0.5% to 3.1%	0.7% to 3.1%	0.7% to 6.3%	0.9% to 4.9%	0.7% to 6.4%
Intra-assay and interassay accuracy	106.9% to 113.6%	101.1% to 107.8%	104.3% to 108.0%	97.0% to 102.3%	101.2% to 106.1%
Matrix stability	Analytes were stable in human plasma after storage for 24 hours at room temperature				
Stock solution stability	Analytes were stable in stock solution after storage for 83 days at -20°C				
Stock solution stress stability	Analytes were stable in stock solution after storage for 6 hours at room temperature				
Freeze-thaw stability (cycles)	Analytes were stable for 3 freeze/thaw cycles in human plasma				
Frozen matrix storage stability (days)	Analytes were stable in human plasma for 140 days at approximately -20°C and 113 days at approximately -70°C				
Dilution	Plasma samples can be diluted up to 20× before analysis				
Reproducibility	Reinjecting samples after storage for 42 hours at room temperature is acceptable				
Selectivity	There were no area responses for the six control blanks analyzed				

Source: Summary of biopharmaceutical studies and associated analytical methods

Abbreviations: HPLC, high performance liquid chromatography; IS, internal standard; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control

14.5.3. LC-MS/MS Method for Studies PVO-1A-101, PVO-1A-102, PVO-1A-103, PVO-1A-104, PVO-1A-201, PVO-1A-202, PVO-1A-301, and PVO-2A-201 (Method 140191)

In eight studies conducted by the Applicant, an LC-MS/MS method (Method 140191) for the determination of plasma concentrations of palovarotene was validated over a concentration range of 5.00 to 2000 pg/mL ([Table 130](#)). For DDI studies, LC-MS/MS methods were developed and validated for measurements of midazolam and its metabolite 1-hydroxymidazolam, and prednisone and its metabolite prednisolone.

Table 130. Bioanalytical Method Specifications and Validation Parameters for Method 140191

Validation Report	Method Validation for the Quantitation of Palovarotene in Human Plasma by Turbo Ion Spray LC/MS/MS
Matrix	Human plasma
Anticoagulant	Lithium heparin
Method description	Protein precipitation extraction followed by turbo ion spray LC-MS/MS in positive ion mode using selected reaction monitoring. The HPLC mobile phase eluent was 1000:10 water/1M ammonium bicarbonate (Solvent A) and NOWPak® acetonitrile (Solvent B). The flow rate was 1000 µL/min.
Injection volume (µL)	20
Sample storage temperature	-70°C
Analyte	Palovarotene
Internal standard (IS)	[13C6] palovarotene
Regression, weighting	1/x2
Recovery of drug	82.6% to 95.4%
Average recovery of IS	90.4%
Standard curve concentrations (pg/mL)	5.00, 10.0, 40.0, 200, 400, 800, 1600, 2000
QC concentrations (pg/mL)	5.0, 15.0, 90.0, 600, 1500
Interassay precision (%CV)	≤8.5%
Intra-assay precision (%CV)	≤13.6%
Interassay accuracy (%Bias)	-1.0% to 8.0%
Intra-assay accuracy (%Bias)	-4.4% to 12.7%
Benchtop stability	Palovarotene was stable in human plasma for nine hours at room temperature
Stock solution stability	Palovarotene was stable in 1 mg/mL DMSO for 141 days at 4°C and 18 hours at room temperature
Freeze-thaw stability	Palovarotene stable in human plasma for four freeze/thaw cycles (-20°C) and five freeze/thaw cycles (-70°C)
Frozen matrix storage stability	Palovarotene was stable in human plasma for 427 days at -20°C and at -70°C
Processed sample stability	Palovarotene was stable in human plasma for 97 hours at room temperature
Dilution	Plasma samples can be diluted up to 250-fold before analysis
Selectivity	No significant chromatographic interferences were detected at either the retention time of the analytes or IS

Source: Summary of biopharmaceutical studies and associated analytical methods

Abbreviations: CV, coefficient of variation; DMSO, dimethylsulfoxide; HPLC, high performance liquid chromatography; IS, internal standard; LC-MS/MS, liquid chromatography with tandem mass spectrometry; QC, quality control

14.5.4. LC-MS/MS Method for Study PVO-1A-104 (Method 191333)

Another LC-MS/MS method for the measurement of palovarotene in seminal fluid and plasma in Study PVO-1A-104 was validated over the range of 1.00 to 250 ng/mL ([Table 131](#)).

Table 131. Bioanalytical Method Specifications and Validation Parameters for Method 191333

Validation Report	Method Validation for the Quantitation of Palovarotene in Human Semen by Turbo Ion Spray LC/MS/MS
Matrix	Human semen
Anticoagulant	Not applicable
Method description	Protein precipitation extraction followed by turbo ion spray LC-MS/MS in positive ion mode using selected reaction monitoring. The HPLC mobile phase eluent was 1000:10 water/1M ammonium bicarbonate (Solvent A) and NOWPak® acetonitrile (Solvent B). The flow rate was 1000 µL/min.
Injection volume (µL)	20
Sample storage temperature	-70°C
Analyte	Palovarotene
Internal standard (IS)	[13C6]-palovarotene
Regression, weighting	1/x ²
Recovery of drug	71.4% to 76.2%
Average recovery of IS	91.2%
Standard curve concentrations (ng/mL)	1.00, 2.00, 10.0, 50.0, 125, 200, 250
QC concentrations (ng/mL)	1.00, 3.00, 75.0, 190
Interassay precision (%CV)	≤8.0%
Intra-assay precision (%CV)	≤10.5%
Interassay accuracy (%Bias)	-7.2% to -1.1%
Intra-assay accuracy (%Bias)	-14.0% to 4.7%
Benchtop stability	Palovarotene was stable in human semen for 24 hours at room temperature
Stock solution stability	Palovarotene was stable in 1 mg/mL DMSO for 322 days at 4°C and 18 hours at room temperature
Freeze-thaw stability	Palovarotene stable in human semen for five freeze/thaw cycles (-20°C) and five freeze/thaw cycles (-70°C)
Frozen matrix storage stability	Palovarotene was stable in human semen for 64 days at -20°C and at -70°C
Processed sample stability	Palovarotene was stable in human semen for 95 hours at room temperature
Dilution	Semen samples can be diluted up to 10-fold before analysis
Selectivity	No significant chromatographic interferences were detected at either the retention time of the analytes or IS

Source: Summary of biopharmaceutical studies and associated analytical methods
Abbreviations: CV, coefficient of variation; HPLC, high performance liquid chromatography; IS, internal standard; LC-MS/MS, liquid chromatography with tandem mass spectrometry; QC, quality control

Reviewer's comments: The LC-MS/MS method validation reports were reviewed and found acceptable. The intra- and interassay accuracy was within 15% of nominal. The intra- and interassay precision was within 15%. Benchtop stability was demonstrated at room temperature.

The period of frozen storage stability at -20°C and -70°C covered corresponding study period and sample analysis period. Freeze-thaw stability was confirmed over $\geq$ three cycles at -70°C.

15. Trial Design: Additional Information and Assessment

15.1. Study PVO-1A-301: Protocol Synopsis

Following is the latest version, Amendment 5, dated October 30, 2020, for this pivotal phase 3 study of palovarotene in patients with FOP.

Title

MOVE Trial: A Phase 3, Efficacy and Safety Study of Oral Palovarotene for the Treatment of Fibrodysplasia Ossificans Progressiva (FOP)

Sponsor

Clementia Pharmaceuticals Inc.

Objectives

Primary Objectives

- To evaluate the efficacy of palovarotene in decreasing HO in adult and pediatric subjects with FOP as assessed by low-dose, whole-body computed tomography (WBCT), excluding head, as compared to untreated subjects from Clementia's FOP natural history study over 24 months.
- To evaluate the safety of palovarotene in adult and pediatric subjects with FOP.

Secondary Objectives

- To evaluate the effect of palovarotene on flare-up rate and proportion of subjects reporting at least one flare-up.
- To evaluate the effect of palovarotene on range of motion (ROM) as assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP.
- To evaluate the effect of palovarotene on physical function using age-appropriate forms of the FOP-Physical Function Questionnaire (FOP-PFQ).
- To evaluate the effect of palovarotene on physical and mental health using age-appropriate forms of the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale.
- To evaluate the pharmacokinetics of palovarotene. Secondary Objective (Part B)
- To continue to provide palovarotene to adult and pediatric subjects with FOP and to monitor longer-term safety.

Secondary Objective (Part C)

- To implement safety measures based on data monitoring committee (DMC) recommendations in order to ensure that assessments of safety continue for up to 2 years post last dose of study treatment for skeletally immature subjects.

Study Design

A phase 3, multicenter, open-label study in adult and pediatric subjects with FOP will be conducted in three parts: Part A, the main part of the study; Part B, the 24-month extension; and Part C, the up-to-2-year post last dose of study treatment follow-up for skeletally immature subjects. Sources of subjects eligible for enrollment in Part A of the MOVE Trial will include: (1) subjects from Study PVO-1A-001 (the natural history study [NHS]); (2) additional subjects clinically diagnosed with FOP with the R206H ACVR1 mutation or other FOP variants reported to be associated with progressive HO (who have not previously participated in any Clementia-sponsored study); and (3) phase 2 Study PVO-1A-202 or Study PVO-1A-204 subjects who cannot receive the chronic/flare-up regimen due to country of residence or those traveling long distances to participate in the phase 2 trial. Up to a maximum of 110 subjects will be enrolled into the MOVE Trial (up to 99 with the R206H mutation and no previous exposure to palovarotene, and up to 11 with other mutations or previous participation in the phase 2 trials), and receive chronic dosing for up to 24 months and undergo flare-up-based treatment should they experience an eligible flare-up or traumatic event as confirmed by the Investigator.

As of December 4, 2019, all subjects <14 years of age were required to interrupt study drug due to a partial clinical hold placed on the palovarotene clinical development program by the US FDA. Treatment will subsequently not be restarted in children <14 years of age.

