PALOVAROTENE FOR THE PREVENTION OF HETEROTOPIC OSSIFICATION IN ADULTS AND CHILDREN (≥ 8 YEARS OF AGE FOR FEMALES AND ≥ 10 YEARS OF AGE FOR MALES) WITH FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (FOP)

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

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List of Abbreviations

Abbreviation	Definition
ACVR1	Activin receptor type 1A
AE	Adverse event
ALK2	Activin receptor-like kinase 2
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BCa	Bias-corrected and accelerated
BCT	Biomechanical computed tomography
BMC	Bone mineral content
BMD	Bone mineral density
BMP	Bone morphogenetic protein
CAJIS	Cumulative Analogue Joint Involvement Scale
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COX-2	Cyclooxygenase-2
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed tomography
CYP	Cytochrome P450
DXA	Dual-energy x-ray absorptiometry
ECG	Electrocardiogram
EOS	End of study
FAS	Full analysis set
FDA	Food and Drug Administration
FOP	Fibrodysplasia ossificans progressiva
FOP-PFQ	FOP-Physical Function Questionnaire
GEE	Generalized Estimating Equations
HCP	Healthcare professional
HED	Human equivalent dose
HO	Heterotopic ossification
IA	Interim Analysis
ICC	International Clinical Council
IND	Investigational New Drug
ITT	Intent-to-Treat

MO	Multiple osteochondromas
NDA	New Drug Application
NHS	Natural History Study
NSAID	Non-steroidal anti-inflammatory drug
PCS	Potentially clinically significant
PK	Pharmacokinetics
PopPK	Population Pharmacokinetics
PPC	Premature physeal closure
PRO	Patient-reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System
PT	Preferred term
RARα	Retinoic acid receptor alpha
RARβ	Retinoic acid receptor beta
RARγ	Retinoic acid receptor gamma
SAE	Serious adverse event
SAP	Statistical Analysis Plan Version 1.2
SD	Standard deviation
SMQ	Standardized Medical Dictionary for Regulatory Activities queries
SOC	System Organ Class
TIS	Thoracic insufficiency syndrome
TGFβ	Transforming growth factor β
TQT	Thorough QT
ULN	Upper limit of normal
US	United States
VFA	Vertebral fracture assessment
WBCT	Whole-body computed tomography
wLME	Weighted linear mixed effects model

1 EXECUTIVE SUMMARY

Palovarotene is an orally bioavailable retinoic acid receptor gamma (RARγ) selective agonist that reduces new heterotopic ossification (HO) to change the progressive and irreversible trajectory of fibrodysplasia ossificans progressiva (FOP). FOP is an ultra-rare, severely disabling, genetic disease that begins in childhood and eventually leads to complete immobilization and decreased life expectancy. In patients with FOP, non-skeletal soft tissues (including muscle, tendons, and ligaments) are progressively replaced by mature bone, resulting in HO that accumulates throughout the body. Eventually, this process results in ankylosis of virtually all joints, locking them into place and rendering movement impossible. Over time, the chest cavity becomes rigid, and restrictive pulmonary disease ensues with secondary effects on cardiopulmonary function, which can lead to premature death. Additional consequences of HO can include compromise of neurovascular structures, leading to nerve compression with entrapment neuropathies, severe pain, and compartment syndrome, as well as development of pressure ulcers and tissue necrosis over protruding HO lesions.

Beginning in early childhood, patients with FOP experience flare-ups that are characterized by pain, swelling, and other signs of inflammation and frequently lead to HO formation. In a retrospective survey of 500 patients with FOP, the mean number of flare-ups reported in the previous 12 months was 1.9 (median 1.0; range of 0 to 7) (Pignolo et al 2016). Flare-ups of FOP can be caused by insults like blunt muscle trauma, surgery, or viral illness, but approximately 50% of flare-ups occur spontaneously without any known precipitating cause (Pignolo et al 2016).

Currently, there are no Food and Drug Administration (FDA)-approved treatment options to prevent HO or slow disease progression in patients with FOP. Treatment primarily involves short courses of high-dose corticosteroids for flare-ups and maintenance with non-steroidal anti-inflammatory drugs (NSAIDs); however, no data have shown that these medications reduce HO or mitigate disease progression (Kaplan et al 2022).

FOP is caused by a gain-of-function variant in the activin receptor type 1A/activin receptor-like kinase 2 (*ACVR1/ALK2*) gene that causes hyperactive bone morphogenetic protein (BMP) signaling, which, in turn, leads to HO formation. Palovarotene targets the altered signaling of the receptor, thereby reducing HO formation in patients with FOP. Palovarotene has received Orphan Drug, Rare Pediatric Disease, Fast-Track, and Breakthrough Therapy Designations for FOP.

Ipsen Biopharmaceuticals, Inc (Ipsen) has submitted a New Drug Application (NDA) for palovarotene for the prevention of HO in adults and children (≥ 8 years of age for females and ≥ 10 years of age for males) with FOP. Given the current understanding of the effect of palovarotene, the Sponsor is prepared to modify the labeled indication from “for the prevention of HO” to “to reduce the formation of HO.”

The target population (≥ 8 years of age for females and ≥ 10 years of age for males) is being proposed to optimize benefit-risk and mitigate the potential consequences of the PPC in the youngest of patients, while still being able to intervene at an early stage of disease progression (note that a partial clinical hold was instituted by the FDA in patients less than 14 years of age due to the PPC finding).

Per the proposed label, patients will receive 5 mg palovarotene once daily. When symptoms associated with a flare-up are reported, or at the time of a traumatic event, chronic dosing is stopped, and the flare-up regimen is initiated. For flare-ups, patients will receive palovarotene 20 mg once daily for 4 weeks followed by 10 mg once daily for 8 weeks. If flare-up symptoms persist beyond 12 weeks, patients can receive treatment extensions in 4-week increments. At the completion of the flare-up dosing regimen, chronic dosing should resume at 5 mg once daily. Dosing will be weight adjusted (details provided in Section 9.3).

Data from the palovarotene clinical program support the proposed chronic and flare-up dosing regimen. In the Phase 2 program, imaging assessed within 7 days of the onset of flare-up showed substantial soft tissue edema, muscle necrosis, and immature HO, demonstrating that HO formation may begin before clinical symptoms present. Therefore, chronic daily treatment was implemented to ensure exposure to palovarotene at the very start of HO formation. Multiple flare-up dosing regimens were evaluated in the Phase 2 studies, and the emerging data suggested that higher doses over longer duration were required to maximally inhibit HO formation. These learnings, along with the nonclinical data, informed that chronic daily palovarotene treatment in combination with increased flare-up dosing upon symptom onset would provide the optimal approach to reduce HO formation.

Prior to the palovarotene development program, efficacy endpoints for use in interventional studies in FOP had never been established, and precedent-setting controlled clinical trials had never been conducted. Study PVO-1A-001 (hereafter referred to as the Natural History Study [NHS]) was the first longitudinal, non-interventional study describing FOP disease characteristics, prospectively evaluating disease progression over 3 years, and assessing the impact of flare-ups on FOP outcomes in 114 patients with FOP. From the NHS, it was determined that HO formation as evaluated by computed tomography (CT) imaging is the only endpoint that is sufficiently sensitive to demonstrate disease progression over the timeframe of a clinical trial to inform efficacy of potential therapeutics. The use of HO formation as a primary endpoint is now widely accepted as the endpoint of choice in this condition (Hsiao et al 2019), and to date all subsequent interventional clinical trials in FOP have used HO formation as a primary efficacy endpoint measure. Additionally, HO formation is an objective endpoint that is the pathognomonic feature of FOP and was shown to correlate with worse physical function (details provided in Section 5.1).

Given the large data set collected in the NHS within the context of an ultra-rare disease, the NHS served as the control arm for the pivotal Phase 3 Study PVO-1A-301 (hereafter

referred to as Study 301). Recognizing the challenges of relying on a natural history comparator, several important characteristics make the NHS an appropriate control group for Study 301. Both studies enrolled comparable FOP patients, and all of the clinical sites that participated in the NHS also participated in Study 301 and followed the same standard of care for treatment of FOP. Importantly, both studies included new HO volume as an objective, standardized outcome assessment that allowed for concurrent blinded interpretation by a central imaging lab.

Study 301 was a multicenter, open-label, Phase 3 study in patients with FOP treated with palovarotene at the proposed dosing regimen for approval (5 mg chronic + 20/10 mg flare-up). Study 301 is the largest prospective longitudinal study evaluating a potential therapeutic in this ultra-rare disease. Together with the NHS, it enrolled approximately 20% of the known FOP global population.

Efficacy assessments, including whole-body computed tomography (WBCT) scans, were conducted every 6 months in Study 301 and every 12 months in the NHS. The primary efficacy endpoint in Study 301 was the annualized change in new HO volume as assessed by low-dose WBCT scan. Based on the pre-specified statistical analysis plan (SAP) for Study 301, 3 interim efficacy analyses were conducted. The original protocol included a weighted linear mixed effects model (wLME) to analyze mean annualized new HO; however, this analysis was later amended to use a Bayesian analysis with a square-root transformation in an attempt to partition the variability in the data and allow more precise estimation of the treatment effects, while reducing the influence of extreme values in HO volume. The Bayesian analysis with square-root transformation at Interim Analysis 2 (IA2) predicted a 4.9% probability that palovarotene would reduce annual mean new HO by > 30% on the square-root scale (~50% on a standard scale), thereby crossing the futility boundary, and an 80% probability that palovarotene would reduce annual mean volume of new HO compared with untreated patients data. As such, administration of palovarotene was paused in patients ≥ 14 years of age (patients younger than 14 years were already paused due to the partial clinical hold) at IA2, and the study data were unblinded. It was realized that a bias was introduced due to the different WBCT visit schedules in the NHS and in Study 301, in conjunction with the square-root transformation, masking the true treatment effect of palovarotene.

This bias can be reduced by either harmonizing the visit schedules, or through analysis without square-root transformation. When appropriately accounting for the different visit schedules, the pre-specified Bayesian model predicted a 91% probability that palovarotene would reduce mean annualized new HO compared with no treatment at Interim Analysis 3 (IA3). When removing the square-root transformation, the model predicted a 99% probability that palovarotene would reduce any new HO compared with no treatment. Additionally, both this Bayesian analysis and any analysis using a square-root transformation cannot accommodate reductions in HO volume over time, i.e. negative new HO volumes. These values were set to zero in these analyses. Post hoc analyses of the raw data at IA2 using the original primary wLME model without square-

root transformation showed a large (59%) reduction in mean annualized new HO in palovarotene-treated patients compared with untreated patients. Based on the totality of the evidence from IA2, eligible patients reinitiated dosing with palovarotene (details in Section 5.3.4). The learnings from the analysis of the IA2 data were incorporated into the larger IA3 dataset as described below.

At IA3, the wLME model showed that palovarotene-treated patients achieved a 54% reduction in mean annualized new HO volume compared with untreated patients (nominal p-value=0.0392). In the target population of females ≥ 8 years of age and males ≥ 10 years of age, palovarotene-treated patients achieved a 49% reduction in new HO volume compared with untreated patients (nominal p-value=0.1124) using this wLME model. Additional wLME analyses performed on data from the 39 patients who transitioned from the NHS to Study 301 showed a 52% reduction in mean annualized new HO volume when patients were treated with palovarotene in Study 301 compared with their time in the NHS without treatment (nominal p-value=0.0634). Analysis over time showed that the trajectory of volume of new HO formation while on palovarotene was reduced through 18 months of follow-up.

Secondary efficacy endpoints in Study 301 included categorical assessment of the prevention of HO formation and the rate of FOP flare-ups. As the number of patients with any new HO did not show a difference between palovarotene-treated and untreated patients, it is understood that the benefit of palovarotene is *reducing* the volume of new HO rather than preventing new HO altogether. The apparent relatively higher flare-up rate in treated patients is likely due primarily to the difference in how flare-ups were captured in the NHS and Study 301, which led to an underestimation of flare-up reporting in the NHS (details are provided in Section 5.3.5.2). More importantly, the volume of new HO formation was still lower in palovarotene-treated patients than untreated patients despite the apparent observed higher flare-up rate. Collectively, these findings support that palovarotene modifies the major underlying cause of disease progression and disability for patients with FOP.

Given the interruption in dosing, the primary evidence of efficacy is derived from the data collected and analyzed in IA3. However, as the study continued, additional efficacy was collected both during off-treatment and following restart of palovarotene. Following the completion of Study 301, an analysis using the entire dataset up to Last-Patient-Last-Visit (September 2022) was conducted in order to evaluate longer-term effect of palovarotene treatment and assess whether efficacy was still maintained. Analyses looking at the overall data including the dosing interruption (Intent-To-Treat or ITT population), as well as in the post-restart period (representing solely time on treatment) were conducted.

As expected, when dosing was interrupted, data from the entire ITT period (representing both time periods on and off treatment) showed a smaller treatment effect than when patients were treated continuously with palovarotene. Despite treatment

interruption, annualized new HO volume for the entire study was still lower in Study 301 than what was observed in the NHS.

Additional supportive evidence is derived from the mechanism of action of palovarotene, which potently inhibits chondrogenesis and HO by decreasing the aberrant mutant ALK2 signaling through the overall reduction in phosphorylation of downstream effectors. In animal pharmacology studies, palovarotene was shown to be effective in reducing HO in several murine models also demonstrated a significant impact of palovarotene treatment on the reduction of new HO.

The Phase 2 program for palovarotene showed that the nonclinical pharmacology studies translated into clinically relevant decreases in HO formation at imaged flare-up body regions when palovarotene was administered as flare-up treatment. In the double-blind, placebo-controlled, Phase 2 Study 201 and the open-label extension, Study 202A/B, palovarotene treatment decreased new HO formation at flare-up body region compared with untreated/placebo flare-ups.

Further support is derived from WBCT data from Study 202 in the propensity score weighting analyses that address differences in baseline data in the 202C population that aligns most closely with that of Study 301. This analysis showed similar efficacy to that observed in Study 301. Additionally, a matched pairs analysis for the 202C population who did not cross over from the NHS and the analysis of those NHS transfer patients demonstrated lower new annualized HO volumes while receiving palovarotene treatment compared with the NHS.

The safety profile of palovarotene is well established from the 164 patients with FOP who received at least one dose of palovarotene in the FOP clinical development program, as well as more than 700 patients from other indications and more than 300 healthy participants. In patients with FOP, these results support the safety of palovarotene, which is consistent with the established profile of other systemic retinoids. Mucocutaneous events were the most commonly reported adverse events (AEs) in patients treated with palovarotene. The majority (76%) of AEs were mild to moderate, and most patients were able to remain on therapy through dose modifications and supportive care. Overall, 12 (8.6%) patients discontinued treatment due to AEs, and dry skin was the only AE that led to treatment discontinuation in more than 1 patient (n=2 [1.4%]).

PPC, along with teratogenicity, are class effects of systemic retinoids, and are important risks of palovarotene that are clearly communicated with a boxed warning in the proposed label. Due to the risk of teratogenicity, palovarotene is contraindicated in pregnancy and pregnancy prevention measures are recommended. Due to PPC, palovarotene is not recommended in females < 8 years of age and males < 10 years of age (the average ages at which pediatric female and male patients achieve approximately 80% of their adult height), and clinical and radiological assessments should be conducted in pediatric patients prior to and during treatment to best inform an

ongoing risk/benefit evaluation. The proposed risk minimization measures will inform and guide patients and clinicians on the safe use of palovarotene.

Overall, the benefits of palovarotene treatment outweigh the potential risks in the target population of patients with FOP. FOP is a devastating disease with no approved therapies. For the first time, an opportunity exists to offer patients living with this ultra-rare condition a disease modifying therapy that reduces new HO accumulation with the potential to preserve their mobility and function over the course of a lifetime. Because heterotopic bone formation in FOP is cumulative with irreversible consequences, early intervention is critical, and the target age recommendation for palovarotene represents a critical time to slow the progression of HO formation and preserve a patient's ability to function over time.

2 BACKGROUND ON FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (FOP)

Summary

- FOP is an ultra-rare, genetic condition that causes severe deformity and disability starting in childhood.
    - FOP is a progressive disease that causes HO, or extraskeletal bone, to accumulate over time.
    - HO is cumulative throughout life, resulting in segments, sheets, and ribbons of extra bone developing throughout the body and across joints that progressively restrict movement and can also lead to other sequelae beyond immobility (eg, skin breakdown and pressure sores).
    - Most patients with FOP require a wheelchair and full-time caregiving by age 25, and the median life expectancy for a person living with FOP is approximately 56 years of age.
    - Surgery for the resection of HO (removal of bone growth) is not recommended in patients with FOP as it can result in the formation of additional new HO due to resultant soft tissue trauma.
    - Fewer than 400 people in the United States (US) have been confirmed to be living with FOP; there are approximately 800–900 known patients worldwide.
    - FOP is primarily caused by an autosomal dominant R206H pathogenic variant in *ACVR1*, which provides a specific target for drug development.
- The clinical course of FOP is characterized by acute episodes of HO formation associated with flare-ups, followed by periods of apparent disease quiescence, during which HO may still form.
- Flare-ups are a substantial contributor to the formation of new HO, and are painful episodes, during which acute inflammation and swelling destroy soft tissue that is then replaced with mature bone.
    - Patients with FOP experience an average of 2 flare-ups per year that last anywhere from several weeks to months.
    - While flare-ups are usually sporadic and unpredictable, they can also be triggered by physical traumas including minor bumps, muscle fatigue, and intramuscular injections as well as major surgeries and influenza-like viral infections.
    - There are no predictors of which flare-ups will lead to HO formation.
- There are currently no FDA-approved treatments to prevent HO formation or disease progression; all treatments for FOP are either palliative or based on anecdotal evidence.

2.1 Overview of FOP

2.1.1 Epidemiology

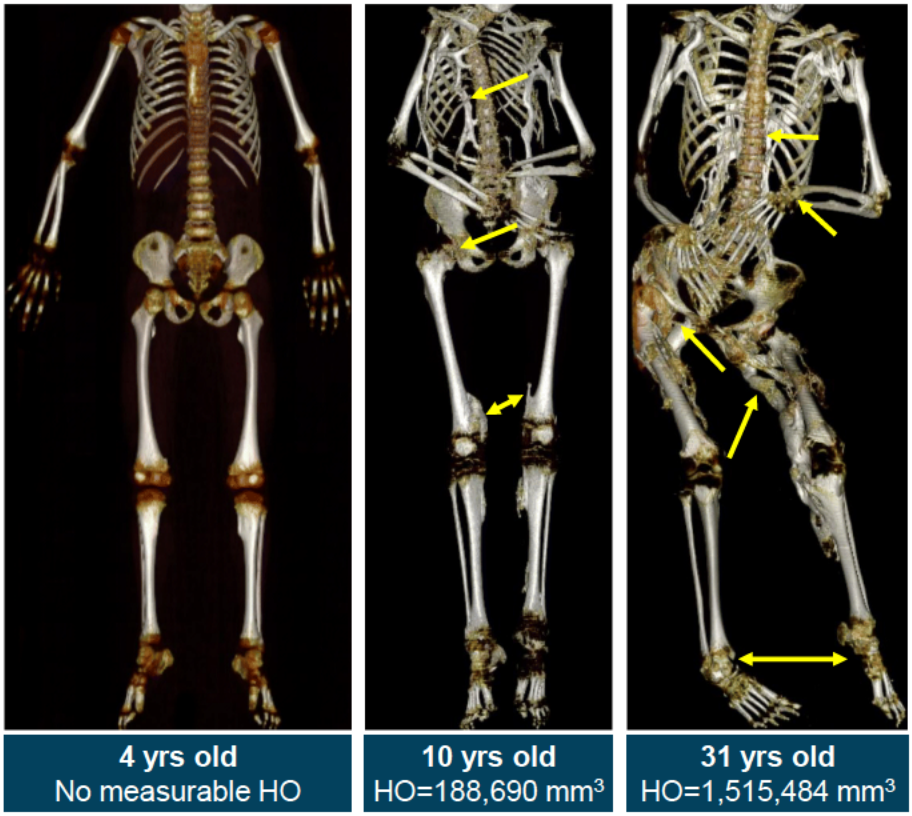
FOP is an ultra-rare disease, with approximately 800–900 confirmed cases worldwide, including fewer than 400 patients in the US (Lilijesthrom et al 2016). The estimated worldwide prevalence of FOP is 0.6–1.4 patients per million people (Baujat et al 2017; Kaplan et al 2022; Lilijesthrom and Bogard 2016). FOP appears to manifest indiscriminately, with no identified preference for geography, ethnicity, race, or sex (Baujat et al 2017).

2.1.2 Pathophysiology

FOP is a genetic disease caused by an autosomal dominant R206H pathogenic variant in *ACVR1*, in which extraskeletal bone, or HO, irreversibly replaces non-skeletal soft tissues (including muscle, tendons, and ligaments) throughout the body. HO formation is spared in smooth and myocardial muscle, as well as several skeletal muscles, including the tongue and extraocular muscles. The reasons these muscles remain unaffected are not yet understood (Kaplan et al 2012; Kaplan et al 2022). Instead of the muscle repair and regeneration that normally occurs in healthy individuals after an injury, HO forms in the injured muscle and soft tissue in patients with FOP through a process of endochondral ossification (Kaplan et al 1994; Kaplan et al 1993). The HO that forms in FOP is histologically normal bone and may contain marrow elements (see Section 3.2.1).

Figure 1 shows CT images of 3 representative patients with FOP at different ages. The patient on the left has no measurable HO at 4 years of age; the patient in the middle at 10 years of age has a number of regions with a substantial volume of HO; and the patient on the right at 31 years of age has obvious near complete joint ankylosis and visible deformities.

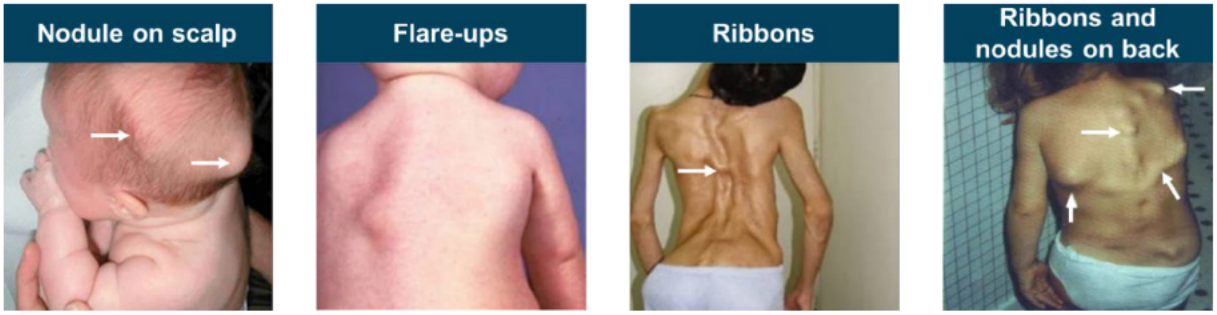
Figure 1: Whole-Body Computed Tomography Images from Representative Patients with FOP



HO=heterotopic ossification; yrs=years
Note: Arrows represent areas with accumulating HO.
Source: Pignolo 2019

HO accumulates throughout the patient's lifetime, resulting in segments, sheets, and ribbons of mature heterotopic bone throughout the body and across joints, progressively restricting movement and impairing basic function (Figure 2) (Hsiao et al 2019; Kaplan et al 2022).

Figure 2: Image of Pediatric Patients with FOP



FOP=fibrodysplasia ossificans progressiva
Source: Kitterman et al 2012

Eventually, this process results in ankylosis of virtually all joints, locking them into place and rendering movement impossible. The consequences of HO can also lead to sequelae beyond immobility and are multifactorial including skin breakdown and pressure sores from increased pressure over heterotopic or normotopic bone, increased skin infections due to creation of difficult to reach body folds, spontaneous or post-traumatic ankylosis of the temporomandibular joints leading to severe disability and resultant difficulties in eating and poor oral hygiene, hearing loss, severe scoliosis and thoracic insufficiency syndrome (TIS) with life-threatening complications, and pain caused by fracture of heterotopic bone, neuropathic pain, related to entrapment syndromes and/or nerve damage, or due to mechanical/compressive causes such as visceral pain from expanding HO (Kaplan 2022).

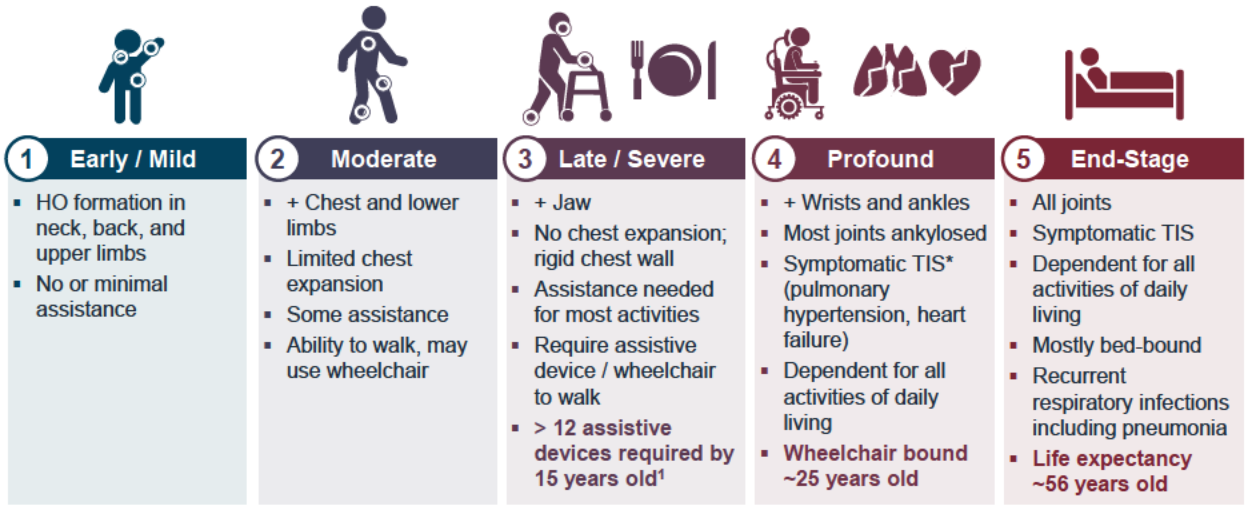
2.1.3 Disease Progression

The clinical course of FOP is characterized by acute episodes of HO formation followed by variable-length periods of apparent disease quiescence, during which acute clinical symptoms are not observed but HO may still form. Progressive restriction and permanent locking of joints secondary to HO throughout the body is a hallmark complication of FOP, including:

- Immobility of temporomandibular joints, which results in severe tooth decay, malnutrition, and weight loss.
- Ankylosis of vertebral and tibio-fibular joints, in addition to malformation and restriction of the hips, which progressively restricts mobility and eventually necessitates use of a wheelchair.
- Partial or complete ankylosis of joints in wrists and fingers, leading to difficulty feeding, using a wheelchair, etc.
- Orthotopic ankylosis of the costovertebral joints, which contributes to TIS and life-threatening complications (Kaplan et al 2022).

FOP follows a predictable pattern and unavoidable progression, which is often classified into 5 clinical stages that characterize the increasing burdens patients face as they lose functionality progressively over time (Figure 3).

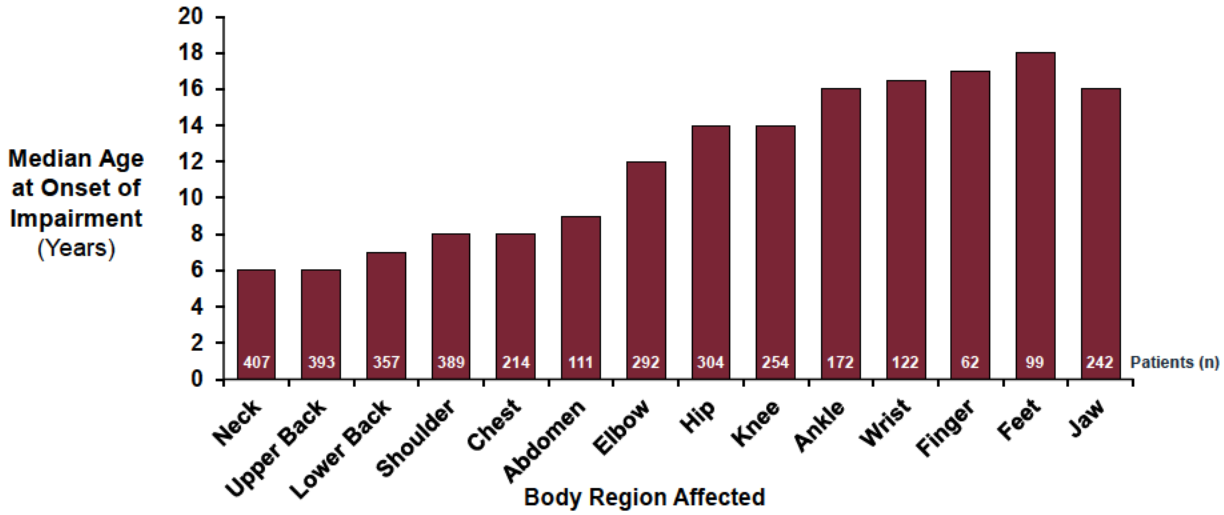
Figure 3: Five Clinical Stages of FOP Progression



FOP=fibrodysplasia ossificans progressiva; HO=heterotopic ossification; TIS=thoracic insufficiency syndrome
Source: Pignolo and Kaplan 2018.
1. Pignolo 2020

Figure 4 shows the median age at which body regions are first affected by HO. The first appearance of HO is typically observed in axial/cranial body regions within the first decade of life (median onset at 6 years of age in the neck and upper back) and progresses to appendicular body regions (proximal to distal) as patients age (median onset at 8 years in shoulder and chest and 14 years in the hip and knee; median onset at 16 years in the jaw and extremities) (Connor and Evans 1982; Pignolo et al 2016).

Figure 4: Median Age at which Body Regions are First Affected by HO



HO=heterotopic ossification
Note: The n number indicates the number of patients with an affected body region among a survey of 500 patients.
Source: Pignolo et al 2016

Individuals with FOP almost universally exhibit a malformation of the great toes at birth, which are typically short and deviated in hallux valgus (Pignolo et al 2011). The median

age at FOP diagnosis is 5 years of age (Pignolo et al 2016). Starting in early childhood (median age of onset during the sixth year of life), HO forms sporadically, usually beginning in the back and neck (stages 1–2). At this point, many patients experience few effects due to HO and can function with minimal assistance.

As patients enter their second decade of life, HO continues to spread through the body (stages 3–4). As shown in Figure 4, joints important for mobility and activities of daily living – the shoulder, elbow, hip, and knee – are typically first affected between the ages of 8 and 12 years (Pignolo et al 2016). The result is a systemic accumulation of unwanted bone throughout the body and across joints, which progressively restricts mobility and degrades overall function (Kaplan and Glaser 2005; Kaplan et al 2010). During these stages, functionality often declines rapidly, as the disease increasingly affects other areas of the body, such as the jaw, wrists, and ankles (Figure 4). Patients often need assistance with most activities of daily living and frequently require an assistive mobility device or wheelchair. By 25 years of age, most patients must use a wheelchair for any mobility and require full-time caregiving for all activities of daily living (Baujat et al 2017; Kaplan et al 2010; Pignolo et al 2020).

In the end stage of FOP (stage 5), complications of HO often cause severe morbidity, resulting in a median life expectancy of approximately 56 years (95% CI: 51–60 years) (Kaplan et al 2010; Lilijesthrom and Bogard 2016).

2.1.4 Assessments of FOP Progression

Prior to the palovarotene clinical program, efficacy endpoints for use in describing disease progression in FOP had not been established, and precedent-setting controlled clinical trials had never been conducted. A number of endpoints were evaluated during the development program in order to determine their potential suitability in describing progression of FOP over time, including formation of new HO, flare-up course, Cumulative Analogue Joint Involvement Scale (CAJIS), FOP-Physical Function Questionnaire (FOP-PFQ), and Patient Reported Outcomes Measurement Information System (PROMIS) described below.

2.1.4.1 Radiographic Imaging of HO

Assessment of presence and amount of HO (baseline) and new HO (post-baseline) were key aspects of the FOP development program, as HO is the pathognomonic feature of FOP.