The efficacy of palovarotene treatment in the MOVE Trial Part A, as measured by the change in new HO volume, will be compared to that observed in untreated subjects who participated in the NHS.

In Part B, the study will be extended for an additional 24 months in order to provide the chronic/flare-up palovarotene dosing regimen to all subjects until commercial availability and to obtain longer-term safety data. No new subjects will be enrolled into Part B.

Chronic Treatment: Part A

Subjects will receive orally administered 5 mg palovarotene once daily (weight-adjusted for skeletally immature subjects [i.e., subjects under the age of 18 years with less than 90% skeletal maturity on hand-wrist radiography at screening]) as chronic dosing for up to 48 months. Note: all weight-based dosing, both chronic and flare-up, will cease when subjects achieve $\geq 90\%$ skeletal maturity based on hand-wrist radiography, but radiographic assessment of the growth plate (performed at Study Months 6, 12, 18, and 24) will continue until these subjects achieve 100% closure of the growth plate at both locations.

Additional radiographic assessments will be performed at Study Months 3, 9, 15, or 21 in those subjects who (1) received the flare-up dosing regimen in the period of time since their last radiographic assessment; and (2) had not achieved 100% skeletal maturity on their last radiographic assessment. All subjects will undergo the procedures and assessments specified in

the Schedule of Assessments Table 1 (see [Table 132](#)), including low-dose, WBCT (excluding head) at Screening and at site visits at Months 6, 12, 18, and 24.

In order to ensure consistent interpretation of the acquired images, a central imaging laboratory will perform blinded reads of all images obtained in this study as well as those obtained from the natural history study (control group) using standardized procedures as documented in the Image Acquisition Guidelines and Independent Review Charter. Remote visits (e.g., at home, at a local medical facility, or via video-conference or telephone contact from clinical site personnel) will occur at Week 6 and at Study Months 3, 9, 15, and 21 unless the Investigator deems that a site visit is necessary; urine pregnancy tests will be performed each month for females of childbearing potential (FOCBP).

Chronic Treatment: Part B

The assessments conducted in Part A will continue into Part B except that WBCT imaging will be performed annually thereafter at Months 36 and 48.

Flare-up-Based Treatment: Parts A and B

Subjects will report potential flare-up symptoms to site personnel; such symptoms include, but are not limited to pain, swelling, redness, decreased range of motion, stiffness, and warmth. Only one symptom is required to define a flare-up. If these symptoms are consistent with previous flare-ups, include a subject-reported onset date, and are confirmed by the Investigator as associated with a flare-up, subjects will immediately begin flare-up-based treatment. Flare-up-based dosing should also be initiated if the Investigator confirms the presence of a substantial high-risk traumatic event likely to lead to a flare-up.

Palovarotene 20 mg for 4 weeks (28 days) once daily. The first dose will be taken upon flare-up or traumatic event confirmation by the Investigator (Flare-up Day 1).

To be followed by palovarotene 10 mg for 8 weeks (56 days) once daily. For a total flare-up treatment duration of 12 weeks (84 days).

If the investigator deems it necessary, the subject can be evaluated at the clinical site to confirm the presence of a flare-up. Based on clinical signs and symptoms as determined by the Investigator, treatment may be extended in 4-week intervals while on-treatment with 10 mg palovarotene and continue until the flare-up resolves and the 4-week extension treatment has been completed.

Subjects will be provided with the appropriate dose of study drug to be used to initiate treatment with palovarotene when a flare-up or traumatic event is confirmed by the investigator.

Flare-up dosing will be weight-adjusted in subjects under the age of 18 years with less than 90% skeletal maturity on hand-wrist radiography at Screening.

Should a subject experience an intercurrent flare-up (defined as a new flare-up location or marked worsening of original flare-up), or substantial traumatic event likely to lead to a flare-up, at any time during flare-up-based treatment, the 12-week dosing regimen will restart upon new intercurrent flare-up or traumatic event confirmation by the Investigator (i.e., 4 weeks of 20 mg palovarotene followed by 8 weeks of 10 mg palovarotene [or weight-based equivalents]). A Flare-up Cycle will include the first flare-up or traumatic event and any subsequent intercurrent flare-ups or traumatic events during the same dosing period. Flare-up Cycle Safety Day 1 is

defined as the first day that study drug is administered for the first flare-up or traumatic event during that cycle. Safety assessments will be performed at Flare-up Cycle Safety Day 1 and then every 12 weeks thereafter until treatment of the last flare-up or traumatic event in the cycle is completed. If any flare-up in a cycle has not resolved after 12 weeks, treatment and safety assessments will be extended, and 10 mg palovarotene (or the weight-based equivalent) will be administered in 4-week intervals until all flare-ups resolve and flare-up-based treatment has been completed. It is possible that subjects may experience more than one Flare-up Cycle during the study.

Subjects receiving flare-up-based treatment will undergo the procedures and assessments specified in the Schedule of Assessments Table 2 (see [Table 133](#)). All assessments will occur remotely unless the Investigator deems it necessary to evaluate subjects at the clinical site.

Once all flare-ups in a cycle have resolved and flare-up-based treatment has been completed, subjects will resume chronic treatment with 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects).

Subjects currently receiving flare-up-based treatment in Study PVO-1A-202 or Study PVO-1A-204 will not enroll into Study PVO-1A-301 until flare-up treatment is complete and at least 4 weeks have elapsed since the last flare-up symptom.

Off-treatment Part C

No study drug will be administered in Part C. For skeletally immature subjects in Part C, added Year 1 (Y1) and Year 2 (Y2) post last dose of study treatment assessments that include linear height, knee height, weight, physical exam, vital signs, radiographic assessments of the knee and hand- wrist, low-dose WBCT imaging, adverse events, and concomitant medications.

Once subjects reach skeletal maturity their participation in Part C will end. The total duration of participation, on and off treatment, is a maximum of 4 years (± 1 month).

Number of Subjects

Up to a maximum of 110 subjects will be enrolled; up to 99 of the enrolled subjects will have the R206H mutation and will not have been previously treated with palovarotene.

Total Number of Sites

Approximately 20 international investigational sites.

Study Population

Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for enrollment:

- Written, signed, and dated informed subject/parent consent; and for subjects who are minors, age-appropriate assent (performed according to local regulations).
- Male or female at least 4 years of age.
- Previous participation in the NHS; or clinically diagnosed with FOP, with the R206H ACVR1 mutation or other FOP variants reported to be associated with progressive HO (who have not previously participated in any Clementia-sponsored study); or participants

in Study PVO-1A-202 or Study PVO-1A-204 who cannot currently receive the chronic/flare-up regimen due to country of residence or those traveling long distances to participate in the phase 2 trial.

- No flare-up symptoms within the past 4 weeks, including at the time of enrollment.
- Females of child-bearing potential must have a negative blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) prior to administration of palovarotene. Male and FOCBP subjects must agree to remain abstinent from heterosexual sex during treatment and for 1 month after treatment or, if sexually active, to use two effective methods of birth control during and for 1 month after treatment. Additionally, sexually active FOCBP subjects must already be using two effective methods of birth control 1 month before treatment is to start. Specific risk of the use of retinoids during pregnancy, and the agreement to remain abstinent or use two effective methods of birth control will be clearly defined in the informed consent and the subject or legally authorized representatives (e.g., parents, caregivers, or legal guardians) must specifically sign this section.
- Must be accessible for treatment and follow-up, and be able to undergo all study procedures. Subjects living at distant locations from the investigational site must be able and willing to travel to a site for the initial and all on-site follow-up visits. Subjects must be able to undergo low-dose, WBCT (excluding head) without sedation.

Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for enrollment:

- Weight <10 kg.
- If currently using vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, or herbal preparations, fish oil, and unable or unwilling to discontinue use of these products during palovarotene treatment
- Exposure to synthetic oral retinoids other than palovarotene within 4 weeks prior to screening
- Concurrent treatment with tetracycline or any tetracycline derivatives due to the potential increased risk of pseudotumor cerebri
- History of allergy or hypersensitivity to retinoids, gelatin, or lactose (note that lactose intolerance is not exclusionary)
- Concomitant medications that are strong inhibitors or inducers of cytochrome P450 (CYP450) 3A4 activity; or kinase inhibitors such as imatinib (see Section 5.2.1).
- Amylase or lipase >2x above the upper limit of normal (ULN) or with a history of chronic pancreatitis.
- Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5x ULN.
- Fasting triglycerides >400 mg/dL with or without therapy.
- Female subjects who are breastfeeding.
- Subjects with uncontrolled cardiovascular, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease.
- Subjects experiencing suicidal ideation (type 4 or 5) or any suicidal behavior within the past month as defined by the Columbia-Suicide Severity Rating Scale (C-SSRS).

- Simultaneous participation in another interventional clinical research study (other than palovarotene studies) within 4 weeks prior to Screening; or within five half-lives of the investigational agent, whichever is longer.
- Any reason that, in the opinion of the Investigator, would lead to the inability of the subject and/or family to comply with the protocol.

Investigational Product

Palovarotene supplied as powder-filled hard gelatin capsules. The capsules may be swallowed whole or opened and the contents added onto specific foods as specified in the dosing instructions.

Dose/Route/Regimen for Chronic Dosing

Palovarotene: 5 mg daily or weight-based equivalents for those subjects who are skeletally immature (<90%) at entry into the study / taken orally with food / at approximately the same time each day. For 5 mg palovarotene, weight equivalent doses for <20 kg, 20 to <40 kg, 40 to <60 kg, and ≥60 kg will be 2.5 mg, 3 mg, 4 mg, and 5 mg, respectively.

Dose/Route/Regimen for Flare-up Dosing

Palovarotene initiated at the start of an eligible flare-up: 20 mg for 4 weeks (28 days), 10 mg for 8 weeks (56 days) for a total of 12 weeks (84 days) (may be extended in 4-week intervals if flare-up is ongoing and continue until flare-up resolves) / weight-adjusted for skeletally immature subjects (<90%) / taken orally with food / at approximately the same time each day.