The use of quantitative HO measures – through imaging, including whole-body CT (WBCT) and by specific body regions (x-ray or CT) – is considered the only characteristic of FOP skeletal disease progression that can show change over the course of a few years (Hsiao et al 2019). Despite significant efforts, no serum biomarkers have been identified as acceptable markers for FOP disease activity, and functional endpoints can only detect loss of function over a patient's lifetime (Pignolo et al 2018). As discussed above, HO has a significant impact on bodily functions depending on where it is located. There is no clear threshold volume to indicate disease

severity, as small amounts of HO can obstruct joint mobility or prevent a patient from being able to sit, for example due to ulceration of the skin or pressure sores over a bone spur of HO. However, it is evident that progression of FOP morbidity is directly associated with increasing HO volume, and so new HO volume is accepted as a primary efficacy endpoint measure in FOP interventional studies (Hsiao et al 2019). Additional support for HO as a key measure of disease progression was obtained from the NHS (details in Section 5.1.2.1)

2.1.4.2 Patient and Physician Flare-up Reporting

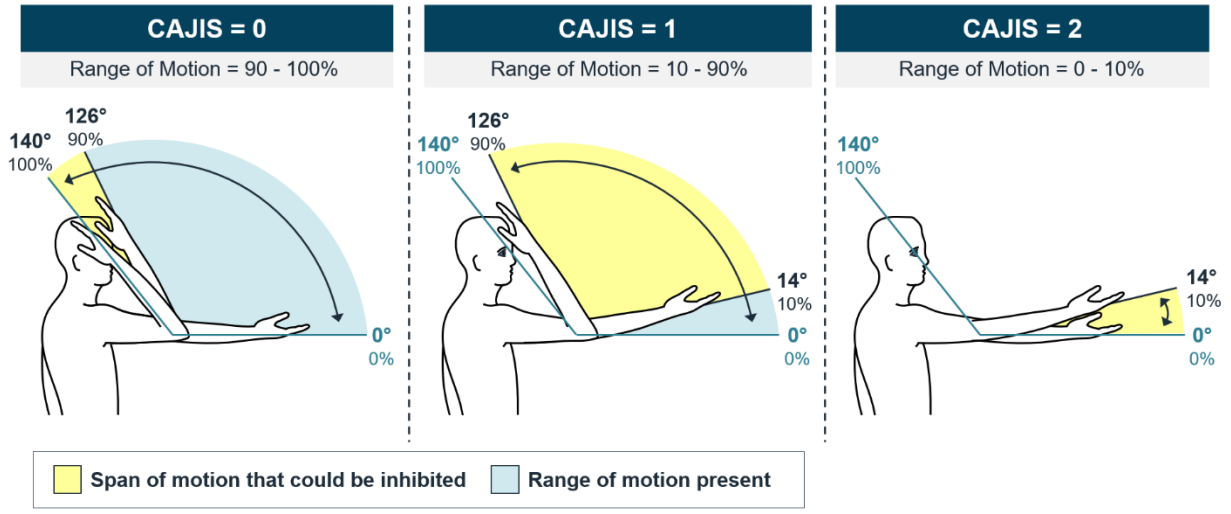
Most people living with FOP experience recurrent and intensely painful flare-ups, during which acute inflammation destroys regions of soft tissue that may be permanently replaced with bone. Flare-ups are characterized by large, painful swellings that are usually red and warm to the touch. These swellings resolve spontaneously within several weeks to months and often result in the transformation of soft tissue into heterotopic bone (Pignolo et al 2016). Patients typically report an average of 2 flare-up episodes per year (Pignolo et al 2019). Importantly, there are no biomarkers or objective measures of symptoms capable of identifying which flare-ups may result in new HO.

Although flare-ups often occur spontaneously, they can also be triggered by physical traumas. Events ranging from minor bumps, muscle fatigue, and intramuscular injections to major surgeries and influenza-like viral infections are known to initiate flare-up episodes that conclude with new HO deposits (Kaplan et al 2008; Scarlett et al 2004).

2.1.4.3 CAJIS (Cumulative Analogue Joint Involvement Scale)

The CAJIS questionnaire was developed by the Investigators from the Center for Research in FOP and Related Disorders and assesses range of motion of 12 joints (shoulders, elbows, wrists, hips, knees, and ankles), in addition to 3 body regions (cervical spine, thoracic/lumbar spine, and jaw). As depicted in Figure 5, each joint/region is scored as essentially normal or not involved (< 10% deficit, score of 0), partially impaired or partially involved (10–90% deficit, score of 1), or functionally ankylosed or completely involved (> 90%, score of 2) (Kaplan et al 2017). The total score range is calculated as the sum of all scores of all joints/regions and ranges from 0 (normal function) to 30 (functionally ankylosed across all regions). It is important to note that the large range of motion captured by a score of 1 (10–90% deficit) makes it difficult to capture small changes that may occur within that range. In addition to the overall score, the CAJIS also assesses ambulation status (walk, walk and use wheelchair, use wheelchair only) and activities of daily living (independent, need some assistance with activities of daily living, need complete help with activities of daily living). The NHS provides further understanding of CAJIS including the association with HO (see Section 5.1.2.2 and 5.1.2.3).

Figure 5: Depiction of Range of Motion by CAJIS Score in Elbow



2.1.4.4 FOP-Physical Function Questionnaire (FOP-PFQ)

The FOP-PFQ assesses the relationship between patient reports of physical impairment and total body HO, thereby providing evidence of HO as a clinically meaningful endpoint (Pignolo et al 2023b). The FOP-PFQ was developed to measure patient-assessed ranges of physical function. This tool was based on FDA Guidance for Industry "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" (Food and Drug Administration 2009). Age-appropriate forms provide a measure of functional impairment experienced by patients and include questions related to activities of daily living and physical performance. The total score across each of the age forms is different due to the differences in the number of questions included. Raw scores, therefore, are transformed to the percentage of the total possible score to normalize across all patients and instruments (adult and pediatric), with higher percentages representing greater functional impairment. Further information can be found in Section 5.1.2.2 from the NHS.

2.1.4.5 Patient Reported Outcomes Measurement Information System (PROMIS)

The PROMIS questionnaire assesses general health in the areas of global physical health (overall physical health, physical function, pain, and fatigue) and global mental health (quality of life, mental health, satisfaction with social activities and emotional problems) using age-appropriate forms.

2.2 Current Treatment Options for FOP

There are no approved treatments for FOP in the US, and no therapies—including those used off-label—have been shown to slow HO accumulation in any meaningful way. All pharmacological interventions are either palliative, to minimize soft tissue swelling and pain during flare-ups, or theoretical and based solely on anecdotal evidence and knowledge of disease etiology (Hsiao et al 2019; Kaplan et al 2022).

The International Clinical Council (ICC) on FOP recommends a 4-day pulse of high-dose corticosteroids (usually prednisone) for management of flare-ups that affect major joints, such as the hips, in addition to the jaw and submandibular area; however, it is acknowledged that this has limited effectiveness. The ICC also recommends corticosteroids to minimize flare-ups immediately following severe soft tissue trauma and during necessary elective surgeries (Kaplan et al 2022).

Non-steroidal anti-inflammatory drugs, cyclooxygenase-2 (COX-2) inhibitors, muscle relaxants, and neuropathic agents, like gabapentin, pregabalin, and tricyclic antidepressants, help alleviate pain. Opioids are used as a third-line option.

Off-label treatments target a variety of known or suspected disease pathways. Examples include: montelukast, a leukotriene inhibitor; cromolyn, a mast cell stabilizer; imatinib, a tyrosine kinase inhibitor; and amino-bisphosphonates, such as pamidronate and zoledronate. Currently, no evidence exists to show any effect of these treatments on overall accumulation of HO (Kaplan et al 2022).

Surgical removal of heterotopic bone is reserved for cases of grave threat to survival because tissue trauma from any procedure will most likely provoke flare-up(s) and additional bone formation (Kaplan et al 1993; Kitterman et al 2005). Prevention, monitoring, and assistance with activities of daily living represent a critical component of disease management (Kaplan et al 2008; Kaplan et al 1993; Kitterman et al 2005).

2.3 Patient Unmet Medical Need

FOP is an ultra-rare, genetic condition that causes severe deformity and disability starting in childhood due to progressive HO accumulation in major joints. Currently, there are no FDA-approved treatments to prevent HO or alter the natural history of FOP, and the only management for FOP is supportive.

Given the lack of effective treatments for FOP, patients have a clear and urgent need for a therapy that can modify their disease course and slow the accumulation of HO so that their mobility and function can be preserved over the course of a lifetime.

3 PRODUCT DESCRIPTION

Summary

- Palovarotene is an oral RARγ selective agonist that has been developed to prevent formation of new HO in patients with FOP.
  - Palovarotene delivers optimal benefits when taken daily as part of an adaptable chronic/flare-up regimen:
    - Chronic dosage is 5 mg daily.
    - Flare-up dosing initiates immediately at onset of flare-up symptoms, at 20 mg/day for 4 weeks, followed by 10 mg/day for 8 weeks; if the flare-up has resolved, chronic dosing at 5 mg can resume. If flare-up symptoms persist, 10 mg/day dosing may continue in 4-week cycles until symptoms resolve.
  - Dosing in patients is adjusted according to weight.
- Palovarotene targets the altered BMP signaling of the variant ACVR1 receptor in patients with FOP, thereby reducing HO formation.

3.1 Proposed Indication and Oral Dosing Regimen

The proposed indication for palovarotene in NDA was the prevention of HO in adults and children (≥ 8 years of age for females and ≥ 10 years of age for males) with FOP. Given the current understanding of the effect of palovarotene, the Sponsor is prepared to modify the labeled indication from "for the prevention of HO" to "to reduce the formation of HO."

The proposed dosing for palovarotene is a chronic/flare-up regimen. Patients receive palovarotene 5 mg once daily (chronic treatment). In patients reporting symptoms associated with a flare-up or trauma, the 5 mg chronic dosing should be stopped and palovarotene should be administered at 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks. If flare-up symptoms persist beyond 12 weeks, patients can receive treatment extensions in 4-week increments. The flare-up 12-week treatment is to be restarted should the patient experience another flare-up (new flare-up location or marked worsening of the original flare-up) at any time during flare-up treatment. At the completion of the flare-up dosing regimen, chronic palovarotene dosing should resume at 5 mg once daily. Dosing will be weight adjusted. Additional details regarding dosing are provided in Section 9.3.

The target population (females ≥ 8 years of age and males ≥ 10 years of age) was identified based on the risk of PPC, together with skeletal maturity, and in conjunction with the knowledge that physical impairment can occur in patients as young as 4 years of age (Pignolo et al 2019). The specific age cutoffs were chosen based on the average ages at which pediatric female and male patients achieve approximately 80% of their

adult height (ie, at 8 and 10 years of age, respectively) to mitigate the potential consequences of PPC in the youngest of patients, while still being able to intervene at the median age of onset of large joint immobility such as the shoulders, hips, and knees, a critical time in disease progression. Appropriate warnings and risk minimization activities will facilitate personalized treatment discussions among physicians, patients, and parents/caregivers. These discussions would allow patients, their caregivers, and their healthcare providers to consider the potential benefits and risks for each individual patient, allowing intervention at the most appropriate time, which is critical to preserving a patient's ability to function.

3.2 Product Overview

Palovarotene, an oral RARγ selective agonist that modulates BMP signaling, has been developed to prevent HO formation in patients with FOP. The rationale for using retinoids to treat FOP is based primarily on the observation that retinoid signaling is a strong inhibitor of chondrogenesis (Pacifici et al 1980). Additional details on clinical pharmacology and dosing are provided in Section 9.

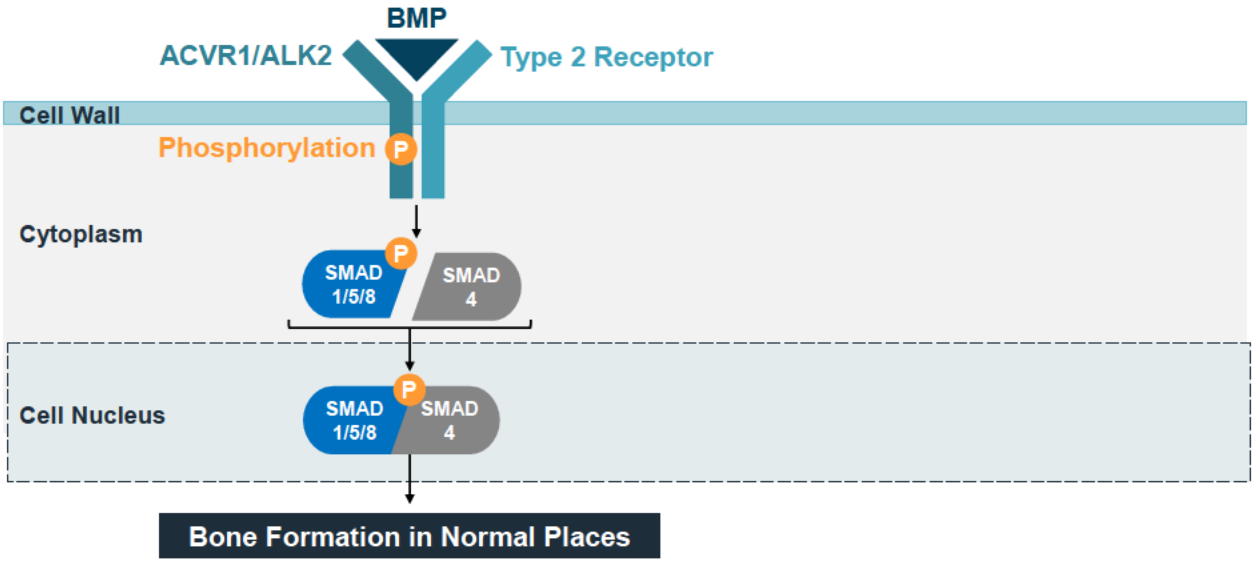
3.2.1 Mechanism of Action

FOP is a genetic condition caused by a gain-of-function missense variant in the *ACVR1/ALK2* gene, which encodes ACVR1/ALK2, a BMP type 1 serine/threonine kinase receptor. In 97% of individuals with FOP, the condition is caused by the ACVR1/ALK2 R206H variant receptor, thereby providing a specific target for drug development (Shore et al 2006; Zhang et al 2013). The primary molecular pathology in FOP involves the BMP signaling pathway (Kaplan et al 2008). In this disease process, the ACVR1/ALK2 variant receptor hyperactivates the BMP/SMAD signaling pathway and, as a result, normal soft tissue repair mechanism is replaced by abnormal bone growth. BMPs belong to the transforming growth factor β (TGFβ) family of extracellular signaling proteins and have a role in bone and cartilage formation. BMPs signal through cell surface receptor complexes that consist of 2 distinct transmembrane serine/threonine kinase receptors: type 1 and type 2.

<u>BMP Signaling in Normal Bone Formation</u>

In the absence of pathogenic variants, BMPs bind to the ACVR1/ALK2 receptor, which induces heterodimerization with the type 2 receptor (Figure 6). Heterodimerization results in phosphorylation of the downstream signaling pathway mediators, receptor-activated SMADs (Nishimura et al 1998). Phosphorylated SMAD 1/5/8 associates with SMAD 4 and translocates to the nucleus to regulate bone forming genes (Nishimura et al 1998). Activin A also belongs to the TGF-β family. Under normal conditions (ie, wild-type ACVR1/ALK2 receptor), Activin A binding to the receptor does not activate the downstream pathway and is not osteogenic.

Figure 6: BMP Signaling in Normal Bone Formation

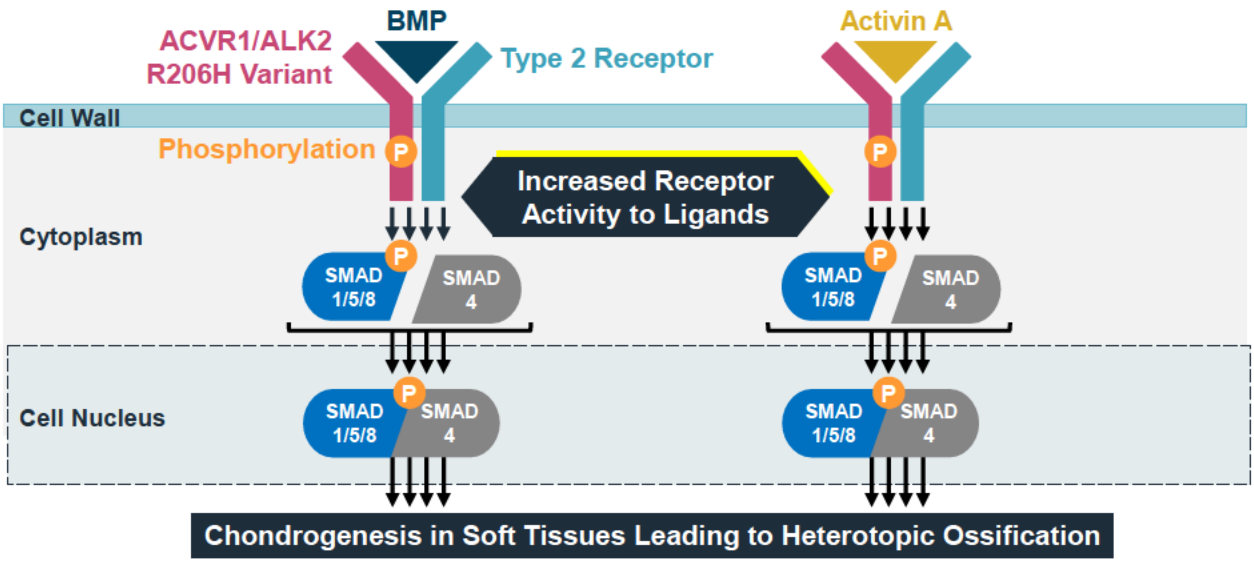


ACVR1=Activin receptor type 1A; ALK2=Activin receptor-like kinase 2; BMP=Bone morphogenetic protein

BMP Signaling in FOP

In FOP, the activating pathogenic variant alters the ACVR1/ALK2 receptor response to BMPs and Activin A (Figure 7); increased sensitivity to BMPs and Activin A binding leads to increased phosphorylation of SMAD 1/5/8, causing new bone formation (Hatsell et al 2015; Shen et al 2009).

Figure 7: BMP Signaling in FOP

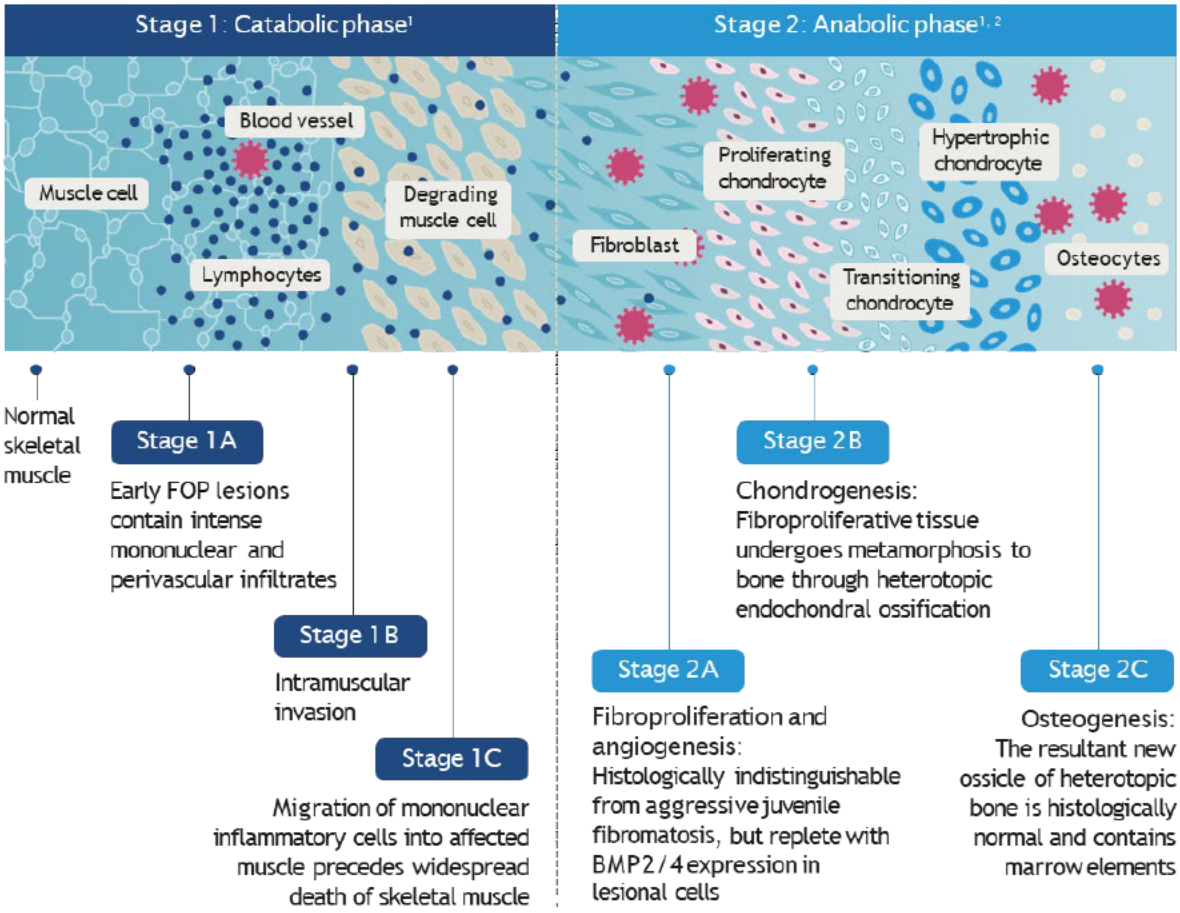


ACVR1=Activin receptor type 1A; ALK2=Activin receptor-like kinase 2; BMP=Bone morphogenetic protein; FOP=Fibrodysplasia Ossificans Progressiva

Disease Pathogenesis

In FOP, soft and connective tissues are replaced by bone through a process of heterotopic endochondral ossification, which proceeds in 2 phases (Figure 8). In the catabolic phase of HO development, normal skeletal muscle is degraded by migration of mononuclear inflammatory cells into affected muscle, leading to widespread death of skeletal muscle (Gannon et al 2001). In the anabolic phase, fibroproliferation and angiogenesis lead to chondrogenesis and ultimately osteogenesis and new HO (Lounev et al 2009).

Figure 8: FOP Disease Pathogenesis



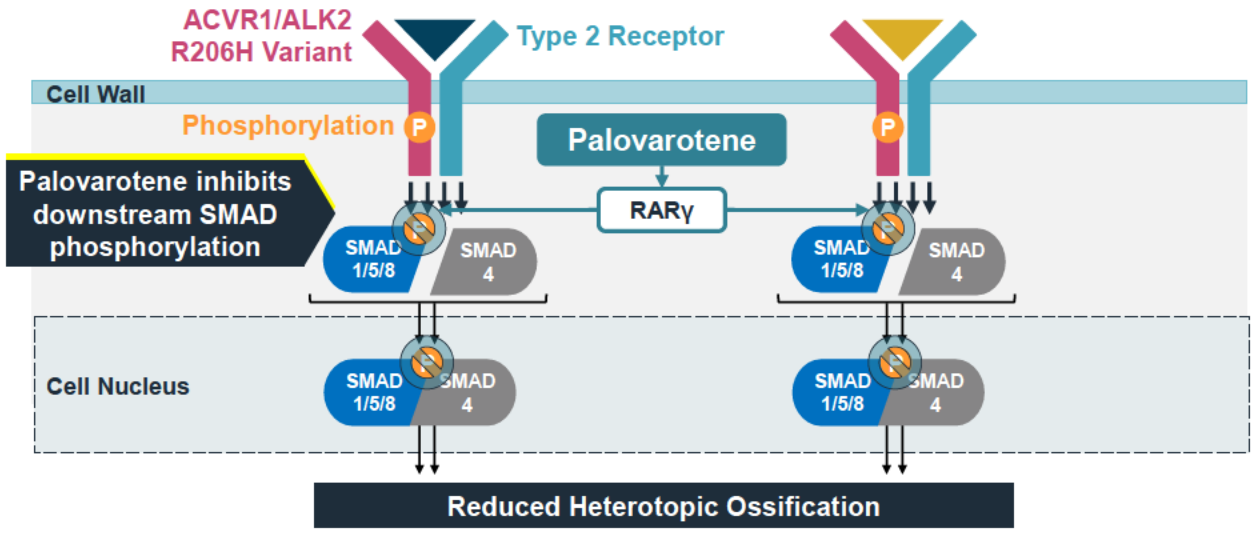
1. Gannon et al, 2001
2. Lounev et al, 2009

Palovarotene Mechanism of Action

Based on preclinical findings, palovarotene prevents HO by reducing inflammatory response and tissue damage during the flare-up catabolic phase and by inhibiting chondrogenesis during the flare-up anabolic phase (Figure 9). Through RARγ activation, palovarotene modulates the SMAD signaling driven by overactive variant ACVR1/ALK2 receptor and inhibits chondrogenic differentiation, thereby diverting mesenchymal progenitor cells from an osseous to a soft tissue fate and allowing for normal tissue repair (Chakkalakal et al 2016; Kaplan et al 2022; Kaplan and Shore

2011; Shimono et al 2011). This hypothesis has been confirmed in a human FOP fibroblast cell line where palovarotene inhibits the overactive ACVR1/ALK2 receptor-mediated aberrant SMAD signaling, and in traumatic HO and FOP mouse models, which showed palovarotene reduces HO formation (Section 8.1).

Figure 9: Palovarotene Mechanism of Action in BMP Signaling



ACVR1=Activin receptor type 1A; ALK2=Activin receptor-like kinase 2; BMP=Bone morphogenetic protein; RARγ=Retinoic acid receptor gamma selective agonist

4 REGULATORY AND CLINICAL DEVELOPMENT HISTORY

Summary

- Palovarotene received Orphan Drug, Fast-Track, Breakthrough Therapy, and Rare Pediatric Disease Designations by the FDA for FOP.
- The clinical development program for palovarotene includes the NHS, Phase 2 Studies 201 and 202, and the pivotal Phase 3 Study 301.
    - In December 2019, patients < 14 years of age stopped receiving palovarotene during a partial clinical hold regarding the risk of PPC.
    - In January 2020, all palovarotene dosing stopped when the second interim analysis (IA2) demonstrated futility; however, based on the totality of evidence from IA2, palovarotene dosing was reinitiated in patients ≥ 14 years of age.
    - Due to the treatment interruptions, the data collected for the purpose of the primary analysis in the Phase 3 study through the third interim analysis (IA3) at 18 months represents the most straightforward and accurate estimate of palovarotene's treatment and can be considered complete as of February 2020.
    - Efficacy data collected through the completion of studies (September 2022) are also included as supportive evidence in the evaluation of palovarotene's efficacy.

4.1.1 Regulatory History

An Investigational New Drug (IND) application for palovarotene went into effect in April 2014. Palovarotene received Orphan Drug Designation in July 2014 and Fast-track Designation in November 2014. Breakthrough Therapy Designation was awarded in July 2017, followed by a Rare Pediatric Disease Designation in February 2019.

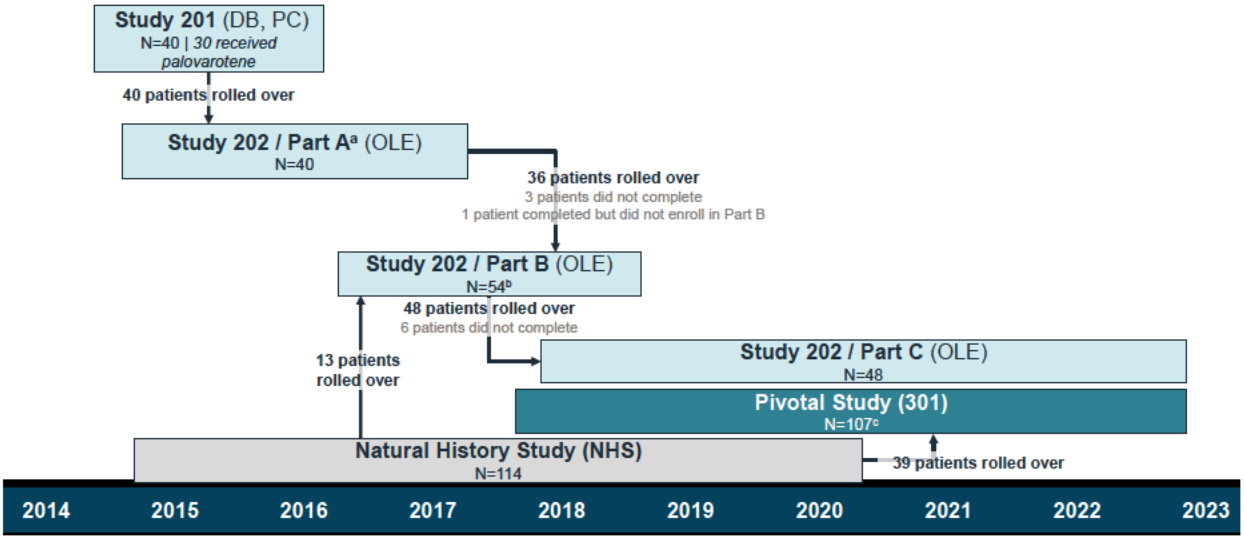
The palovarotene NDA was initially submitted on March 21, 2021 and withdrawn on August 12, 2021 after discussions between the FDA and Sponsor, to allow for a full verification of the data and the generation of additional analyses. The NDA was subsequently submitted again on April 29, 2022, and a Complete Response Letter was issued on December 23, 2022 requesting additional data and analyses to support the efficacy of palovarotene. A complete response to this Complete Response Letter was submitted on February 16, 2023 and included data through the completion of the Phase 2 and 3 trials.

4.1.2 Clinical Development History

The palovarotene development program for treatment of individuals with FOP is the first clinical program for this ultra-rare genetic disorder comprising both interventional trials and an NHS. Clinical development for the treatment of patients with FOP began in 2014

with the NHS and the first Phase 2 study (Study PVO-1A-201 [hereafter referred to as Study 201]), followed by Study PVO-1A-202 (hereafter referred to as Study 202) and a pivotal Phase 3 study (Study 301) (Figure 10). Along with the external control group from the NHS, the total number of individuals contributing data from the Phase 2 and 3 trials represents approximately 25% of the world's known population with FOP. Details on the Phase 2 and 3 studies, as well as the NHS, are provided in Section 5.

Figure 10: Timeline of Palovarotene Interventional Trials



CT=computed tomography; DB=double-blind; OLE=open-label extension; PC=placebo-controlled

[a] Six patients transferred from Study 202A to Study PVO-1A-203 which was only active for a brief period and limited data were captured (ie, no CT imaging was obtained). Patients could enroll back into Study 202 when Study 203 was terminated.

[b] Five de novo patients enrolled into Study 202B

[c] Sixty-eight de novo patients enrolled into Study 301

NOTE: Patients ≥ 14 years of age who completed Study 301 or Study 202C and met enrollment criteria were eligible for a rollover Study CLIN-60120-452 for continued access.

The FDA instituted a partial clinical hold in December 2019 for patients < 14 years of age based on the identified risk of PPC, and dosing was stopped in that patient population. Although the clinical hold was not lifted for patients < 14 years of age, the current protocols were updated to indicate that these study participants be followed for safety off treatment. In January 2020, dosing was also interrupted in patients ≥ 14 years of age when the pre-specified statistical analysis demonstrated futility in Study 301, crossing the pre-specified boundary. However, additional post hoc analyses using raw data and other appropriate statistical methods showed strong clinical benefit, and an amendment to the protocol was issued to adapt the statistical language in the Phase 3 protocol and allow patients ≥ 14 years of age to begin to resume dosing as early as April 2020. The median time off treatment for those who restarted palovarotene was 7 months.

Based on the pre-specified SAP, 3 interim efficacy analyses and 1 final analysis were planned. Due to the treatment interruptions, the data collected for the purpose of the primary analysis in the Phase 3 study through the third interim analysis (IA3) at 18

months represents the most straightforward and accurate estimate of palovarotene's treatment and can be considered complete as of February 2020. Nevertheless, efficacy data collected through the completion of Phase 2 and 3 studies are also included as supportive evidence in the evaluation of palovarotene's efficacy. As such, analyses looking at the overall data to Last-Patient-Last-Visit (September 2022), including the dosing interruption (ITT population), as well as in the post-restart period (representing solely time on treatment) were conducted. Taking into account the treatment interruptions mentioned above, the overall ITT period represents an average of 25 months on palovarotene treatment and 13 months off treatment, and the post-restart period represents an average of 14 months on reinitiated palovarotene treatment.

5 CLINICAL EFFICACY

Summary

- Results from the NHS and Phase 2 studies, as well as nonclinical data, contributed to the understanding of FOP disease progression and informed dose selection for the Phase 3 pivotal study (Study 301).
- Study 301 was a Phase 3, multicenter, open-label study that evaluated the efficacy and safety of the chronic/flare-up treatment regimen of palovarotene in patients ≥ 4 years of age with FOP.
  - Study 301 represents the first Phase 3 study of an investigational agent in patients with FOP and demonstrated a reduction in new HO volume.
  - Data from patients participating in the NHS – the largest prospective analysis of FOP disease characteristics and progression – served as the control arm for the pivotal 301 study.
- Analysis of IA2 results in Study 301 suggested that the pre-specified primary analysis, a Bayesian compound Poisson model with square-root transformation, introduced bias that inappropriately masked the treatment effect and led to crossing futility.
  - Post hoc analysis of the raw data at IA2 demonstrated a 59% reduction in mean annualized new HO volume in palovarotene-treated patients compared with untreated patients and therefore the study continued.
- At IA3, following the recognition of the impact of the square-root transformation and visit schedule on the estimation of palovarotene treatment effect, all analyses that controlled for these factors showed consistent efficacy.
  - The pre-specified Bayesian analysis with square-root transformation modified to collapse visits in the first year of Study 301 to align with NHS schedule fitted a 36% reduction in new HO volume on the standard scale (16% reduction on the square-root scale) and 91% probability of any reduction.
  - Bayesian analysis without square-root transformation fitted a 39% reduction in new HO volume and 99% probability of any reduction.
  - Using the wLME model (which utilizes data as observed), palovarotene-treated patients had a 54% reduction in mean annualized new HO volume compared with untreated patients (nominal p-value=0.0392).
- Additional sensitivity and subgroup analyses, as well as analyses of longer-term data to Last-Patient-Last-Visit showed continued evidence of efficacy.