The weight-adjusted palovarotene doses for skeletally immature subjects and dose de-escalation for flare-up and chronic dosing are:

Weight Range Category	20-mg Equivalent	15-mg Equivalent*	10-mg Equivalent	7.5-mg Equivalent*	5-mg Equivalent	2.5-mg Equivalent*
<20 kg	10 mg	7.5 mg	5 mg	3 mg	2.5 mg	1 mg
20 to <40 kg	12.5 mg	10 mg	6 mg	4 mg	3 mg	1.5 mg
40 to <60 kg	15 mg	12.5 mg	7.5 mg	5 mg	4 mg	2 mg
≥60 kg	20 mg	15 mg	10 mg	7.5 mg	5 mg	2.5 mg

* In the event of dose de-escalation from 20-mg, 10-mg, or 5-mg equivalents, respectively.

Comparator	In This Single-Arm Treatment Study, the Control Reference Group Will Be the Untreated Subjects Who Participated in the NHS
Assessments of efficacy	<u>Primary endpoint:</u> • The annualized change in new heterotrophic ossification (HO) volume as assessed by low-dose, whole-body computed tomography (WBCT) (excluding head) compared to untreated subjects from the NHS over 24 months. <u>Secondary endpoints assessed in Parts A and B:</u> • The proportion of subjects (key secondary endpoint) with any new HO. • The change from baseline in the number of body regions with new HO. • The proportion of subjects reporting flare-ups. • The flare-up rate per subject-month exposure. <u>Exploratory endpoints assessed in Parts A and B:</u> • Change from baseline in range of motion (ROM) assessed by CAJIS. • Change from baseline in physical function using age appropriate forms of the fibrodysplasia ossificans progressiva Physical Function Questionnaire (FOP-PFQ). • Change from baseline in physical and mental function for subjects ≥15 years old and mental function for subjects <15 years old using age appropriate forms of the PROMIS Global Health Scale.
Assessments of safety	Safety evaluations will include adverse event (AE) and serious AE (SAE) reporting, electrocardiograms, vital signs (temperature, respiratory rate, blood pressure, and heart rate), physical examination, body weight and height, laboratory parameters (hematology, biochemistry, and urinalysis), urine pregnancy tests for FOCBP, and concomitant medication reporting. Concomitant medications will include treatment per standard of care, which may or may not include corticosteroids (e.g., prednisone at 2 mg/kg PO to a maximum dose of 100 mg daily) for 4 days. Evaluation of subjects under the age of 18 enrolled with open epiphyses will include knee (anterior/posterior [AP] view) and hand-wrist radiographs (posterior/anterior [PA] view) for assessment of epiphyseal growth plate and distal femoral angle; tibial and femoral long bone lengths; and standardized stadiometry and knee height for assessments of linear growth (in triplicate). If there is evidence of partial or complete premature growth plate closure (with or without growth deceleration) study drug may be continued, interrupted, de-escalated, or discontinued. Dose modification decisions will be made by the Investigator upon review of the subject's clinical and radiographic information and following discussion of the risk/benefit with the subject/parent. The Investigator may consult with the Applicant and the Data Monitoring Committee (DMC). In addition, bilateral hand-wrist and knee growth plate morphology will be assessed by WBCT scan safety read (performed every 6 months up to Month 24 in Part A, and annually thereafter in Parts B and C). Bilateral hip growth plate morphology will also be assessed for avascular necrosis in all subjects. Limb/joint AEs in these subjects will be evaluated by clinical and radiographic assessments as deemed appropriate by the Investigator. Adverse event severity will be assessed and reported according to criteria defined in the protocol (mild, moderate, severe). Adverse events known to be associated with retinoids (e.g., mucocutaneous events) will be further graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, 14 June 2010.

Comparator	In This Single-Arm Treatment Study, the Control Reference Group Will Be the Untreated Subjects Who Participated in the NHS
Assessments of safety (cont'd)	Subjects 8 years of age and older will be assessed for suicidal ideation and behavior every 3 months using the age-appropriate C-SSRS and at all visits during a flare-up cycle. The DMC will assess the safety of the subjects during the course of the study. The DMC can recommend temporary or permanent stopping of the study at any time if there are significant safety concerns. The DMC can also make recommendations for potential dose modifications for individual subjects in the event of treatment-related adverse bone effects. The DMC Charter includes recommended safety stopping rules (see Section 7.7).
Clinical genotyping	On Screening/Study Day 1, a blood sample will be collected and the ACVR1 gene-coding region will be sequenced to assess for the presence of an FOP-associated mutation of the ACVR1 gene for new subjects or for subjects who have not undergone previous genotyping as part of Study PVO-1A-001. Subjects enrolling from Study PVO-1A-202 or Study PVO-1A-204 do not need to undergo repeat genotyping. Any subject enrolled who does not have an ACVR1 mutation known to be associated with FOP will be discontinued. If the Investigator has any reason to believe a subject does not possess an FOP mutation, enrollment may be delayed until the genotype is confirmed.
Pharmacokinetics	Pharmacokinetics of palovarotene will be assessed at the first 3-month safety assessments during chronic-based treatment; if samples cannot be obtained during the first 3-month safety assessment, then they can be obtained during any subsequent 3-month safety visit in Part A (i.e., up to Month 24). Pharmacokinetics will also be assessed twice during flare-up-based treatment: once during the 20-mg regimen at any time between Study Days 4 to 28, and once during the 10-mg regimen at any time between Study Days 32 to 84, for the first treated flare-up only. If this is not possible for the first treated flare-up, pharmacokinetic blood samples can be obtained during any subsequent flare-up dosing cycle. Pharmacokinetic blood samples will be collected at predose and 3, 6, 10, and 24 hours postdose for the three time points listed above. The following palovarotene pharmacokinetic parameters will be determined where possible by model independent analysis using WinNonlin™: $C_{max,ss}$, $C_{min,ss}$, $T_{max,ss}$, $AUC_{0-24,ss}$, λ_z, $t_{1/2}$, and CL/F.

Comparator	In This Single-Arm Treatment Study, the Control Reference Group Will Be the Untreated Subjects Who Participated in the NHS
Statistical analysis	<u>Analysis Populations</u> The principal enrolled population (principal EP) includes all subjects with the R206H ACVR1 mutation who have not previously been treated with palovarotene and who sign the informed consent form and meet all eligibility criteria of the MOVE Trial. The principal full analysis set (principal FAS) includes all enrolled subjects in the Principal EP who have a baseline HO volume measurement and at least one postbaseline HO volume measurement in the MOVE Trial. For efficacy comparisons to the NHS, the Principal FAS will also include subjects enrolled in the NHS with available baseline and at least one postbaseline HO volume measurements. The principal per-protocol set (principal PPS) is a subset of the Principal FAS including subjects with no major protocol deviations that are expected to interfere with assessments of the primary endpoint, and with at least 80% compliance to the study drug regimen, assessed over the first 24 months of participation in Part A. For efficacy comparisons to the NHS, the Principal PPS will also include subjects in the NHS with available baseline and at least one postbaseline HO volume measurement and with no major protocol deviations over 24 months that are expected to interfere with assessments of the primary endpoint. The principal safety set (principal SS) includes all enrolled subjects receiving at least one dose of palovarotene in the MOVE Trial. For safety comparisons to the NHS, the Principal SS will also include subjects enrolled in the NHS with available postbaseline follow-up. The principal pharmacokinetic set (principal PS) includes all enrolled subjects receiving at least one dose of palovarotene and providing evaluable pharmacokinetics data in the MOVE Trial. Subjects who do not have the R206H ACVR1 mutation or who have received previous treatment with palovarotene in PVO-1A-202 or PVO-1A-204 will comprise the Supplementary EP, the Supplementary FAS, the Supplementary PPS, the Supplementary SS, and the Supplementary PS, with these populations defined analogously as above for the subjects with the R206H ACVR1 mutation.

Comparator	In This Single-Arm Treatment Study, the Control Reference Group Will Be the Untreated Subjects Who Participated in the NHS
Statistical analysis (cont'd)	<u>Primary Efficacy Analysis</u> The primary efficacy endpoint is the annualized change in new HO volume (as assessed by low-dose WBCT, excluding head) over 24 months in Part A. The primary efficacy analysis comparing the annualized change in new HO volume between subjects treated with palovarotene and untreated subjects will be conducted using a Bayesian compound Poisson distribution in the Principal FAS. The Principal FAS is used to match the NHS population which was restricted to subjects with the R206H mutation and no previous palovarotene exposure. Hypothesis testing will be performed using random samples generated via Gibbs sampling from the posterior distribution of the treatment effect variables. The primary efficacy endpoint will be summarized for the supplementary FAS. There will be three early interim efficacy analyses and one final analysis. The first interim analysis will occur when 35 subjects complete 1-year of follow-up; the second and third interim analyses will occur when all subjects enrolled in the Principal EP have completed (i.e., have WBCT data) 12 months and then 18 months of follow-up, respectively. The interim analyses will include the Month 6 WBCT results when that is the only observation available from a subject in the current study. An O'Brien-Fleming alpha spending function will be used to specify the alpha level threshold for determination of treatment effect significance at each interim analysis and the final analysis. Using the percentage of patient years of follow-up as an approximation to the statistical information available at each analysis and assuming a one-sided, overall type I error rate of 2.5%, the one-sided significance thresholds are 0.0058, 0.0103, 0.0156, and 0.0190 for the first, second and third interim analyses, and the final analysis, respectively. Study success will be declared if the posterior probability that palovarotene reduces the annualized change in new HO volume is greater than 1 minus the one-sided significance threshold. For example, the posterior probability that palovarotene reduces the annualized change in new HO volume must be greater than 0.9810 to declare study success at the final analysis. A futility analysis was conducted for the second interim analysis based on the prespecified criteria using square-root transformation and on additional analyses without the square-root transformation. Based on feedback received by the DMC following the second interim analysis, the futility analysis conducted at the third analyses will use the predefined model with and without square-root transformation to assess whether the study shows insufficient evidence of efficacy. If the efficacy criteria have not been met by the final analysis of Part A the study may be terminated.
<i>Efficacy will be described for Parts A and B together</i>	
Sample size determination	The sample size was determined via simulation based on the available WBCT HO volumes from the NHS, and the observed efficacy of palovarotene treatment in the phase 2 studies. With the NHS contributing untreated follow-up information on approximately 90 subjects, and 80 subjects originally planned for enrollment into the current study in the Principal FAS population (including approximately 45 from the NHS), the probability of declaring statistical significance is 0.51, 0.79, 0.89 at the first, second, and third interim analyses, respectively, if palovarotene treatment reduces the mean number of body regions with new HO in 1 year by 30%, and reduces the new HO volume conditional on new HO in a body region by 50% compared to the NHS control group. The overall power of the study is 0.92. The increase in the number of enrolled subjects will not substantially change the power of the trial or have a significant impact on the primary or secondary statistical analyses.