5.1 Non-interventional: Natural History Study (NHS)

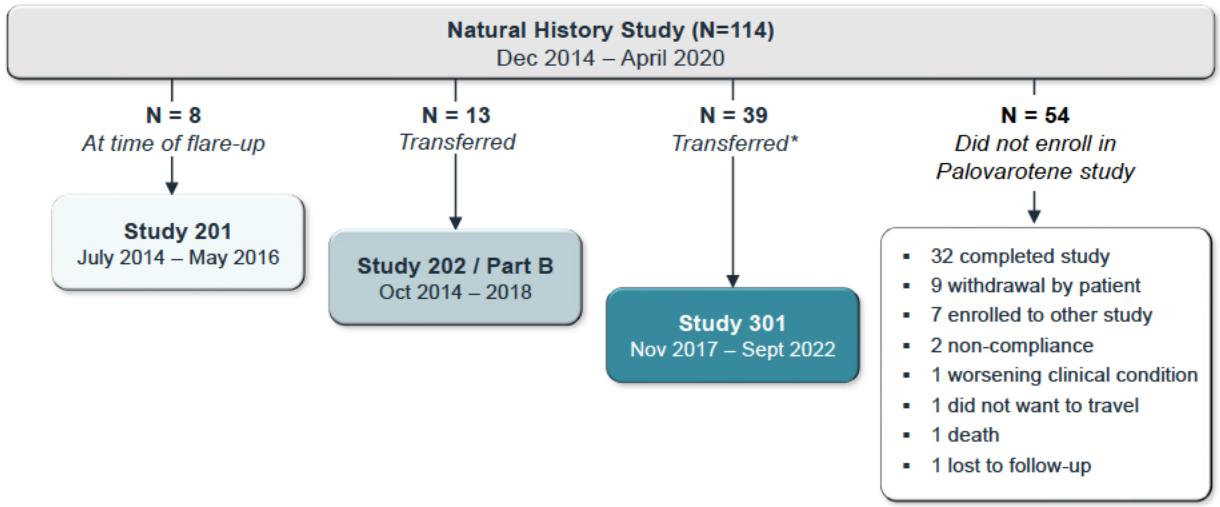
5.1.1 NHS Design

The NHS was the first longitudinal, non-interventional study describing FOP disease characteristics, prospectively evaluating disease progression over 3 years, and

assessing the impact of flare-ups on FOP outcomes. The NHS included 114 patients ≤ 65 years of age with FOP who were confirmed to have the *ACVR1/ALK2 R206H* variant and represents the only comprehensive prospective study of FOP disease progression. Inclusion and exclusion criteria are provided in Section 10.1.

As the NHS was run concurrently with the interventional trials, patients in the NHS had the option to enroll into a palovarotene clinical trial if they met the enrollment criteria. As shown in Figure 11, 60 patients from the NHS enrolled in Studies 201, 202B, or 301; the remaining 54 patients from the NHS did not enroll in a palovarotene study for various reasons.

Figure 11: Overview of Patients Who Enrolled in the NHS and Transferred to Another Palovarotene Clinical Study



DB=double-blind; OLE=open-label extension; PC=placebo-controlled
*All patients were offered the ability to enter Study 301; 1 patient enrolled after completing the NHS.

The NHS included low-dose CT scans to assess HO at flare-up sites and imaging assessments of total body HO by WBCT (excluding head) and additional assessments of disease progression such as the FOP-Physical Function Questionnaire (FOP-PFQ) and the Cumulative Analogue Joint Involvement Scale (CAJIS) evaluation.

Key Objectives for Flare-up Data

- To evaluate the extent of HO at the flare-up site by low-dose CT scans; soft tissue swelling at the flare-up site as assessed by MRI, or ultrasound in patients unable to undergo MRI; differences in functional endpoints and PROs associated with the flare-up site; association of new HO with changes in functional endpoints and PROs; functional endpoints/PROs by new HO and baseline edema; association of new HO with baseline edema status.

Key Objectives for Progression of Disease Data

- To evaluate the progression of new bone deposition and change in total body HO burden as measured by low-dose WBCT scan (excluding head), and to

determine whether changes in HO burden are associated with changes from baseline in functional endpoints (CAJIS) and PROs (FOP-PFQ).

- To evaluate the correlation between the endpoints showing disease progression; changes over 12, 24, and 36 months for the PROs; and changes in WBCT HO status and volume at Months 12, 24, and 36.

5.1.2 Key Findings from NHS

5.1.2.1 HO as a Key Measure of Disease Progression

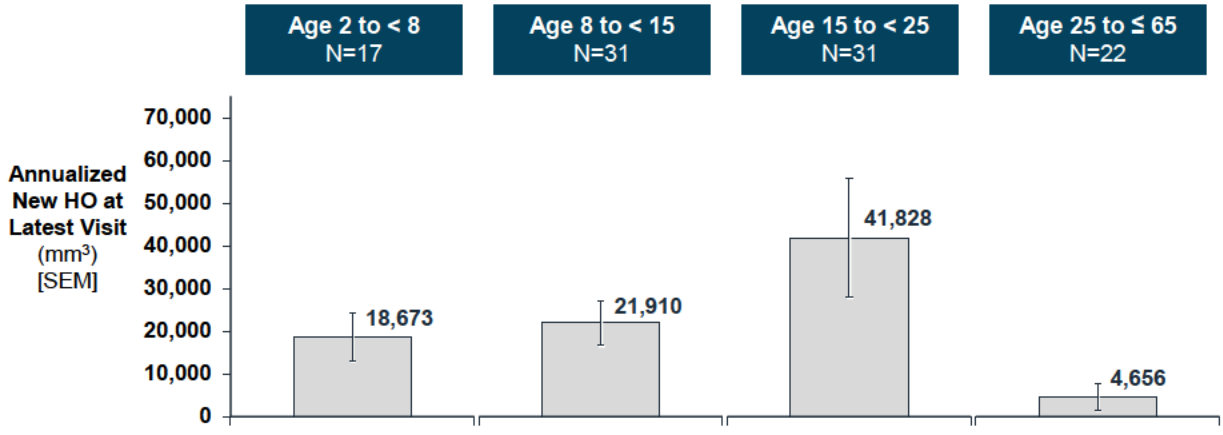
Findings from the NHS established that HO was a key measure of disease severity and progression, leading to its use as the primary efficacy endpoint in Study 301 (Pignolo et al 2023a).

The volume of HO at the flare-up site was assessed by low-dose CT scans at baseline and Week 12. The mean volume of new HO across all imaged flare-ups at Week 12 was 6,903 mm^3 (including volumes=0 mm^3) and 28,760 (including volumes > 0 mm^3). Flare-ups in patients aged 15 to < 25 years had the highest volume of new HO.

The extent of total body HO was assessed by low-dose WBCT scan (excluding head) and analyzed by incidence and volume of new HO post-baseline. The percentage of patients with new HO from baseline was 60.9% in the first year, 68.1% in the second year, and 82.0% in the third year, demonstrating that over time, virtually all patients will develop new HO.

Total HO examined by age group showed that the greatest increases in HO volume across all timepoints were observed in patients 8 to < 15 and 15 to < 25 years of age (Figure 12). This finding speaks to when, in the lifetime of a patient, the most new HO occurs. Although patients 25 to ≤ 65 years of age had the lowest volume of new total HO at annual visits, approximately 50% still continued to form HO over the duration of their participation in the study. The lower volumes in these patients may be attributed to the fact that they already had a substantial volume of HO at baseline.

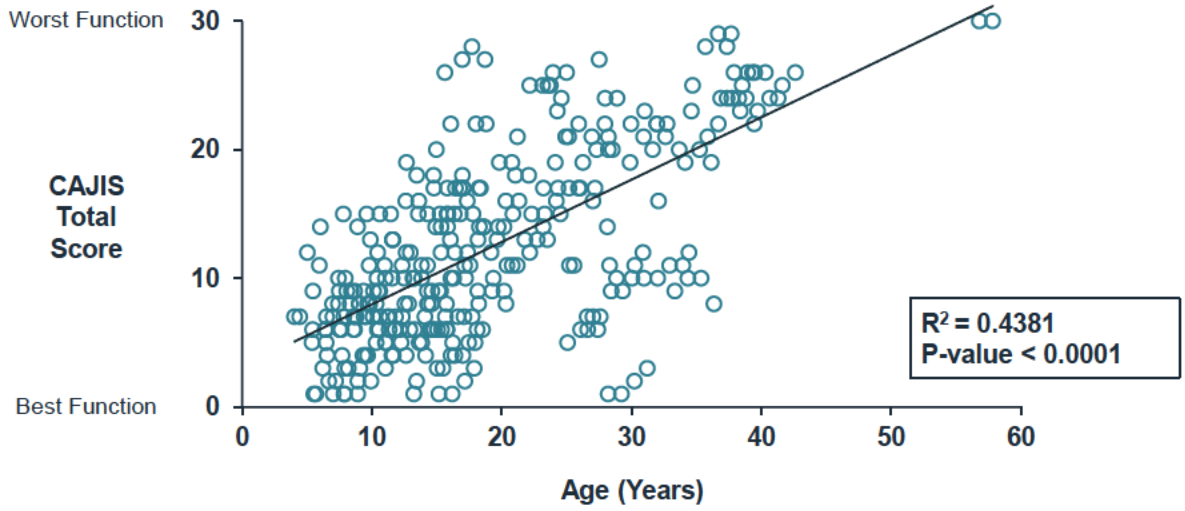
Figure 12: Annualized New HO Volume by Age in the NHS



5.1.2.2 CAJIS and FOP-PFQ

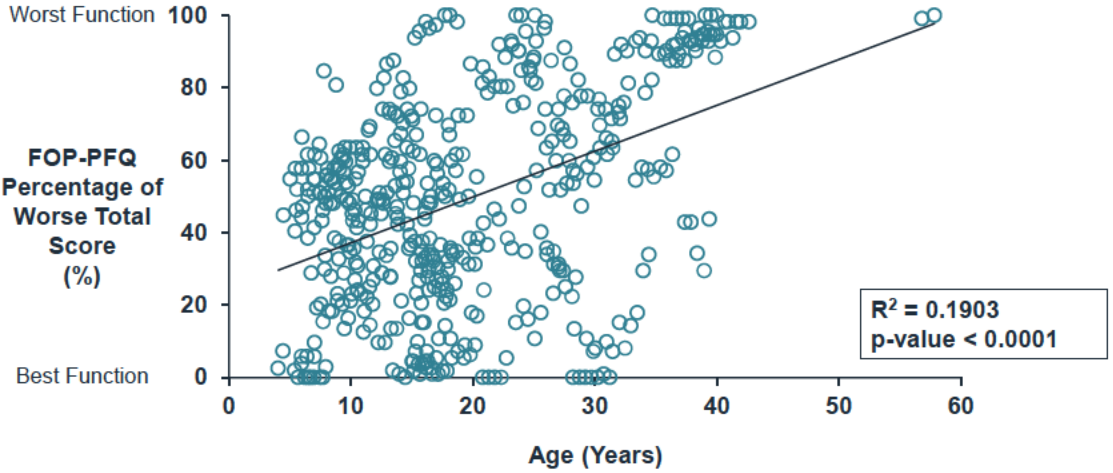
The relationships between CAJIS total score and age and FOP-PFQ total score and age are shown in Figure 13 and Figure 14, respectively. CAJIS total score was strongly correlated with age; based on linear regression analysis, every 1-year increase in age would be associated with a 0.49-unit worsening in CAJIS total score. FOP-PFQ percentage of worst total score was also positively correlated with age. Based on the linear regression analysis, every 1-year increase in age would be associated with a 1.3% worsening in FOP-PFQ percentage of worst total score. These findings suggest that CAJIS total score and FOP-PFQ percentage of worst total score are endpoints that may be useful to assess progression of FOP over the lifetime of a patient but would show minimal change over 1–3 years (Pignolo et al 2018).

Figure 13: CAJIS Total Score versus Age in the NHS



CAJIS=Cumulative Analogue Joint Involvement Scale

Figure 14: FOP-PFQ Percentage of Worst Total Score versus Age in the NHS



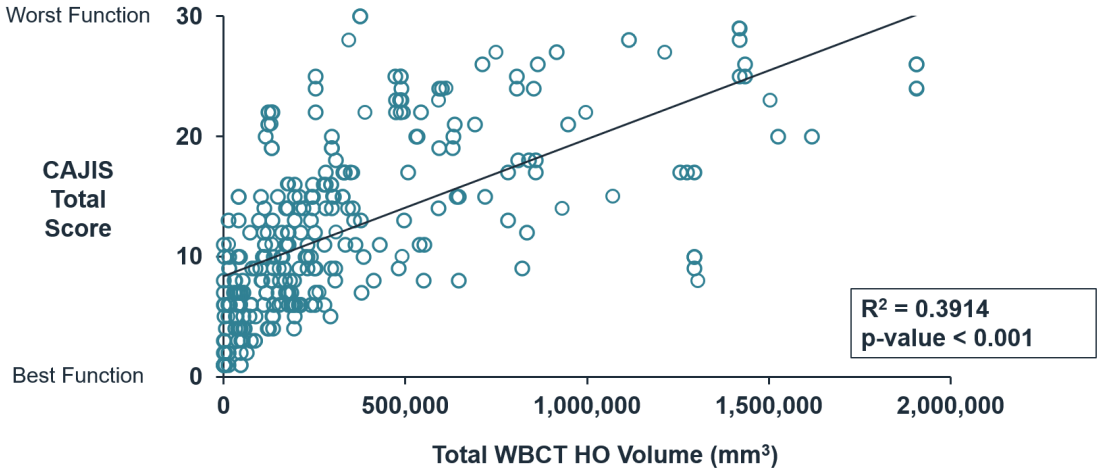
FOP-PFQ=Fibrodysplasia Ossificans Progressiva-Physical Function Questionnaire

At Study Months 12, 24, and 36/EOS, the change in mean CAJIS total score worsened by 0.6, 0.9, and 1.6 units, respectively, with no clear differences across the age categories. These findings correspond to the linear regression analysis that estimated an annual increase in CAJIS of 0.49 and are similar to the 0.5 annual increase across all ages reported by Kaplan et al (2017). The changes in FOP-PFQ total worst score at Months 12, 24 and 36/EOS were 4.4%, 4.5%, and 7.3%, respectively, with no clear differences across the age categories. Although these values are greater than the linear regression model estimated annual change of 1.3%, when evaluated using the median values (3.7%, 2.7%, and 4.0%), the changes more closely match. While both of these measures of physical function progressively worsened during the follow-up period, the changes were relatively small in relation to the size of the scales (30-point scale for CAJIS and 100% for FOP-PFQ).

5.1.2.3 Relationship Between WBCT HO Volume and Functional Outcomes

Cross-sectional analysis demonstrated that higher total body HO volume is correlated with worse physical function, as assessed by the physician (CAJIS; Figure 15).

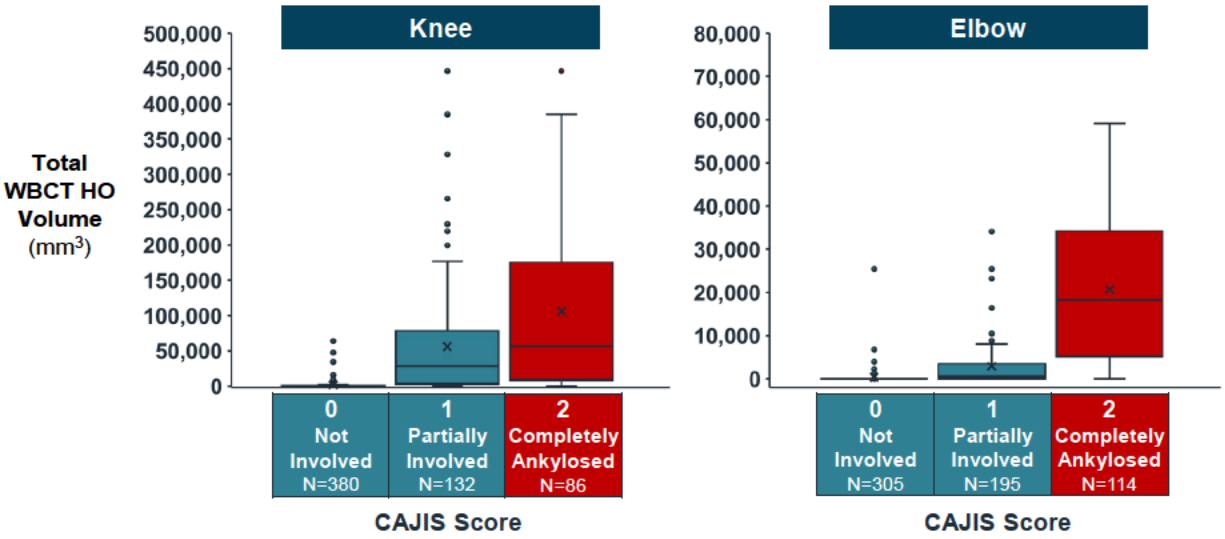
Figure 15: Correlation Between Total HO and CAJIS in the NHS



CAJIS=Cumulative Joint Involvement Scale; HO=heterotopic ossification; WBCT=whole-body computed tomography
Natural History Study: Assessments conducted at Day 1, Month 12, Month 24, and Month 36.

The NHS also showed that those body regions with worse function had higher mean HO volumes. Figure 16 shows mean HO volume by joint-specific CAJIS score within the knee and elbow from all patient visits in the NHS. Each specific body region is scored as essentially normal or not involved (< 10% deficit, score of 0), partially impaired or partially involved (10–90% deficit, score of 1), or functionally ankylosed or completely involved (> 90% deficit, score of 2). These data show that higher (ie, worse) joint-specific CAJIS scores were associated with higher mean volumes of HO within that joint region — further supporting the use of HO volume as the primary endpoint in Study 301.

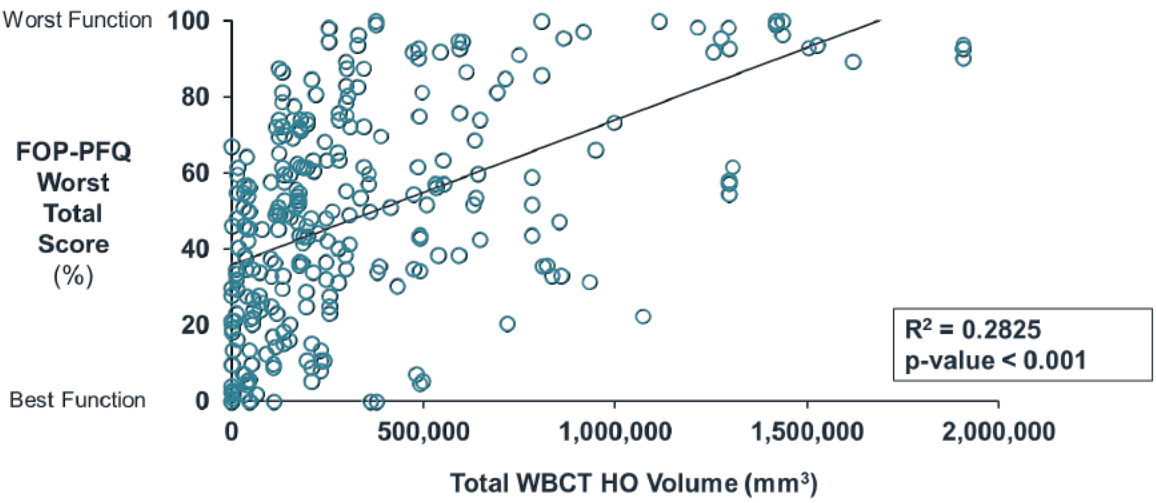
Figure 16: HO Volume by CAJIS Score in Knee and Elbow in the NHS (All Annual Visits Combined)



HO=heterotopic ossification; CAJIS=Cumulative Joint Involvement Scale; WBCT=whole-body computed tomography
Note: x indicates mean, horizontal line indicates median, top whisker indicates highest observation ≤ 1.5xIQR (interquartile range), bottom whisker indicates lowest observation ≥ 1.5xIQR, dots outside of error bars indicate individual data points.

Similar to physician-assessed physical function (ie, CAJIS), worse patient-assessed physical function on the FOP-PFQ was correlated with higher total body HO volume (Figure 17).

Figure 17: Correlation Between Total HO and FOP-PFQ in the NHS



FOP-PFQ=FOP-Physical Function Questionnaire; HO=heterotopic ossification; WBCT=whole-body computed tomography
Natural History Study: Assessments conducted at Day 1, Month 12, Month 24, and Month 36.

Overall, these findings support that HO volume is a clinically meaningful endpoint and support the premise that reducing HO formation can preserve mobility and function.

Accordingly, the use of HO formation as a primary endpoint is widely accepted as the endpoint of choice in this condition and to date all interventional clinical trials in FOP have used HO formation as a primary efficacy endpoint measure (Hsiao et al 2019).

Additionally, the scope and strength of the NHS were sufficient for it to serve as the control arm for the pivotal Study 301 (details provided in Section 5.3.1.3).

5.2 Phase 2 Studies (Studies 201 and 202)

5.2.1 Phase 2 Study Designs

The Phase 2 program was designed to determine whether the convincing animal pharmacology data with palovarotene would translate into efficacy in individuals with FOP. As such, the initial Phase 2 studies evaluated the effect of short-term palovarotene treatment on HO formation following the onset of a flare-up. The Phase 2 program was adapted based on emerging data.

Phase 2 clinical development consisted of 2 interventional studies, Study 201 and Study 202. These studies, along with the NHS, provided important safety data and 12-week flare-up outcome data across different palovarotene dosing regimens. Additionally, the assessment of total body HO burden by WBCT was introduced into the Phase 2 program during Study 202B when the chronic/flare-up dosing was initiated in skeletally mature patients and extended to all patients in Study 202C. Studies 201 and 202 are described below.

Study 201 was a multicenter, randomized, double-blind, placebo-controlled study in patients with FOP (Pignolo et al 2022) that investigated dosing during flare-ups only. The effect of different weight-adjusted daily flare-up doses of palovarotene (10 mg for 2 weeks followed by 5 mg for 4 weeks [palovarotene 10/5 mg]); or 5 mg for 2 weeks followed by 2.5 mg for 4 weeks [palovarotene 5/2.5 mg]) or placebo administered within 7 days of flare-up initiation on HO formation at the flare-up location was evaluated. The 10/5 mg dose was chosen based on the nonclinical pharmacology data and available clinical safety data (from other indications). The 5/2.5 mg dose was subsequently added following the enrollment of children < 15 years of age. This study provides assessment of palovarotene efficacy in preventing new HO at the flare-up body region as assessed by imaging following 6 weeks of flare-up treatment.

A total of 40 patients were randomized: 10 to placebo, 9 to palovarotene 5/2.5 mg, and 21 to palovarotene 10/5 mg. All patients completed the 12-week study and enrolled into Part A of the 202 open-label extension (Study 202 Part A).

Study 202 began as an open-label extension from Study 201 that was carried out in several parts as described below:

- Part A was the first part of the open-label extension of Study 201 in which palovarotene was evaluated in patients who experienced additional flare-ups that qualified for treatment. The intention of Study 202A was to further investigate the efficacy and safety of palovarotene at weight-adjusted daily doses of 10/5 mg

(10 mg for 2 weeks followed by 5 mg for 4 weeks), the dose that was anticipated to be tolerable and effective. Similar flare-up assessments to Study 201 (including CT imaging of the flare-up site) were performed for the 20 patients who received palovarotene 10/5 mg for a total of 28 flare-ups.

- Part B was the second part of the open-label extension study. Based on emerging nonclinical and clinical data, 2 additional palovarotene dosing schedules were evaluated in Part B. Patients with ≥ 90% skeletal maturity received 5 mg chronic and 20/10 mg flare-up dosing (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. Skeletally immature pediatric patients received palovarotene 20/10 mg flare-up dosing with weight-adjusted doses. A total of 54 patients entered Part B: 36 patients who previously participated in Part A and 18 new skeletally mature patients. A total of 52 flare-ups were evaluated in 33 patients, using similar flare-up assessments (including imaging) as for Study 201 and 202A.
- Part C was the third part of the open-label extension study and was initiated around the same time as Study 301. This part of Study 202 extended 5 mg chronic and 20/10 mg flare-up dosing to all patients, including skeletally immature pediatric patients. Only patients who previously participated in Part B participated in Part C (ie, no new patients were enrolled). Flare-up site imaging was not performed in Part C as efficacy was assessed by annual WBCT scans.

The following sections present the flare HO outcomes (Study 201 and Study 202 Parts A and B).

5.2.2 Phase 2 Flare-up Results

The data obtained in the double-blind placebo-controlled Study 201, and the pooled flare-up outcome data from Studies 201 and 202 and the NHS summarized below, show that palovarotene decreases total new HO volume at the flare-up site at 12 weeks compared with untreated/placebo flare-ups. These results not only demonstrate the translatability of the animal pharmacology data into humans, but also provide supporting evidence of efficacy to that obtained in the Phase 3 Study 301 (Section 5.2.3.3).

In Study 201, the primary endpoint percentage of patient responders as defined by no or minimal new HO at the flare-up site compared with baseline as assessed by plain radiographs at Week 6. Using this definition, the percent of responders was 88.9% in the placebo group, 88.9% in the palovarotene 5/2.5 mg group, and 100% in the 10/5 mg group (p=0.1664). Examination of these results compared to those from CT scan revealed that plain radiographs were not as sensitive as CT scans to measure new HO formation. Therefore, additional analyses by CT scan (or plain radiograph for subjects without CT scan) were evaluated as follows.

Patients in the 10/5 mg palovarotene group had fewer flare-ups with new HO at Week 12 (15%) compared with the 5/2.5 mg palovarotene (44%) and placebo groups (40%). Patients in the 10/5 mg palovarotene group with edema at baseline (evaluated by MRI or ultrasound), indicative of a more severe flare-up, had a lower incidence of new HO at Week 12 than those with edema in the 5/2.5 mg palovarotene and placebo groups (Table 1).

Table 1: Summary of Results from Study 201

	Placebo N=10	Palovarotene 5/2.5 mg N=9	Palovarotene 10/5 mg N=17
Patients with New HO at Week 12	40.0%	44.4%	15.0%[a]
Total Volume (mm^3) of New HO at Week 12, mean (SD)	16,182 (41,644)	1,185 (3,188)	3,858 (11,861)
Edema at Baseline (N)	6	6	8
Edema at Baseline and New HO at Week 12, n/N (%)	3 (50.0)	4 (66.7)	2 (25.0)

HO=heterotopic ossification; NRS=numeric rating scale; SD=standard deviation
[a] Based on denominator of 20, which includes 3 scans that were not evaluable.

All patients completed Study 201 and enrolled into Study 202A, during which any subsequent flare-ups were treated with open-label palovarotene 10/5 mg regimen. Study 202B evaluated 5 mg chronic and 20/10 mg flare-up dosing in skeletally mature patients and 20/10 mg flare-up only dosing in skeletally immature patients.

To understand flare-up outcomes and the potential treatment benefit of the palovarotene flare-up regimens, the data obtained in the palovarotene flare-up treatment groups from Studies 201 and 202 were compared with pooled data from placebo-treated flare-ups in Study 201 and untreated flare-ups from the NHS.

Hierarchical bootstrap resampling was conducted to account for patients contributing multiple flare-ups and for the non-normal distribution of HO volumes. The bootstrapped estimates of the analysis of covariance (ANCOVA) standard errors were used to construct 95% bias-corrected and accelerated (BCa) bootstrap CIs. While assessments of statistical significance were based on these 95% CIs, p-values were also calculated, assuming equivalent SEs under the null and alternative hypotheses, by varying the significance level of the CI and noting when the null value is excluded.

In the overall population, 20/10 mg provided the strongest evidence of a treatment effect (3,045 mm^3) with an approximate 72% reduction in new HO volume relative to placebo/untreated patients (10,780 mm^3). The difference yielded a p-value of 0.04 using ANCOVA with BCa bootstrap and covariate adjustment including flare-up location as hip/knee/shoulder versus other locations. These results are supported by the 10/5 mg flare-up dose (3,010 mm^3; 72% reduction; p=0.11) and the chronic/flare-up regimen (5,624 mm^3; 48% reduction; p=0.54). Combining data for the two 20/10 mg doses, the reduction in new HO (4,818 mm^3) was 55% (p=0.24). These findings supported bringing

the 20/10 mg palovarotene dose forward to the pivotal Study 301 as the flare-up treatment component.

In summary, the flare-up outcome data demonstrate that although palovarotene did not entirely prevent new HO formation, it effectively reduced new HO volume at the flare-up body region at Week 12, supporting the annualized new HO volume outcomes observed in Study 301.

5.2.3 Phase 2 WBCT Results

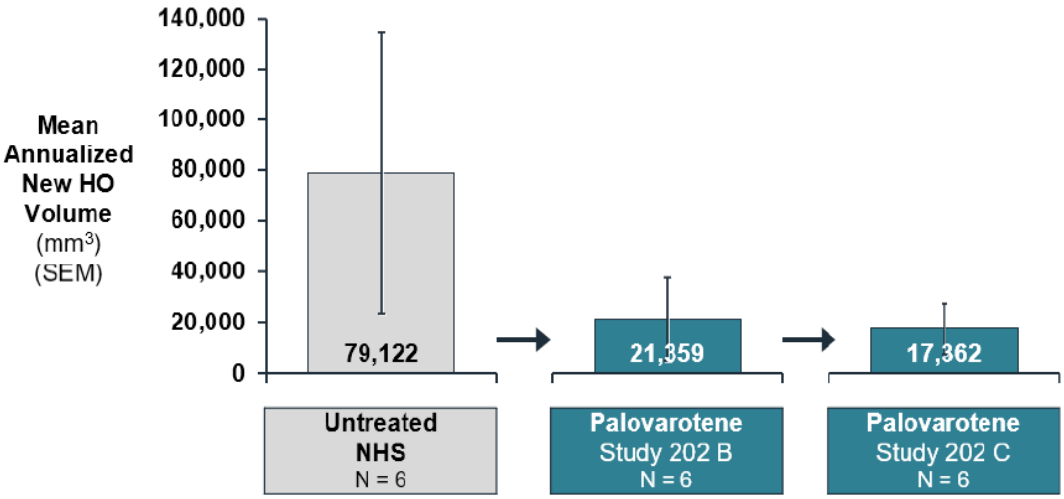
The assessment of total body HO burden by WBCT was introduced into the Phase 2 program during Study 202B. However, due to key differences in enrollment criteria, flare-up definitions and treatment protocols, the annualized new HO results from Study 202B do not accurately reflect palovarotene's treatment effect. Differences in flare-up definition and treatment included requiring at least two flare-up symptoms, initiation of study drug within 7 days of flare-up symptom onset and no treatment of inter-current flare-ups or traumas. Furthermore, most patients who enrolled in Study 202 came from Study 201, which required an active flare-up for enrolment (and many continued experiencing active flare-ups in Study 202B). Given these major differences, the analyses below focus on Study 202C population (including all subjects who had a Part C baseline, defined as the first WBCT scan in Part C that was not obtained during a flare-up or within 1 month of the end of a flare-up, and at least one post-baseline scan).

Although Study 202C better aligns with Study 301, there are still limitations in making direct comparisons to the NHS and Study 301. Statistical models are limited in their ability to demonstrate a comparison; this is partly because Study 202 was neither designed nor powered to be compared with the NHS or Study 301. Additionally, differences in populations need to be accounted for. To account for these differences, analyses were performed in patients who transferred from NHS into Study 202 (and thus serve as their own control), as well as a matched pairs and a propensity score weighting, described below. Lastly, it is known that flare-ups as well as traumas are associated with an increased risk of forming large volumes of HO (Kaplan 2022), and thus it is key to administer flare-up treatment with palovarotene at each of those occurrences. To determine the impact of not having all flare-ups and traumas treated in the Phase 2 studies, an analysis was performed to categorize subjects by flare-up treatment status and is also summarized below.

5.2.3.1 Patients who Transitioned from the NHS to Study 202

Thirteen patients participated in the NHS and subsequently transferred into Study 202B. Of these, an analysis of annualized new HO volume by study participation was performed for those 6 patients who had a baseline and at least one post-baseline WBCT scan in the NHS, Study 202B, and 202C in order to follow their progression across the NHS and all parts of Study 202 (Figure 18). In the 6 patients who provided HO data in all 3 studies, the mean annualized new HO volume was 73% and 78% lower in Study 202B (21,359 mm^3) and 202C (17,362 mm^3), respectively, compared with the NHS (79,122 mm^3).