Table 132. Protocol Synopsis Table 1: Study PVO-1A-301: Schedule of Assessments for Chronic Treatment

Table 1. Schedule of Assessments for Chronic Treatment									
Assessment/Procedure	Part A (Main Study)					Part B (Extension)			Parts A & B
	Screening/ Study Day 1 ¹ Site Visit (-1 month)	Every Month Remote Visit ² (±1 week)	Week 6 Telephone Contact (±1 week)	Months 3, 9, 15, 21 Remote Visit ³ (±2 weeks)	Months 6, 12, 18, 24 Site Visit ³ (±1 month)	Every Month Remote Visit ² (±1 week)	Months 27, 33, 39, 45 Remote Visit ² (±2 weeks)	Months 30, 36, 42, 48 Site Visit ³ (±1 month)	EOT/EOS Site Visit ³ (±1 month)
Informed consent/assent ^{4,5}	X								
Inclusion/exclusion	X								
Knee and hand-wrist radiographs ⁶	X			X ⁷	X		X ⁷	X	X
Linear and knee height growth assessments (<18 years) ⁶	X				X			X	X
Medical history (including FOP history)	X								
Physical examination	X				X			X	X
Hearing test	X ⁸				Months 12, 24 only			Months 36, 48 only	X
Linear height (subjects ≥18 years)	X								
Body weight	X			X	X		X	X	X
Electrocardiogram	X				X			X	X
Dispense study drug ⁹	X		As needed from Study Day 1 through Month 48						
Study drug treatment		Continuous from Study Day 1 through Month 48							
Dispense/review subject diary		Dispense diary as needed and review at every subject contact ¹⁰							
Subject diary assessment for onset of flare-up symptoms		From Study Day 1 through Month 48							
Vital signs	X			X	X		X	X	X
C-SSRS (age-appropriate) ¹¹	X			X	X		X	X	X
Assess for child-bearing status (females only) and pregnancy prevention measures (females and males)	X			X	X		X	X	X
Hematology	X ⁴				X			X	X
Biochemistry (includes lipids, serum pregnancy test)	X ⁴				X			X	X
Urinalysis ¹²	X ⁴				X			X	X
Pregnancy test ¹³		X				X			X
FOP-PFQ (age-appropriate)	X				X			X	X
PROMIS Global Health Scale	X				X			X	X

Assessment/Procedure	Part A (Main Study)					Part B (Extension)			Parts A & B
	Screening/ Study Day 1 ¹ Site Visit (-1 month)	Every Month Remote Visit ² (±1 week)	Week 6 Telephone Contact (±1 week)	Months 3, 9, 15, 21 Remote Visit ² (±2 weeks)	Months 6, 12, 18, 24 Site Visit ³ (±1 month)	Every Month Remote Visit ² (±1 week)	Months 27, 33, 39, 45 Remote Visit ² (±2 weeks)	Months 30, 36, 42, 48 Site Visit ³ (±1 month)	EOT/EOS Site Visit ³ (±1 month)
CATIS	X				X			X	X
Low-dose, WBCT scan (excluding head) ¹⁴	X				X			Months 36, 48 only	X
Prior/concomitant medications		At every subject contact ¹⁰							
Adverse events ¹⁵		At every subject contact ¹⁰							
Pharmacokinetic blood sample ¹⁶				Month 3 only					
Genotyping ¹⁷	X								

¹ The first day that study drug is administered will be defined as Study Day 1.

² Assessments other than knee and hand-wrist radiographs will be performed remotely (eg, at the subject's home by qualified study personnel, at a local medical facility, or via video-conference or telephone contact from clinical site personnel) unless the Investigator deems that a site visit is necessary. Monthly remote visits will only be conducted for FOCBP subjects.

³ Subjects who decide to stop treatment more than 1 month after an annual visit but who remain in the study will undergo all assessments included in an annual visit as part of their EOT assessments. If the next annual visit is in less than 6 months, the EOT will serve as their EOS assessments and will conclude their participation in the study if subjects decide not to participate in Part C. If the next annual visit is in more than 6 months, these subjects will be assessed again at the next annual visit and undergo all assessments included in an annual visit. This will serve as their EOS assessment and will conclude their participation in the study if subjects decide not to participate in Part C.

⁴ May be obtained remotely.

⁵ Subjects currently receiving flare-up-based treatment in Study PVO-1A-202 or Study PVO-1A-204 will not enroll into Study PVO-1A-301 until flare-up treatment is complete and at least 4 weeks have elapsed since the last flare-up symptom.

⁶ At Screening, subjects under the age of 18 years will undergo knee (AP view) and hand-wrist radiographs (PA view, preferable on the left side) to determine whether they have open epiphyseal growth plates and to assess the distal femoral angle; they will also undergo standardized measurements of linear and knee height. (Subjects enrolling from the NHS or the Phase 2 studies that underwent knee and hand-wrist radiographs within 1 month of Screening will not need to have radiographs repeated at Screening.) Those subjects found to be skeletally immature will continue knee and hand-wrist radiographs, and linear and knee height measurements (all in triplicate) at Months 6, 12, 18, 24, 30, 36, 42, and 48. Limb/joint AEs in these subjects will be evaluated by any clinical and radiographic assessments deemed appropriate by the Investigator. Once a subject has achieved 100% skeletal maturity (confirmed by radiography and defined by growth plate closures), knee and hand-wrist radiographs will no longer be required. In addition, once a subject is 18 years old, linear and knee height growth assessments will no longer be required. If 100% skeletal maturity is not achieved at both locations, then only the location that is still maturing would need to be monitored.

⁷ Knee and hand-wrist radiograph assessments will be performed at Months 3, 9, 15, 21, 27, 33, 39, or 45 (±2 weeks) in those subjects who (1) received flare-up dosing in the period of time since their last assessment; and (2) had not achieved 100% skeletal maturity on their last assessment. These radiographic assessments will be conducted at the clinical site unless the Investigator determines they can be performed at a local medical facility. All assessments will be performed at the clinical site if the radiographs cannot be performed locally.

Assessment/Procedure	Part A (Main Study)					Part B (Extension)			Parts A & B
	Screening/ Study Day 1 ¹ Site Visit (-1 month)	Every Month Remote Visit ² (±1 week)	Week 6 Telephone Contact (±1 week)	Months 3, 9, 15, 21 Remote Visit ² (±2 weeks)	Months 6, 12, 18, 24 Site Visit ³ (±1 month)	Every Month Remote Visit ² (±1 week)	Months 27, 33, 39, 45 Remote Visit ² (±2 weeks)	Months 30, 36, 42, 48 Site Visit ³ (±1 month)	EOT/EOS Site Visit ³ (±1 month)
⁸ The initial hearing test may be obtained at Month 6 (or at the next possible visit) if it was not performed at Screening. ⁹ Except at EOT/EOS/Month 48. ¹⁰ Includes telephone contact by clinical site personnel at Week 6. ¹¹ C-SSRS will be used for subjects 8 years of age and older. The adult form will be used for subjects 12 years and older; the pediatric form will be used for subjects 8 to 11 years old. ¹² If urinalysis results are abnormal, then a microscopic evaluation should be completed. ¹³ Pregnancy testing will be performed monthly for females of child-bearing potential. A urine pregnancy test will be performed only when a serum pregnancy test is not obtained. ¹⁴ The last low-dose, WBCT scan (excluding head) from the NHS will be used as the baseline assessment for those subjects enrolling from the NHS as long as the scans were performed within 1 month of Screening/Study Day 1. The last low-dose, WBCT scan (excluding head) from Study PVO-1A-202 or Study PVO-1A-204 will be used as the baseline assessment for those subjects on chronic treatment enrolling from the Phase 2 study, as long as the scans were performed within 6 months of Study Day 1. All other subjects (ie, subjects who will start chronic treatment during Study PVO-1A-301) will undergo a low-dose, WBCT scan (excluding head) at Screening/Study Day 1. ¹⁵ At each AE assessment, the Investigator must ask the subject about any joint-related complaints. ¹⁶ Blood samples for pharmacokinetic assessment will be collected during the first 3-month safety assessment at predose and 3, 6, 10, and 24 hours post-dose; if samples cannot be obtained during the first 3-month safety assessment, then they can be obtained during any subsequent 3-month safety visit up to Month 24. ¹⁷ Blood samples may be obtained remotely for new subjects or for subjects who have not undergone previous genotyping as part of Study PVO-1A-001. Subjects enrolling from Study PVO-1A-202 or Study PVO-1A-204 do not need to undergo repeat genotyping. CAJIS = Cumulative Analogue Joint Involvement Scale for FOP; C-SSRS = Columbia-Suicide Severity Rating Scale; EOS = end of study; EOT = end of treatment; FOP = Fibrodysplasia Ossificans Progressiva; PFQ = physical function questionnaire; PROMIS = Patient Reported Outcomes Measurement Information System; WBCT = whole body computed tomography.									

Table 133. Protocol Synopsis Table 2: Study PVO-1A-301: Schedule of Safety Assessments During Flare-up-Based Treatment (Subjects With a Flare-up in Parts A and B)

Table 2. Schedule of Assessments for Flare-up-based Treatment (Subjects with a Flare-Up in Parts A and B)							
Assessment/Procedure	FLARE-UP CYCLE SAFETY ASSESSMENTS						
	Remote Visits ^{1,2} (±4 days)						
	Flare-up Cycle Safety Day 1 ³	Every 12 Weeks ³					
Vital signs and body weight	X	X					
Hematology ⁴	X	X					
Biochemistry (includes lipids) ⁴	X	X					
Urinalysis ^{4,5}	X	X					
Columbia-Suicide Severity Rating Scale	X	X					
Pregnancy testing ⁶	X	Every 4 weeks					
Study drug dispensing	As needed from Cycle Day 1 to end of treatment of last flare-up in a cycle ⁷						
Study drug treatment	Continuous from Cycle Day 1 to end of treatment of last flare-up in a cycle ^{3,8,9}						
Dispense/review subject diary	Dispense diary as needed and review at every subject contact						
Prior/concomitant medications	At every subject contact						
Adverse events	At every subject contact						
Treatment/Assessment/Procedure	FLARE-UP TREATMENT AND PHARMACOKINETICS ⁸						
	Flare-up Day 1 ^{4,11,12}	High Dose Treatment	Low Dose Treatment				
Flare-up treatment (first flare-up or restart for intercurrent flare-up) ^{10,11}	X	Week 1 to 4 (4 weeks)	Weeks 4 to 12 (8 weeks)	4-Week Extension (if applicable)			
Flare-up(s) status/end date confirmation ¹⁰	X		End of Week 12	End of Each 4-Week Extension			
Pharmacokinetic blood sample ¹³		X	X				
¹ All visit windows are ±4 days. ² Remote visits will be performed at the subject's home by qualified study personnel or at a local medical facility, unless the Investigator deems that a site visit is necessary. Remote visits during treatment extension, if applicable, will occur every 12 weeks until all flare-ups within a cycle have resolved and treatment has been completed. ³ A Flare-up Cycle will include the first flare-up and any subsequent intercurrent flare-ups or traumatic events during the same dosing period. Flare-Up Cycle Safety Day 1 is defined as the first day that study drug is administered for the first flare-up or traumatic event upon confirmation by the Investigator. Flare-up cycle safety assessments will be performed on Flare-up Cycle Safety Day 1 and then every 12 weeks thereafter until treatment of the last flare-up or traumatic event within a Flare-up Cycle is completed. If treatment of the last flare-up or traumatic event in a cycle resolves within 4 weeks of the last flare-up cycle safety assessment, then another flare-up cycle safety visit does not need to be performed. Once all flare-ups in a cycle have resolved and flare-up-based treatment has been completed, subjects will resume chronic treatment with 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects). It is possible that subjects may experience more than one Flare-up Cycle during the study. Note that the Flare-up Cycle Safety assessments will also be applicable to any treated high-risk traumatic event likely to lead to a flare-up. ⁴ Subjects with normal or non-clinically significant abnormal laboratory results observed within 1 month of starting flare-up-based treatment will not need to have Flare-up Cycle Safety Day 1 laboratory tests repeated. The Investigator will determine whether subjects with clinically significant abnormal laboratory results in the most recent assessment will need to be re-assessed prior to beginning flare-up-based treatment. The only exception is for pregnancy testing, which must be performed at the start of each Flare-up Cycle and every 4 weeks thereafter until treatment of the last flare-up or traumatic event is completed. However, if a pregnancy test was performed within 4 weeks prior to the start of treatment for a flare-up or traumatic event, treatment will not be delayed pending repeat pregnancy testing. ⁵ If urinalysis results are abnormal, then a microscopic evaluation should be completed. ⁶ Pregnancy testing will be performed for females of child-bearing potential. A urine pregnancy test will be performed only when a serum pregnancy test is not obtained.							

- ⁷ Subjects will be provided with the appropriate dose of study drug to be used to initiate treatment when a flare-up or traumatic event is confirmed by the Investigator. Flare-up-based treatment can begin immediately after the Investigator confirms the presence of an eligible flare-up or traumatic and prior to availability of safety laboratory results, unless the Investigator determines that the results are required prior to treatment initiation (eg, clinically significant abnormal laboratory test results requiring follow-up).
- ⁸ A flare-up, or substantial high-risk traumatic event likely to lead to a flare-up, will be treated with a minimum of 4 weeks (28 days) of 20 mg palovarotene, followed by 8 weeks (56 days) of 10 mg palovarotene (or weight-based equivalent) for a total of 12 weeks (84 days). If the flare-up has not resolved after 12 weeks, treatment will be extended in 4-week intervals until the flare-up resolves.
- ⁹ Should a subject experience an intercurrent flare-up, or substantial high-risk traumatic event likely to lead to a flare-up, at any time during flare-up-based treatment, the 12-week (84 day) dosing regimen will restart upon confirmation by the Investigator (ie, 4 weeks of 20 mg palovarotene followed by 8 weeks of 10 mg palovarotene [or weight-based equivalents]). This may occur more than once during a Flare-up Cycle.
- ¹⁰ Flare-up status will be assessed at Flare-up Day 1 for every flare-up and flare-up end date will be recorded when a flare-up resolves. Flare-up status will also be assessed at Week 12 of the initial flare-up (if only one flare-up) or the last ongoing intercurrent flare-up (if more than one flare-up); if any flare-up is still ongoing, the on-going flare-up(s) will be assessed every 4 weeks until the last flare-up has resolved.
- ¹¹ Flare-up Day 1 is the first day of treatment for a flare-up/substantial high-risk traumatic event (after confirmation by the Investigator).
- ¹² Flare-ups will be evaluated remotely, or by telephone or video-conferencing, unless the Investigator deems that a site visit is necessary. This will include subject-reported current flare-up location, symptoms, and probable causes.
- ¹³ Pharmacokinetics of palovarotene dosing will be assessed twice: once during the 20-mg regimen at any time between Study Days 4 and 28 and once during the 10-mg regimen at any time between Study Days 32 and 84, for the first treated flare-up only. If not possible for the first treated flare-up, pharmacokinetic blood samples can be obtained during any subsequent flare-up dosing up to Month 24. Blood samples will be collected at predose and 3, 6, 10, and 24 hours post-dose.

Note: study procedures that require sedation will not be performed.

Table 134. Protocol Synopsis Table 3: Study PVO-1A-301: Schedule of Assessments for Treatment Extension, Part C

Table 3. Schedule of Assessments for Part C	
Assessment/Procedure	Y1 and Y2/SC Post Treatment Site Visit¹
Informed consent ^{2, 3}	X
Knee and hand-wrist radiographs ^{4, 5}	X
Linear and knee height growth assessments (<18 years)	X
Physical examination	X
Body weight ²	X
Vital signs ²	X
Low-dose, WBCT scan (excluding head)	X
Prior/concomitant medications ²	At every subject contact
Adverse events ⁶	At every subject contact

¹ Year 1 (Y1), Year 2 (Y2) visits following the last dose of study medication will be done within the 4-year total study duration from enrolment in Part A.
Y1 to be completed in the window of ≥ 6 - <18 months post last dose of study medication. If Part A or B EOS date is within the Y1 window then the EOS will serve as the Y1 visit. If Part A or B EOS date is prior to Y1 window then Y1 should be scheduled ≥ 6 months from Part A or B EOS date but still within the Y1 window. If Y1 is completed within 6 months of when Month 48 (Part B) is to occur, then Y1 will serve as the Part C study completion (SC) visit.
Y2 to be completed ≥ 18 - 24 months post last dose of study medication and will serve as the Part C study completion (SC) visit. If Part A or B EOS date is within the Y2 window then the EOS will serve as the Y2 visit (Y2 not required) as well as the Part C study completion (SC) visit. If Part A or B EOS date or Y1 date (if applicable) is prior to Y2 window then Y2 should be scheduled ≥ 6 months from the Part A or B EOS date or the Y1 date, whichever is later, but still within the Y2 window.
If subjects had their last dose of study medication and completed Part A or B EOS more than 2 years prior to their consent for Part C, then these subjects will complete Y2 following their consent for Part C and no later than 48 months (+1 month) from Study Day 1 (first day that study drug is administered). This will serve as their Part C study completion (SC) visit and will conclude their participation in the study.

² Assessments may be performed remotely (eg, at the subject's home by qualified study personnel, at a local medical facility, or via videoconference or telephone contact from clinical site personnel) unless the Investigator deems that a site visit is necessary.

³ Part C informed consent is required prior to conducting Part C assessments/procedures.

⁴ Subjects found to be skeletally immature will continue knee and hand-wrist radiographs, and linear and knee height measurements (all in triplicate) at Year 1 (Y1) and Year 2 (Y2). Limb/joint AEs in these subjects will be evaluated by any clinical and radiographic assessments deemed appropriate by the Investigator. Once a subject has achieved 100% skeletal maturity (confirmed by radiography and defined by growth plate closures), knee and hand-wrist radiographs will no longer be required and this will serve as their Part C study completion. In addition, once a subject is 18 years old, linear and knee height growth assessments will no longer be required. If 100% skeletal maturity is not achieved at both locations, then only the location that is still maturing would need to be monitored.

⁵ Knee and hand-wrist radiograph assessments will be conducted at the clinical site unless the Investigator determines they can be performed at a local medical facility. All assessments will be performed at the clinical site if the radiographs cannot be performed locally.

⁶ At each AE assessment, the Investigator must ask the subject about any joint-related complaints.

EOS = end of study, SC = study completion

16. Efficacy: Additional Information and Assessment

Details of prespecified Bayesian analysis

There are two components of the Bayesian analysis for the annualized rate of change of new HO volume. The first component, denoted as K , is the number of body regions with new HO. The second component, denoted as Z , is the new HO volume per region where new HO has occurred. Multiplication of these two components is used to estimate the annualized new HO for each study. The treatment effect is measured by the ratio of the annualized new HO for subjects in Study 301, divided by the annualized new HO for NHS subjects. The Bayesian model only counts the occurrence of positive new HO as an event.