Figure 18: Annualized New HO Volume for Patients Who Transferred from the NHS to Study 202 with at Least One Post-baseline WBCT Scan in Each Study



HO=heterotopic ossification; NHS=natural history study (Study PVO-1A-001); SEM=standard error of the mean; WBCT=whole-body computed tomography

It is important to note that although the annualized new HO volume for these transition patients during their participation in Study 202 was similar to the entire NHS population, a reduction consistent with the treatment effect in Study 301 is observed when using their own untreated annualized new HO volume as the comparator.

5.2.3.2 Matched Pairs and Propensity Score Weighting Analysis in Study 202C vs Patients who Participated in the NHS

Matched pairs and propensity score weighting analyses were performed to increase comparability between populations.

The matched pairs analysis was conducted on change in HO volume using data from patients receiving palovarotene in Study 202C and patients in the NHS who did not go on to receive palovarotene in Study 202C. All patients who crossed over from the NHS to Study 202 were excluded from the analysis. In the 19 patients who were successfully matched and had no significant differences in baseline characteristics (age, sex, months since last flare-up, age-adjusted HO volume, and CAJIS) there was a 43% reduction in annualized new HO in treated compared with untreated patients (Table 2).

An analysis was also performed using propensity score weighting of baseline characteristics. The stabilized and unstabilized weighting analysis performed for Study 202C vs the NHS resulted in a 36% reduction in annualized new HO volume in treated compared with untreated patients (Table 2).

Table 2: Matched and Propensity Score Weighting Analysis of Reduction in New HO Volume in Study 202 C and NHS Patients[a,b]

Analysis:	Palovarotene Study 202C	Untreated NHS	Mean Difference (202C-NHS)	p-value
Matched analysis	**N=19**	**N=19**		
Annualized New HO Volume mm^3				
Mean ± SD	16120 ± 55303	28428 ± 40292	-12308 ± 15698	0.44
Median (range)	662 (-47921, 223093)	10433 (-1586, 125466)	–	–
IQR	-6116, 21206	0, 40949	–	–
Weighted analysis	**N=21**	**N=93**		
Stabilized weighting				
Annualized New HO Volume mm^3				
Mean ± SD	13718 ± 52977	21566 ± 38200	-7848 ± 12220	0.49
Median (range)	0 (-47921, 223083)	6609 (-37944, 206354)	–	–
IQR	-10419, 7848	0, 26020	–	–

HO=heterotopic ossification; IQR=interquartile range; SD=standard deviation.
[a] Means and standard deviations are shown for continuous characteristics; counts and percentages are shown for categorical characteristics, unless otherwise noted.
[b] Statistical comparisons were assessed using 2 sample t-tests for continuous variables, and chi-squared tests for categorical variables.

Given the small sample size these results were not statistically significant, however were directionally consistent with prior analyses showing that palovarotene treatment was associated with less annualized new HO compared with no treatment in the NHS.

5.2.3.3 Analysis of WBCT in Study 202C Patients Optimally Treated with Palovarotene

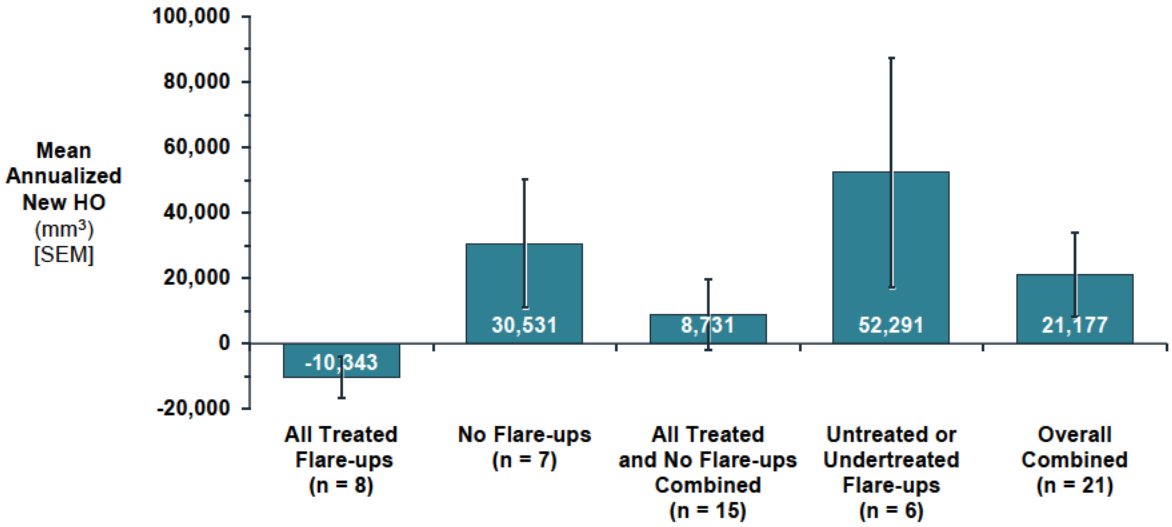
To determine the impact of not having all flare-ups and traumatic events treated in Study 202C, an analysis was performed to categorize patients by flare-up treatment status as described below. Although patients in Study 202C were to receive optimal palovarotene flare-up dosing, this was not always the case. Potential reasons for this may be related to clinical trial fatigue (Ashley 2021) due to the long participation of most of these patients in the Phase 2 program (including > 6 years at the time of data cutoff), as well as multiple changes to the dosing regimen introduced by the different protocol amendments since the start of Study 202.

Figure 19 summarizes the annualized new HO volume up to the NDA data cutoff by flare-up treatment categorization:

- Treated Flare-ups: consists of patients who had all flare-ups adequately treated with palovarotene flare-up dosing.

- Untreated/Undertreated Flare-ups: consists of patients who had at least one flare-up event that was not treated with palovarotene (eg, a flare-up was reported but the patient either did not receive palovarotene or received less than 6 weeks of palovarotene treatment)
- No Flare-ups: consists of patients who reported no flare-ups, or flare-up symptoms or major traumatic event for which glucocorticoids were administered.
- Treated Flare-ups and No Flare-ups Combined: this combined category is most similar to the patients evaluated in Study 301 during which there were patients who had no flare-ups and patients who had flare-ups that were adequately treated.

Figure 19: Annualized New HO Volume (mm^3) by flare-up treatment categorization in Study 202C (Principal FAS)



FAS=Full Analysis Set; HO=heterotopic ossification

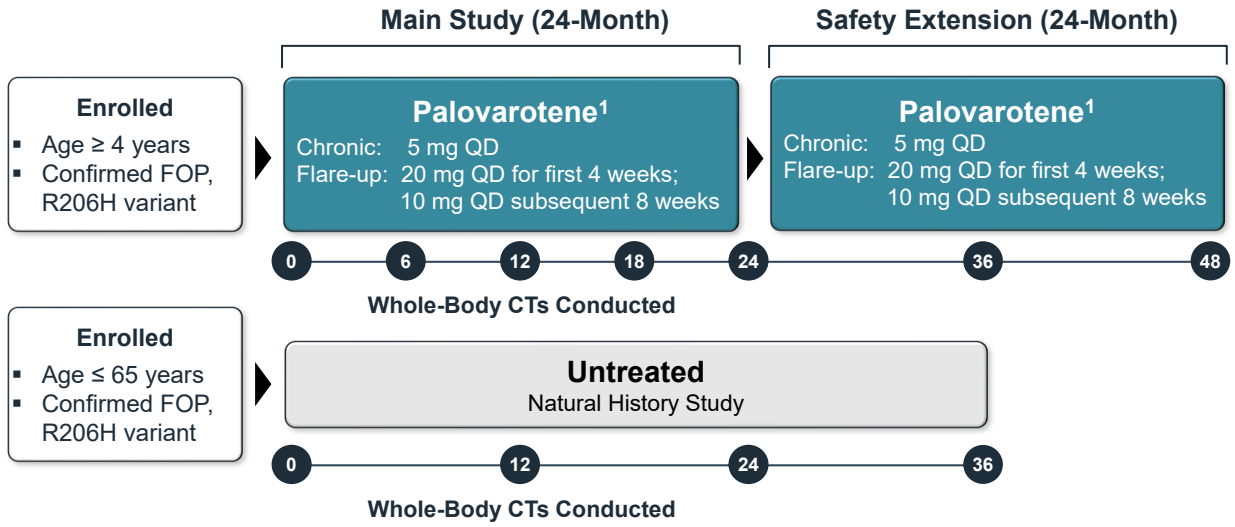
Based on this analysis, approximately 29% of patients (6/21) in Study 202C were untreated/undertreated, which likely impacted the volume of annualized new HO formation. As would be expected, compared with patients with all treated flare-ups, patients with untreated/undertreated flare-ups had a much greater annualized new HO volume (-10,343 mm^3 vs 52,291 mm^3). It is also notable that patients who did not report any symptomatic flare-ups formed a substantial amount of new HO inconsistent with what was observed in both the Study 301 and NHS. One potential reason for this could be due to under-reporting of flare-up symptoms. The annualized new HO volume in the combined group that best approximate the Study 301 population was similar to that observed in Study 301 (8,731 mm^3 in 202C vs. 9,427 mm^3 in 301), and less than in the NHS (23,656 mm^3).

5.3 Pivotal Phase 3 Study: Study 301

5.3.1 Phase 3 Study Design

The primary evidence supporting the benefit of palovarotene for the treatment of FOP is derived from a large, global, multicenter Phase 3 Study (Study 301), which together with the NHS external comparator represents approximately 20% of the known FOP global population. Study 301, now clinically complete, evaluated the efficacy and safety of the chronic/flare-up treatment regimen of palovarotene in patients ≥ 4 years of age with FOP. In accordance with the partial clinical hold put in place in December 2019, patients between 4–13 years of age stopped treatment but continued to be followed for safety. The study period was 24 months, with the option to extend an additional 24 months. Radiographs and WBCT scans were conducted every 6 months throughout the study period and every 12 months during the study extension (Figure 20).

Figure 20: Pivotal Phase 3 Study 301 Design



CT=computed tomography; FOP=fibrodysplasia ossificans progressiva; R206H=activating variant in bone morphogenetic protein type 1 receptor gene *ACVR1/ALK2*; QD=once daily
1. All dosing was weight adjusted in patients < 18 years of age with less than 90% skeletal maturity, as measured by hand-wrist radiography

The primary efficacy endpoint in Study 301 was annualized change in new HO volume as assessed by WBCT (details provided in Section 10.2). Secondary efficacy endpoints included:

- Proportion of patients with new HO at Month 12
- The flare-up rate per patient-month exposure through Month 24

Exploratory endpoints included change from baseline in CAJIS score at Month 24 and change from baseline in FOP-PFQ worst score at Month 24. As established in the NHS, the CAJIS and FOP-PFQ are not sufficiently sensitive to demonstrate the loss of physical function in untreated patients over the course of a clinical trial (Section 5.1.2) and were therefore included as exploratory only.

5.3.1.1 Dose Selection for Phase 3

Multiple flare-up dosing regimens were evaluated during the Phase 2 studies, and the emerging data suggested that higher doses over longer duration were required to maximally inhibit HO formation at the flare-up body region. Therefore, the dose utilized for flare-ups in Study 301 was 20 mg daily for the first 4 weeks, followed by 10 mg for the remaining 8 weeks (the 20/10 mg flare-up regimen), or weight-adjusted equivalent for skeletally immature patients with extension of 10 mg flare-up dosing for those with persistent symptoms. If a patient experienced a confirmed intercurrent or worsening flare-up (a new flare-up location or marked worsening of an original flare-up), or a substantial high-risk traumatic event likely to lead to a flare-up at any time during flare-up-based treatment, the 12-week flare-up dosing regimen restarted. Chronic dosing of palovarotene was added to the palovarotene dosing regimen in this study based on findings from both nonclinical and clinical data including the NHS and Phase 2 flare-up CT images that showed substantial soft tissue edema, muscle necrosis, and immature HO within the first 7 days of the onset of a flare-up in some of the images, demonstrating that HO formation may begin before clinical symptoms present.

5.3.1.2 Choice of Total Body HO Volume as Primary Endpoint Measure

Total body HO volume was measured via WBCT scans every 6 months for 24 months during the main study period, and patients had the option to continue treatment for an additional 24 months as part of the extension period, with 12-month assessment intervals. Data from patients in the NHS, which included yearly WBCT scans, were used as untreated comparators, in accordance with the approved study protocol.

As discussed in Section 4.1.2, efficacy endpoints for use in interventional studies in FOP had not been established prior to the palovarotene development program. The annualized change in whole-body HO volume was chosen as the primary endpoint in Study 301 for the following reasons established by the NHS (Section 5.1): (1) HO formation is the pathognomonic feature of FOP; (2) measurable changes in whole-body HO are demonstrated over 1–2 years and thus are sufficiently sensitive to detect disease progression in untreated patients, and a potential treatment effect in treated patients; (3) cross-sectional analyses demonstrate significant correlations between whole-body HO volume and functional evaluations and patient-reported outcomes (PROs); and (4) changes in functional evaluations and PROs are not sufficiently sensitive to demonstrate disease progression over the course of a clinical trial. In addition, HO is an objective endpoint that can be measured in a standardized, blinded manner by a central imaging laboratory.

The use of HO formation as a primary endpoint is widely accepted as the endpoint of choice in this condition (Hsiao et al 2019), and to date all interventional clinical trials in FOP have used HO formation as a primary efficacy endpoint measure.

5.3.1.3 Choice of NHS for Comparison

The NHS provides a unique and valuable dataset that is being utilized to better understand FOP. The 114 patients in the NHS are representative of the worldwide population of individuals with FOP (7 study sites representing patients from 24 countries). The analysis of these data provides important information about clinical measures in FOP that describe disease progression over time. Moreover, the flare-ups studied in the NHS expand the understanding of the duration and outcomes of untreated flare-up symptoms.

According to regulatory guidances, a well-designed and conducted natural history study may be able to serve as an external control group for interventional trials in rare diseases (Food and Drug Administration 2001; Food and Drug Administration 2019). However, the use of a natural history study as an external control involves several well-recognized challenges. Without randomization of parallel groups, additional steps need to be taken to ensure that differences in patient characteristics, methods of outcome assessment, background standards of care, or other factors do not unduly bias the comparison of outcomes between groups. Key characteristics that mitigate these challenges and support the use of the NHS as an external control for Study 301 are detailed below, drawn from several sources including International Conference on Harmonization and FDA guidance documents (Food and Drug Administration 2001; Food and Drug Administration 2019; Pocock 1976):

- The primary outcome of annualized new HO volume, assessed via low-dose WBCT scan, is an objective measure that was obtained using equivalent image acquisition protocols in the NHS and Study 301. An independent, central imaging laboratory quantified HO volume in all scans, with the interpretation following a predefined procedure to blind reviewers to whether the scan originated from the NHS or Study 301 and the timing of the post-baseline assessments. Although the timeframe of the acquisition of WBCT scans from both studies did not occur over the exact same timeframe, the studies did overlap and all scans were read concurrently such that all scans from the NHS were interspersed with scans from Study 301 in a blinded manner to be assessed for HO. The consistent and blinded assessment of this objective outcome measure should exclude the possibility that the read process of HO could be biased between studies.
- The NHS enrolled patients with FOP due to the *ACVR1/ALK2 R206H* variant up to 65 years of age. Although the enrolment criteria for Study 301 were more restrictive than in the NHS, only 4 patients failed screening by meeting those additional selection criteria (one for elevated triglycerides, one for elevated amylase/lipase, one for suicidal ideation and one for flare-up symptoms within the past 4 weeks). Therefore, the differences in the enrolment criteria should not have had an effect on comparability between cohorts to enable valid efficacy comparisons.
- Patients in the NHS and Study 301 were treated with consistent standards of care and background therapy. The standard of care for FOP remains unchanged

since the start of these studies (Kaplan et al 2022). Symptomatic treatment, including prednisone use, was permitted in both trials. Medication use at the time of flare-up was collected in the NHS, facilitating comparison to Study 301. Additional sensitivity analyses also supported the comparability of the NHS and Study 301 (details provided in Section 5.3.4.4).

- Enrollment of the NHS was completed before enrollment in Study 301 began, but both studies ran during concurrent timeframes, with all NHS clinical study sites also participating in Study 301.
- At the time of Study 301 initiation, the NHS had enrolled 114 patients with a duration of follow-up from approximately 12 to 36 months. Patients in the NHS were eligible for enrollment into Study 301, and it was anticipated that at least 50% would participate. In addition, patients who had not participated in the NHS were also enrolled into Study 301. Furthermore, given the paucity of recognized prognostic factors in FOP, there is limited opportunity for selection bias between the NHS and Study 301.