The number of body regions with new HO in subject i for WBCT scan j with duration w_{ij} (the time between scan j and the previous scan) is distributed as

$$K_{ij} \sim \text{Poisson}(\lambda_{i,j} * w_{ij} * \theta_{1,t(i,j)}), \text{ where}$$

$$\log(\lambda_{i,j}) = \log(\lambda_i) + \beta_1 X_{1,i} + \beta_2 X_{2,i,j}$$

The subject-level rate $\lambda_{i,j}$ is gamma distributed and accounts for correlation in measurements from the same subject; $t(i)$ is an indicator function equal to 1 if the subject was on treatment at the time of the j^{th} WBCT scan and 0 if the subject was not on treatment. The marginal distribution of the number of body regions with new HO follows a negative binomial distribution. Setting $\theta_{1,0}=1$, the variable $\theta_{1,1}$ is the multiplicative effect of palovarotene treatment on the rate of body regions with new HO. Covariates adjust for differences in the rate of new HO based on the subject's sex, $X_{1,i}$, and age at time of scan, $X_{2,i,j}$. Age at the time of scan is a factor variable equal to 0 for <18 years old and 1 for ≥ 18 years old. Covariate effects $\exp(\beta_1)$ and $\exp(\beta_2)$ are multiplicative effects of sex and age on the rate of body regions with new HO.

The new HO volume (square root of the volumetric increase in that region) in region r , $\sqrt{Z_{ijr}}$ where new HO has occurred for subject i in scan j is distributed as:

$$\sqrt{Z_{ijr}}/1000 \sim N\left(\alpha * \alpha_r * \theta_{2,t(ii)}, \frac{\alpha_r^2}{\tau_{t(ij)}}\right)$$

The variable $\theta_{2,1}$ is the multiplicative effect of palovarotene treatment on the new HO volume conditional on new HO occurring. The α_r are region-specific variables that contribute to the mean of new HO and the variance; the restrict $\alpha_r = \alpha_{r'}$ is imposed, where r and r' are a left and right region pair, (e.g., right arm versus left arm). The precision variables, τ_0 and τ_1 , allow variability to differ between new HO volume in treated subjects versus untreated subjects. The treated effect is $\gamma = \theta_{1,1} * \theta_{2,1}$. The priors for variables in Bayesian Compound Poisson Distribution are as follows:

The prior distribution for subject level rate λ_i is Gamma(a , b) where a and b are in turn both distributed as Gamma(1,1).

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The prior distribution for the covariate coefficients β_1 and β_2 for sex and age respectively is $N(0, 2^2)$.

$\alpha \sim N(0, 1)$

$\alpha_r \sim \text{Uniform}(0, 4)$

$\tau_0, \tau_1 \sim \text{Gamma}(1, 0.01)$

$\theta_{1,1}, \theta_{2,1} \sim \text{Uniform}(0, 2)$

Additional Analyses on Influence of Large Values

Table 135. wLME for Annualized New HO Volume (No Square-Root Transformation and Negatives Included) for Palovarotene-treated and Untreated Subjects, Replacing Annualized New HO >100 cm³ with 100 cm³ (Principal FAS)

	Study 301 N=97	NHS N=101	Difference (95% CI)	P-Value
Threshold analysis (HO volumes >100 cm ³ set to 100 cm ³)	8.7	17.7	-9.1(-15.8, -2.3)	0.01

Source: Table 25 in ISE.

The annualized new HO wLME LSmean estimate and SEM are from a mixed model with dependent variable annualized new HO and independent variables including fixed effects of treatment and baseline total HO/baseline age and a random subject effect. Wilcoxon p-value 0.0003

Abbreviations: CI, confidence interval; FAS, full analysis set; HO, heterotopic ossification; N, number of subjects; NHS, natural history study

Similar analyses with different thresholds from 90 cm³ (new HO >90 cm³ set to 90 cm³) to 5 cm³. Results were nominally significant.

Table 136. Sensitivity Analyses on Influence of Large Values

Threshold (cm ³)	Study 301	NHS	Difference	LCL	UCL	p-value
100 (Table 25 in ISE)	8.686	17.742	-9.057	-15.848	-2.266	0.01
90	8.5	17.3	-8.8	-15.4	-2.2	0.01
70	8.0	15.6	-7.6	-13.5	-1.7	0.0125
50	7.0	13.6	-6.5	-11.4	-1.7	0.01
30	4.8	10.3	-5.5	-9.1	-1.8	0.004
10	1.2	4.85	-3.6	-5.5	-1.7	0.0004
5	-0.2	2.6	-2.8	-4.2	-1.4	0.0003

Source: FDA reviewers' analyses

Analyses of New HO with different thresholds from 90 cm³ (new HO >90 cm³ set to 90 cm³) to 5 cm³. New HO values exceeding threshold value were set to the threshold value. The annualized new HO wLME LSmean estimate and SEM are from a mixed model with dependent variable annualized new HO and independent variables including fixed effects of treatment and baseline total HO/baseline age and a random subject effect.

Abbreviations: ISE, integrated summary of effectiveness; LCL, lateral collateral ligament; NHS, natural history study, UCL, ulnar collateral ligament

Baseline Balance Assessments Before and Propensity Score Weighting

Table 137. Summary of Balance Before Propensity Score Weighting

Variable	Study 301		Standardized Mean Difference	Variance Ratio
	Means (N=97)	NHS Means (N=101)		
Propensity score, mean (min, max)	0.52 (0.2, 0.67)	0.48 (0.17, 0.67)	0.42	0.80
Baseline Age	15.08	18.00	-0.33	0.79
Female (%)	0.47	0.45	0.04	1
Baseline rate of HO	13.38	16.30	-0.22	0.88
CAJIS	9.80	12.07	-0.38	0.68
Time since last flare up (month)	22.86	19.32	0.11	1.02

Source: FDA reviewer

A standardized mean difference between -0.2 and 0.2 indicates good balance. Baseline rate of HO is the baseline total HO divided by age.

Abbreviations: CAJIS, Cumulative Analogue Joint Involvement Scale; HO, heterotopic ossification; NHS, natural history study

Table 138. Summary of Balance After Propensity Score Weighting

Variable	Study 301		Standardized Mean Difference	Variance Ratio
	Means (N=97)	NHS Means (N=101)		
Propensity score, mean (min, max)	0.5 (0.2, 0.67)	0.5 (0.17, 0.67)	0	1.14
Age	16.83	16.60	0.025	1.32
Female (%)	0.45	0.45	0	1.0
Baseline rate of HO	15.17	15.11	0.0046	1.1
CAJIS	10.98	10.92	0.0091	0.89
Time since last flare up (month)	21.64	21.09	0.017	0.83

Source: FDA reviewer

A standardized mean difference between -0.2 and 0.2 indicates good balance. Baseline rate of HO is the baseline total HO divided by age.

Abbreviations: CAJIS, Cumulative Analogue Joint Involvement Scale; HO, heterotopic ossification; NHS, natural history study

Table 139. Summary of Balance After 1:1 Nearest Neighbor Matching

Variable	Study 301		Standardized Mean Difference	Variance Ratio
	Means (N=61)	NHS Means (N=61)		
Propensity score	0.51	0.51	0.04	1
Age	15.70	15.15	0.062	1.27
Female (%)	0.39	0.39	0	1.0
Baseline rate of HO	13.70	13.11	0.045	1.22
CAJIS	10.49	10.18	0.052	0.72
Time since last flare up (month)	21.18	18.40	0.21	0.93

Source: FDA reviewer

A standardized mean difference between -0.2 and 0.2 indicates good balance. Baseline rate of HO is the baseline total HO divided by age. Exact match on sex and age group (<12;12 to <18;>=18)

Nearest neighbor with caliper 0.2 on other covariates; N=61 matched

Abbreviations: CAJIS, Cumulative Analogue Joint Involvement Scale; HO, heterotopic ossification; NHS, natural history study.

17. Clinical Safety: Additional Information and Assessment

17.1. Study PVO-1A-201: Safety Tables

Table 140, [Table 141](#), and [Table 142](#) below summarize data in the target indication population (FOP patients age $\geq 8/10$ years). All subject completed the 6-week course of treatment; there were no discontinuations due to an adverse event (AE) or other reason. There was one SAE of vessel puncture site pain in a subject receiving the 10/5 regimen.

Table 140. Baseline Demographic and Clinical Characteristics, Safety Population, Age at First Entry $\geq 8/10$ Years (FAS), Trial PVO-1A-201

Characteristic	Placebo N=10	PVO 5/2.5 mg N=7	PVO 10/5 mg N=19
Sex, n (%)			
Female	7 (70.0)	5 (71.4)	9 (47.4)
Male	3 (30.0)	2 (28.6)	10 (52.6)
Age, years			
Mean (SD)	21.2 (13.7)	20.7 (7.6)	24.2 (9.7)
Median (min, max)	15.5 (9, 53)	22 (10, 29)	22 (11, 44)
Age group, years, n (%)			
<14	3 (30.0)	2 (28.6)	1 (5.3)
≥ 14	7 (70.0)	5 (71.4)	18 (94.7)
Race, n (%)			
Asian	1 (10.0)	0	0
Black or African American	0	1 (14.3)	1 (5.3)
Multiple	0	0	2 (10.5)
Not Available	3 (30.0)	0	5 (26.3)
White	6 (60.0)	6 (85.7)	11 (57.9)
Ethnicity, n (%)			
Hispanic or Latino	1 (10.0)	1 (14.3)	2 (10.5)
Not Hispanic or Latino	6 (60.0)	6 (85.7)	12 (63.2)
Not Reported	3 (30.0)	0	5 (26.3)
Country of participation, n (%)			
France	3 (30.0)	0	5 (26.3)
Great Britain	1 (10.0)	1 (14.3)	0
United States	6 (60.0)	6 (85.7)	14 (73.7)

Source: adsl.xpt; Software: R

Abbreviations: N, number of patients in treatment group; n, number of patients with given characteristic; PVO, palovarotene; SD, standard deviation

Table 141. Overview of Adverse Events, Safety Population, Age at First Entry $\geq 8/10$ Years (FAS), Trial PVO-1A-201

Event Category	PVO 5/2.5 mg vs. Placebo			PVO 10/5 mg vs. Placebo	
	Placebo N=10 n (%)	PVO 5/2.5 mg N=7 n (%)	Risk Difference (%) (95% CI)	PVO 10/5 mg N=19 n (%)	Risk Difference (%) (95% CI)
SAE *	0	0	0 (0, 0)	1 (5.3)	5.3 (-4.8, 15.3)
SAEs with fatal outcome	0	0	0 (0, 0)	0	0 (0, 0)
Life-threatening SAEs	0	0	0 (0, 0)	0	0 (0, 0)
AE leading to permanent discontinuation of study drug	0	0	0 (0, 0)	0	0 (0, 0)
AE leading to dose modification of study drug	1 (10.0)	0	-10.0 (-28.6, 8.6)	1 (5.3)	-4.7 (-25.9, 16.4)
AE leading to interruption of study drug	1 (10.0)	0	-10.0 (-28.6, 8.6)	1 (5.3)	-4.7 (-25.9, 16.4)
AE leading to reduction of study drug	0	0	0 (0, 0)	0	0 (0, 0)
AE leading to dose delay of study drug	0	0	0 (0, 0)	0	0 (0, 0)
Other	0	0	0 (0, 0)	0	0 (0, 0)
Any AE	10 (100)	7 (100)	0 (0, 0)	19 (100)	0 (0, 0)
Severe and worse	0	0	0 (0, 0)	0	0 (0, 0)
Moderate	2 (20.0)	2 (28.6)	8.6 (-33.1, 50.2)	8 (42.1)	22.1 (-11.2, 55.4)
Mild	8 (80.0)	5 (71.4)	-8.6 (-50.2, 33.1)	11 (57.9)	-22.1 (-55.4, 11.2)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that developed or worsened after administration of the first dose of study drug to the end of dosing as follows: (first dose date) $\leq$ (AE start date) $\leq$ (last dose date) +7 days. For the FOP-FAS, TEAEs also included AEs after enrollment for subjects in Study PVO-1A-202/Part A who were not dosed due to the absence of a flare-up. Duration is 6 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Severity as assessed by the investigator.

*SAE count shown differs from the CSR due to differing TEAE definitions between the ISS datasets (used in this report) and individual study datasets.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; PVO, palovarotene; SAE, serious adverse event

Table 142. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Age at First Entry ≥8/10 Years (FAS), Trial PVO-1A-201

System Organ Class FMQ (Narrow)	Placebo N=10 n (%)	PVO 5/2.5 mg N=7 n (%)	PVO 5/2.5 mg vs. Placebo Risk Difference (%) (95% CI)	PVO 10/5 mg N=19 n (%)	PVO 10/5 mg vs. Placebo Risk Difference (%) (95% CI)
Blood and lymphatic system disorders (SOC)					
Anemia	1 (10.0)	0	-10.0 (-28.6, 8.6)	1 (5.3)	-4.7 (-25.9, 16.4)
Endocrine disorders (SOC)					
Hyperglycemia	1 (10.0)	0	-10.0 (-28.6, 8.6)	0	-10.0 (-28.6, 8.6)
Gastrointestinal disorders (SOC)					
Dry Mouth	1 (10.0)	3 (42.9)	32.9 (-8.2, 74.0)	6 (31.6)	21.6 (-6.4, 49.6)
Diarrhea	0	0	0 (0, 0)	3 (15.8)	15.8 (-0.6, 32.2)
Nausea	2 (20.0)	0	-20.0 (-44.8, 4.8)	5 (26.3)	6.3 (-25.4, 38.0)
Constipation	0	1 (14.3)	14.3 (-11.6, 40.2)	0	0 (0, 0)
Dyspepsia	1 (10.0)	0	-10.0 (-28.6, 8.6)	0	-10.0 (-28.6, 8.6)
Vomiting	2 (20.0)	0	-20.0 (-44.8, 4.8)	1 (5.3)	-14.7 (-41.5, 12.0)
Abdominal Pain	2 (20.0)	0	-20.0 (-44.8, 4.8)	0	-20.0 (-44.8, 4.8)
General disorders and administration site conditions (SOC)					
Dizziness	0	1 (14.3)	14.3 (-11.6, 40.2)	2 (10.5)	10.5 (-3.3, 24.3)
Local Administration Reaction	0	0	0 (0, 0)	2 (10.5)	10.5 (-3.3, 24.3)
Peripheral Edema	0	0	0 (0, 0)	2 (10.5)	10.5 (-3.3, 24.3)
Fatigue	0	1 (14.3)	14.3 (-11.6, 40.2)	1 (5.3)	5.3 (-4.8, 15.3)
Pyrexia	1 (10.0)	2 (28.6)	18.6 (-19.7, 56.9)	0	-10.0 (-28.6, 8.6)
Infections and infestations (SOC)					
Viral Infection	0	0	0 (0, 0)	2 (10.5)	10.5 (-3.3, 24.3)
Nasopharyngitis	0	2 (28.6)	28.6 (-4.9, 62.0)	1 (5.3)	5.3 (-4.8, 15.3)
Bacterial Infection	1 (10.0)	0	-10.0 (-28.6, 8.6)	0	-10.0 (-28.6, 8.6)
Metabolism and nutrition disorders (SOC)					
Lipid Disorder	0	1 (14.3)	14.3 (-11.6, 40.2)	1 (5.3)	5.3 (-4.8, 15.3)
Musculoskeletal and connective tissue disorders (SOC)					
Back Pain	0	0	0 (0, 0)	1 (5.3)	5.3 (-4.8, 15.3)
Arthralgia	5 (50.0)	1 (14.3)	-35.7 (-76.1, 4.7)	9 (47.4)	-2.6 (-40.9, 35.6)
Myalgia	1 (10.0)	0	-10.0 (-28.6, 8.6)	1 (5.3)	-4.7 (-25.9, 16.4)
Nervous system disorders (SOC)					
Headache	3 (30.0)	1 (14.3)	-15.7 (-54.2, 22.7)	7 (36.8)	6.8 (-28.9, 42.6)
Paresthesia	1 (10.0)	1 (14.3)	4.3 (-27.6, 36.2)	0	-10.0 (-28.6, 8.6)

System Organ Class FMQ (Narrow)	Placebo N=10 n (%)	PVO 5/2.5 mg N=7 n (%)	PVO 5/2.5 mg vs. Placebo Risk Difference (%) (95% CI)	PVO 10/5 mg N=19 n (%)	PVO 10/5 mg vs. Placebo Risk Difference (%) (95% CI)
Psychiatric disorders (SOC)					
Insomnia	0	0	0 (0, 0)	1 (5.3)	5.3 (-4.8, 15.3)
Irritability	0	0	0 (0, 0)	1 (5.3)	5.3 (-4.8, 15.3)
Parasomnia	0	0	0 (0, 0)	1 (5.3)	5.3 (-4.8, 15.3)
Renal and urinary disorders (SOC)					
Renal and Urinary Tract Infection	1 (10.0)	0	-10.0 (-28.6, 8.6)	0	-10.0 (-28.6, 8.6)
Respiratory, thoracic and mediastinal disorders (SOC)					
Cough	0	0	0 (0, 0)	1 (5.3)	5.3 (-4.8, 15.3)
Skin and subcutaneous tissue disorders (SOC)					
Pruritus	1 (10.0)	1 (14.3)	4.3 (-27.6, 36.2)	8 (42.1)	32.1 (3.1, 61.1) *
Rash	0	2 (28.6)	28.6 (-4.9, 62.0)	3 (15.8)	15.8 (-0.6, 32.2)
Erythema	0	2 (28.6)	28.6 (-4.9, 62.0)	2 (10.5)	10.5 (-3.3, 24.3)
Alopecia	0	0	0 (0, 0)	1 (5.3)	5.3 (-4.8, 15.3)
Vascular disorders (SOC)					
Hemorrhage	0	4 (57.1)	57.1 (20.5, 93.8) *	2 (10.5)	10.5 (-3.3, 24.3)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that developed or worsened after administration of the first dose of study drug to the end of dosing as follows: (first dose date) ≤ (AE start date) ≤ (last dose date) +7 days. For the FOP-FAS, TEAEs also included AEs after enrollment for subjects in Study PVO-1A-202/Part A who were not dosed due to the absence of a flare-up.

Duration is 6 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PVO, palovarotene; SOC, system organ class

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Not applicable.

19. Other Drug Development Considerations: Additional Information and Assessment

Not applicable.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

Inspections of the following clinical site investigators were conducted: Dr. Edward Hsiao (Studies 001, 201, 202, 301); Dr. Mona Al Mukaddam (Studies 001, 202, 301); and Dr. Edna Mancilla (Study 301). Dr. Hsiao was issued a Form 483 (VAI) regarding several late-reported SAEs; these were all reported and there were no concerns raised regarding data integrity. The other two inspections were NAI.

21. Labeling Summary of Considerations and Key Additional Information

Not applicable as this application will receive a complete response.

22. Postmarketing Requirements and Commitments

The following postmarketing requirements (PMR)/postmarketing commitments (PMC) were communicated to the Applicant during the review cycle should this application be approved. The PMRs/PMCs listed below would not be required to be addressed in a complete response resubmission of this application and may continue to be addressed in the postmarketing period should this application be approved in the future.

Nonclinical

Conduct carcinogenicity studies in two species to assess the carcinogenic potential from long-term oral exposure to palovarotene.

Clinical Pharmacology

PMR: Conduct a clinical study to evaluate the impact of hepatic impairment on the pharmacokinetics of palovarotene in subjects with moderate (Child- Pugh B) and severe (Child- Pugh C) hepatic impairment relative to healthy adult subjects with normal hepatic function, in accordance with the study design described in guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003). Submit the subject-level datasets with the final report.

PMC: Conduct a clinical drug-drug interaction study to evaluate the effect of a moderate CYP3A4 inducer on the pharmacokinetics of palovarotene in healthy adult subjects, to assess the magnitude of exposure change of palovarotene, and to determine the appropriate dosing recommendations for palovarotene when used concomitantly with a moderate CYP3A4 inducer. Design and conduct the study in accordance with the guidance for industry *Clinical Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*. Submit the patient-level datasets with the final report.

Clinical

The review team is considering whether a long-term safety study would be beneficial given the prolonged flare-up dosing in some subjects that occurred in Study PVO-1A-301. The higher flare-up dosing for prolonged periods of time may predispose patients to adverse events associated with retinoids.

23. Financial Disclosure

Table 143. Covered Clinical Studies: Studies 201, 202A/B/C, 301, NHS

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 139		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): none		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

24. References

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Guidance for Industry

Draft Guidance for Industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

Guidance for Industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010)

Guidance for Industry *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry* (January 2020)

25. Review Team

Table 144. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Noreen Cabellon, MS
Nonclinical Reviewer	Lydia Haile, PhD
Nonclinical Team Leader	David Carlson, PhD
Office of Clinical Pharmacology Reviewer(s)	Xiaomeng Xu, PhD; Xiaolei Pan, PhD; Elyes Dahmane, PhD; Ying-Hong Wang, PhD; Peng Zou, PhD*
Office of Clinical Pharmacology Team Leader(s)	Justin Earp, PhD; Manuela Grimstein, PhD; Amal Ayyoub, PhD*
Clinical Reviewer	Stephen Voss, MD
Clinical Team Leader	Theresa Kehoe, MD; Shannon Sullivan, MD, PhD
Statistical Reviewer	Alexander Cambon, PhD
Statistical Team Leader	Feng Li, PhD
Cross-Disciplinary Team Leader	Theresa Kehoe, MD
Division Director (pharm/tox)	Todd Bourcier, PhD
Division Director (OCP)	Jaya Vaidyanathan, PhD
Division Director (OB)	Mark Rothmann, PhD
Division Director (clinical)	Theresa Kehoe, MD
Office Director (or designated signatory authority)	Lisa Yanoff, MD

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

* Former reviewer who drafted and contributed to the review while employed at FDA

Table 145. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Joseph Leginus, PhD Suong Tran, PhD Ali Mohamadi, PhD Akm Khairuzzaman, PhD Xueli Zhu, PhD Erin Kim, PhD Parnali Chatterjee, PhD Haritha Mandula, PhD Caryn McNab Nowrin Kakon, MLS (ASCP) ^{CM}
OPDP	Meena Savani, PharmD
DMPP	Nyedra Booker, PharmD, MPH
OSI	Ling Yang, MD, PhD Min Lu, MD, PhD
OSE/DEPI	Po-Yin Chang, PhD Yandong Qiang, MD, PhD, MHS, MPH
OSE/DMEPA	Corwin Howard, PharmD Madhuri Patel, PharmD
OSE/DRM	Cristen Lambert, PharmD Yasmeen Abou-Sayed, PharmD Laura Zendel, PharmD
OSE/DPV	Amy Chen, PharmD Ali Niak, MD Daniel Woronow, MD
DPMH	Ethan Hausman, MD Shetarra Walker, MD Jeannie Limpert, MD Tamara Johnson, MD
Clinical Data Scientist	Zachary Moldwin, PharmD Deangelo McKinley

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DMPP: Division of Medical Policy Programs; DRM, Division of Risk Management; DPV: Division of Pharmacovigilance; DPMH: Division of Pediatrics and Maternal Health; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Table 146. Signatures of Reviewers

See next page for signature table.

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Lisa B. Yanoff, MD	OND/OCHEN	All sections ☐ Authored ☐ Contributed ☒ Approved
Signatory Authority	Signature: {See appended electronic signature page}		
Clinical	Theresa E. Kehoe, MD	OND/OCHEN/ DGE	All sections ☐ Authored ☐ Contributed ☒ Approved
Cross-Disciplinary Team Lead	Signature: {See appended electronic signature page}		
Clinical	Shannon Sullivan, MD, PhD	OND/OCHEN/ DGE	☒ Authored 1, 2, 11 ☒ Contributed 3, 6, 7, 9, 10, 12, 15, 17, 20, 23 ☒ Approved All Sections
Team Leader	Signature: Shannon D. Sullivan -S Digitally signed by Shannon D. Sullivan -S Date: 2022.12.22 12:32:05 -05'00'		
Clinical	Stephen Voss, MD	OND/OCHEN/ DGE	☒ Authored 3, 6.2.2, 6.3.3, 6.3.4, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 10, 15, 17, 20, 23 ☒ Contributed 1,2, 6.2.1, 6.3.2, ☐ Approved
Reviewer	Signature: Stephen R. Voss -S Digitally signed by Stephen R. Voss -S Date: 2022.12.22 11:32:21 -05'00'		
Regulatory Project Management	Elisabeth Hanan, MS	OND/ORO/ DROCHEN	Section 12 ☒ Authored ☒ Approved
Chief, Project Management Staff	Signature: Elisabeth Hanan -S Digitally signed by Elisabeth Hanan -S Date: 2022.12.22 10:44:26 -05'00'		
Regulatory Project Management	Noreen Cabellon, MS	OND/ORO/ DROCHEN	Section 12 ☒ Authored ☐ Approved
Regulatory Project Manager	Signature: Noreen N. Cabellon -S Digitally signed by Noreen N. Cabellon -S Date: 2022.12.22 10:37:21 -05'00'		

Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Pharmacology/ Toxicology	Todd Bourcier, PhD	OND/OCHEN/ DPTCHEN	Section 5.1, 7.1, 7.7, 8.3, 8.4, 13, 22 ☐ Authored ☐ Contributed ☒ Approved
Division Director	Signature: Todd M. Bourcier -S Digitally signed by Todd M. Bourcier -S Date: 2022.12.21 09:57:50 -05'00'		
Pharmacology/ Toxicology	David Carlson, PhD	OND/OCHEN/ DPTCHEN	☐ Authored ☒ Contributed 7, 13, 22 ☒ Approved 5, 7, 8, 13, 22
Supervisor	Signature: David B. Carlson -S Digitally signed by David B. Carlson -S Date: 2022.12.21 09:42:28 -05'00'		
Pharmacology/ Toxicology	Lydia Haile, PhD	OND/OCHEN/ DPTCHEN	☒ Authored 7, 13 ☒ Contributed 5, 8, 22 ☐ Approved
Reviewer	Signature: Lydia A. Haile -S Digitally signed by Lydia A. Haile -S Date: 2022.12.21 09:11:33 -05'00'		
Clinical Pharmacology	Jayabharathi Vaidyanathan, PhD	OTS/OCP/DCEP	Section 5, 6.1, 8.1, 8.2, 14.1, 14.2, 14.5 ☐ Authored ☐ Contributed ☒ Approved
Associate Director	Signature: Jayabharath Vaidyanathan -S Digitally signed by Jayabharath Vaidyanathan -S Date: 2022.12.21 10:25:05 -05'00'		
Clinical Pharmacology	Xiaomeng Xu, PhD	OTS/OCP/DCEP	☒ Authored 5, 8.1, 8.2, ☒ Contributed 5, 6.1, 8.1, 8.2, 14.1, 14.2, 14.5 ☐ Approved
Reviewer	Signature: Xiaomeng Xu -S Digitally signed by Xiaomeng Xu Date: 2022.12.21 10:05:07 -05'00'		
Clinical Pharmacology /Pharmacometrics	Justin Earp, PhD	OTS/OCP/DPM	Section 5.1, 6.1, 7.7, 8.1, 14.3 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	Signature: Justin C. Earp -S Digitally signed by Justin C. Earp -S Date: 2022.12.21 15:59:09 -05'00'		

Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology/ Pharmacometrics	Xiaolei Pan, PhD	OTS/OCP/DPM	Section 5.1, 6.1, 7.7, 8.1, 14.3 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	Signature: Xiaolei Pan -S Digitally signed by Xiaolei Pan -S Date: 2022.12.21 10:56:17 -05'00'		
Clinical Pharmacology/ Pharmacometrics	Elyes Dahmane, PhD	OTS/OCP/DPM	Section 8.1, 14.3 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	Signature: Elyes Dahmane -S Digitally signed by Elyes Dahmane -S Date: 2022.12.21 10:36:02 -05'00'		
Clinical Pharmacology/ Pharmacometrics	Manuela Grimstein, PhD	OTS/OCP/DPM	Section 8.1, 8.2, 14.4 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	Signature: Yuching Yang -S Digitally signed by Yuching Yang -S Date: 2022.12.21 15:22:29 -05'00' On behalf of Manuela Grimstein		
Clinical Pharmacology/ Pharmacometrics	Ying-Hong Wang, PhD	OTS/OCP/DPM	Section 8.1, 8.2, 14.4 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	Signature: Ying-hong Wang -S Digitally signed by Ying-hong Wang -S Date: 2022.12.21 16:20:52 -05'00'		
Statistical	Mark Rothmann, PhD	OTS/OB/DBII	Sections 6.2.1, 6.3.1, 6.3.2, 16 ☐ Authored ☐ Contributed ☒ Approved
Division Director	Signature: Yun Wang -S Digitally signed by Yun Wang -S Date: 2022.12.22 10:29:16 -05'00' On behalf of Mark Rothmann		
Statistical	Feng Li, PhD	OTS/OB/DBII	Sections 6.2.1, 6.3.1, 6.3.2, 16 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	Signature: Feng Li -S Digitally signed by Feng Li -S Date: 2022.12.22 08:03:52 -05'00'		

Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Statistical	Alexander Cambon, PhD	OTS/OB/DBII	Sections 6.2.1, 6.3.1, 6.3.2, 16 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	Signature: Alexander Cambon - S Digitally signed by Alexander Cambon -S Date: 2022.12.22 07:13:48 -05'00'		

Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THERESA E KEHOE
12/22/2022 02:34:25 PM

LISA B YANOFF
12/23/2022 08:18:49 AM