It is important to note that while the above characteristics support the use of the NHS as an external control for the assessment of HO in Study 301, a key difference between the NHS and Study 301 was in the capture of flare-up data. As discussed in Section 5.3.5.2 in more detail, there was less frequent patient contact in the NHS, a lack of specific assessment for flare-up status in the NHS until the last protocol amendment, and a lack of a pre-defined specification that only 1 symptom was required to identify a flare-up in NHS, which would likely lead to under-reporting of flare-ups. Another key difference between these 2 studies was the timing of WBCT assessments, which was annually in the NHS and bi-annually in Study 301. As described in Section 5.3.1.5, it is important to account for this difference in the assessment schedule when analyzing the annualized new HO using Bayesian statistics.

5.3.1.4 Enrollment Criteria

A maximum of 110 patients ≥ 4 years of age were to be enrolled, including up to 99 patients with both the *ACVR1/ALK2 R206H* variant and no previous exposure to palovarotene and up to 11 additional patients who either had variants other than *ACVR1/ALK2 R206H* or who had previously participated in Phase 2 trials.

Patients eligible for enrollment in Study 301 included:

- Patients clinically diagnosed with FOP with the *ACVR1/ALK2 R206H* variant or other FOP variants reported to be associated with progressive HO who had not previously participated in any sponsored trials
- All patients from the NHS

A full list of inclusion and exclusion criteria are provided in Section 10.1.

5.3.1.5 Statistical Methods

Analysis Population

The efficacy endpoints were analyzed using the Principal Full Analysis Set (FAS) and include assessments collected on or before the dosing interruption on 04 December 2019 for patients < 14 years of age (pause due to partial FDA clinical hold) and 24 January 2020 for patients ≥ 14 years of age (pause due to futility). The Principal FAS included all enrolled patients who had a baseline WBCT HO volume measurement and at least 1 post-baseline WBCT HO volume measurement.

Interim Analyses

Based on the pre-specified SAP, 3 interim efficacy analyses and 1 final analysis were planned. The first interim analysis would be conducted when 35 patients completed 1 year of follow-up. The second and third interim analyses would be conducted when all patients completed (ie, had WBCT HO volume data) 12 months and 18 months of follow-up, respectively.

At IA2, the futility boundary was crossed, and the Sponsor paused dosing, as required in the protocol and the data were unblinded. The review of the post hoc analyses showed evidence of benefit of palovarotene, and it was thus decided that palovarotene could be continued in patients ≥ 14 years of age.

Primary Endpoint Analyses

The pre-specified primary efficacy analysis, introduced in Protocol Amendment 1 (before IA2), used a Bayesian compound Poisson model that parameterizes the new HO volume by the number of body regions with new HO (volume of new HO > 0 mm^3) and the new HO volume per region given that there is new HO. The model for the primary analysis incorporated a square-root transformation of HO volume per region per timepoint and required that new HO volumes be non-negative, such that negative values, which correspond to a larger volume of HO at baseline than at a post-baseline timepoint (and can happen due to bone remodelling, measurement variability, or an artifact of the imaging), are set to zero. The requirement for changes in volume to be non-negative stems from the definition of new HO in a region implemented in the model as corresponding to volume of new HO > 0 mm^3. Covariates are included in the primary efficacy analysis via the model for the number of body regions with new HO to adjust for potential explained differences in the rate of new HO based on the patient's sex and age (< 18, ≥ 18 years) at study entry.

The Original Protocol included a wLME model with total HO volume at baseline divided by age at baseline as fixed effects, a random subject effect, and weights proportional to observation time as the primary efficacy analysis method, with no square-root transformation. However, the protocol was amended to use the Bayesian analysis with square-root transformation when early emerging data from the NHS, using a different single-reader paradigm, showed more variability (ie, extreme values) than anticipated. The square-root transformation shrinks larger values toward zero more than smaller

values (eg, 4 is closer to 5 than 16 is to 25) and thus was expected to reduce the variance.

Note that, as was realized after IA2 at which futility was observed, the Bayesian analyses in which square-root transformation is applied to new HO in each body region in each time interval are biased against palovarotene and this bias seems to explain much of the difference in the results between with and without square-root transformation analyses. This is due to the more frequent WBCT scans collected during Study 301, which were acquired every 6 months, relative to in the NHS, which were conducted annually.

To illustrate the impact of the WBCT assessment timepoint differences, consider the following 2 examples:

Example 1:

2 patients – both with identical new HO volume increases of 8,000 mm^3 in one body region in the NHS and Study 301 over the first year:

- In the NHS, the volume would appear as 8,000 mm^3 over 12 months.
- In Study 301, the volume could be split across two 6-month intervals: 4,000 mm^3 in the first 6-month interval and 4,000 mm^3 in the next 6-month interval.
- **Without square-root transformation**, the sum of new HO volume is the same in both patients (8,000 mm^3).
- **With square-root transformation**, the new HO volume in the NHS is $\sqrt{8000}=89.4$, while the sum of the square-roots in Study 301 is $\sqrt{4000}+\sqrt{4000}=63.2+63.2=126.4$, which is substantially larger than 89.4.

While each patient accumulated the same HO volume, when using the square-root transformation it would have inappropriately appeared as if the annualized new HO volume was greater in the treatment arm, biasing against palovarotene.

Example 2:

2 patients – 1 patient with twice as much new HO volume increase in the NHS (8,000 mm^3) compared with a second patient in Study 301 (4,000 mm^3) in one body region over the first year:

- In the NHS, with square-root transformation ($\sqrt{8,000}$), the volume is 89.4 mm^3 over 12 months
- In Study 301, with the square-root transformation, the volume could be split across two 6-month intervals: 44.7 mm^3 ($\sqrt{2,000}$) in the first 6-month interval and 44.7 mm^3 ($\sqrt{2,000}$) in the next 6-month interval.
- **Without square-root transformation**, the sum of new HO volume is twice as much in the NHS compared with Study 301 (8,000 vs 4,000 mm^3).

- **With square-root transformation**, the transformed data in the NHS is $\sqrt{8,000}=89.4$ mm^3, while the sum of the transformed data in Study 301 is $\sqrt{2,000}+\sqrt{2,000}=44.7+44.7=89.4$ mm^3.

While the patient in Study 301 actually had a notable 50% reduction in HO volume, the treatment effect is completely masked by inappropriately using the square-root transformation. Additionally, applying a square-root transformation ignores the empirical data of the negative values in both the palovarotene and the untreated groups. It is therefore appropriate that analyses which can accommodate the data as collected described below (including the wLME, the original pre-specified statistical model) be performed and duly considered in a comprehensive assessment of the efficacy of palovarotene.

Additional details regarding the statistical analyses are provided in Section 10.4.

To support the results on the corrected primary analysis, additional analyses were performed to show the robustness of the results to outliers, negative values, missing data, imbalances/covariates between the NHS and Study 301, as well as sensitivity and supplementary analyses. Results of the primary analysis and supporting sensitivity analyses are provided in Section 5.3.4.

Secondary Endpoint Analyses

The proportion of patients with any new HO and the number of body regions with any new HO were compared across studies using estimates from the Bayesian primary efficacy analysis. Additional analyses were also performed in which the proportions of patients with any new HO at 12 months were compared with a Fisher exact test and the number of body regions with any new HO at 12 months were compared using negative binomial regression.

The proportion of patients with any flare-ups and the flare-up rate per patient-month exposure were analyzed using a Fisher exact test for the difference in proportions and negative binomial regression, respectively.

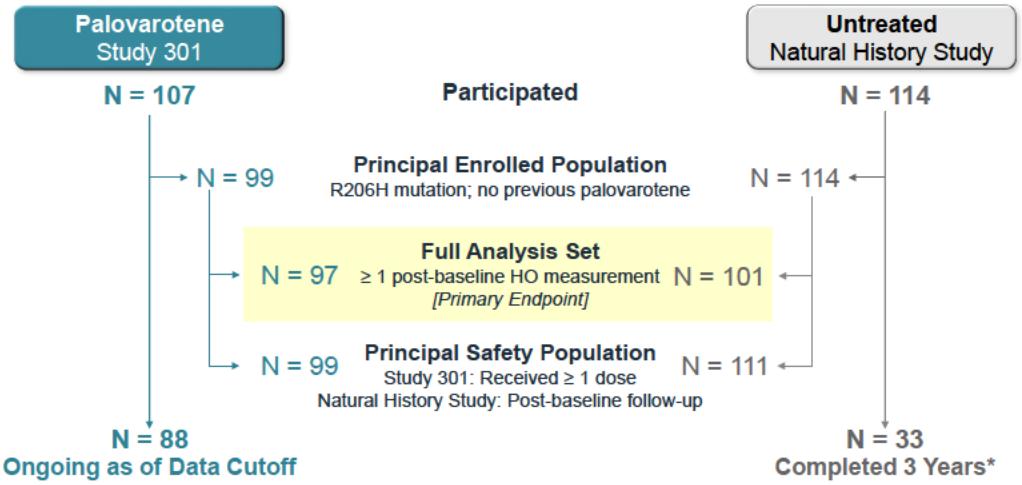
5.3.2 Patient Disposition

A total of 107 patients participated in Study 301 and 114 in the NHS (Figure 21). The Principal Enrolled Population includes 99 palovarotene-treated patients who met all inclusion criteria, including confirmation of an *ACVR1/ALK2 R206H* variant. Eight palovarotene-treated patients who met the additional eligibility criteria comprise the Supplementary Enrolled Population. All patients in the NHS had the *ACVR1/ALK2 R206H* variant.

The primary analysis was conducted on data from all patients from the Principal Enrolled Population who had at least 1 post-baseline assessment. The Principal Safety Population includes all patients from the Principal Enrolled Population who received at least 1 dose of palovarotene and all untreated patients with post-baseline follow-up.

Most palovarotene-treated patients (82%) in Study 301 remained on study through 18 months. The primary reasons for discontinuation were withdrawal by patient (10%) and AEs (5.6%). At the time of the February 2020 data cutoff, 88 palovarotene-treated patients were ongoing in Study 301. No patients had completed the study by the data cutoff date. A total of 114 untreated patients participated in the NHS, and 81 patients discontinued the study. Of patients who discontinued, the majority transitioned into a palovarotene study (39 enrolled into Study 301, 21 enrolled into Study 201 or 202).

Figure 21: Patient Disposition in Pivotal Phase 3 Study 301 at IA3



HO=heterotopic ossification; R206H=activating variant in bone morphogenetic protein type 1 receptor gene *ACVR1/ALK2*.
*Majority transitioned to other palovarotene studies
Note: February 2020 data cutoff date

5.3.3 Baseline Demographics

Demographic and baseline characteristics in the overall population are summarized in Table 3. The demographics of the overall population are sufficiently similar to support comparison of the results between the studies and are representative of patients with FOP. Both groups were generally balanced with respect to demographic information except for age category. Most patients in both groups were younger than 18 years of age but with a higher percentage of palovarotene-treated patients (76%) than untreated patients (60%) in this age category. Baseline medications are provided in Section 10.2.

Almost all patients in both groups had experienced a flare-up, with a median of 1 flare-up within the past 12 months prior to study in both groups. The mean number of flare-ups within the past 12 months (1.4 in palovarotene-treated patients and 2.5 in untreated patients) was higher than the median (1.0 in palovarotene-treated patients and 1.0 in untreated patients); however, the difference in mean number of flare-ups recalled by the patient within the past 12 months between treated and untreated patients is almost entirely due to number of flare-ups reported by 3 NHS patients, which were extreme outliers (30, 37, and 40 flare-ups). Without these flare-ups reported, all far larger than the next largest of 10 in either treated or untreated patients, the means are much more

similar (1.4 in palovarotene-treated patients and 1.6 in untreated patients), underscoring the similarity of the 2 groups.

On average, palovarotene-treated patients were younger by approximately 2.5 years than untreated patients. This age difference is reflected in the lower baseline total WBCT HO volumes and lower CAJIS and FOP-PFQ scores in palovarotene-treated patients compared with untreated patients. The age difference does not necessarily mean that the palovarotene group were less likely to progress over time but rather that, due to their age, they had less time for HO development and consequent functional impairment at the time of enrollment. In fact, they may have been more likely to progress given their younger age. For example, the NHS data suggest that patients with FOP will form approximately 25,000 mm^3 of new HO per year; if 62,500 mm^3 of total WBCT HO volume is added to the observed baseline volume in palovarotene-treated patients, the “age-adjusted” volume would be approximately 332,000 mm^3 – and thus similar to untreated patients. The same calculations can be performed for CAJIS (estimated annual change of 0.5 units) and FOP-PFQ (estimated annual change of 1.3%), giving “age-adjusted” values of 11.3 and 47.6, respectively.

Table 3: Demographics and Baseline Characteristics for Palovarotene-treated and Untreated Patients (Principal Safety Set)

	Palovarotene (N=99)	Untreated (N=111)
Age, years		
Mean (SD)	15.1 (9.6)	17.5 (9.8)
Median (min, max)	13.0 (4, 61)	15.0 (4, 56)
Age category, n (%)		
< 18 years	75 (75.8)	66 (59.5)
≥18 years	24 (24.2)	45 (40.5)
Sex, n (%)		
Male	53 (53.5)	60 (54.1)
Female	46 (46.5)	51 (45.9)
Race, n (%)		
White	70 (70.7)	81 (73.0)
Other/Unknown	29 (29.3)	30 (27.0)
Ethnicity, n (%)		
Hispanic or Latino	19 (19.2)	23 (20.7)
Not Hispanic or Latino	69 (69.7)	72 (64.9)
Not reported*	11 (11.1)	16 (14.4)
Total WBCT HO volume (mean)	269,461	308,252
Total regions with HO (mean)	6.4	6.2
CAJIS total score (mean)	10.0	11.8
FOP-PFQ worst score (mean)	44.3	47.0
Patients with history of flare-up, n (%)	99 (100.0)	108 (97.3)
Number of flare-ups within past 12 months		
Mean (SD)	1.4 (1.86)	2.5 (5.98)
Median (min, max)	1.0 (0, 8)	1.0 (0, 40)
Time since last flare-up, months*		
Mean (SD)	24.5 (36.99)	18.9 (31.11)
Median (min, max)	10.3 (1, 199)	6.3 (0, 181)

SD=standard deviation; max=maximum; min=minimum.
Note: The Principal Safety Set for Study 301 includes all enrolled patients receiving at least 1 dose of palovarotene. The Principal Safety Set for the NHS includes patients enrolled with available post-baseline follow-up for the purposes of comparison to Study 301, where applicable.
* Time since last flare-up (months) was calculated as [(ICF-Last flare-up start date)/30.4375]+1

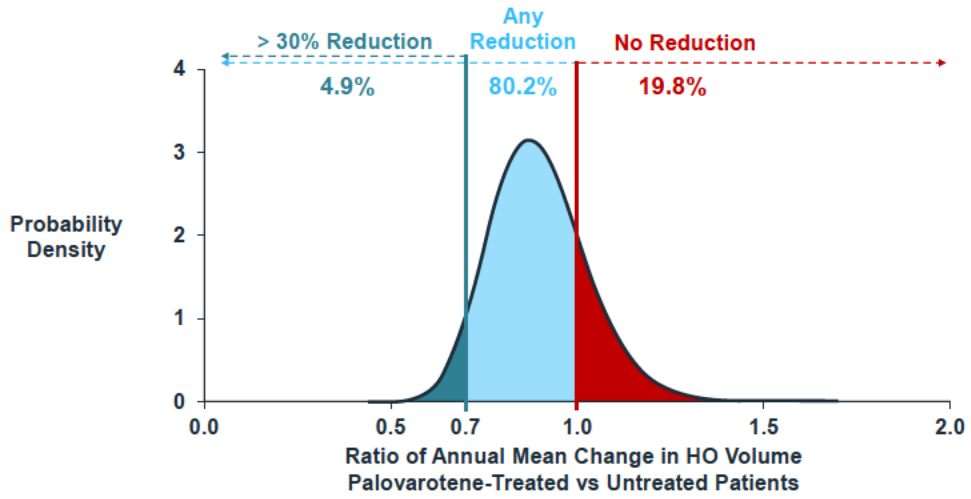
5.3.4 Primary Efficacy Endpoint Results: Mean Annualized New HO Volume

5.3.4.1 Pre-Specified Bayesian Analysis

At IA2, the pre-specified Bayesian compound Poisson model with square-root transformation predicted a 4.9% probability that palovarotene would reduce annual mean new HO volume by ≥ 30% on the square-root scale compared with no treatment,

thus crossing the futility boundary. The model also predicted an 80% probability that palovarotene would reduce new HO volume compared with no treatment. The model fitted a 38% reduction on the standard scale (11% on the square-root scale) for palovarotene-treated patients compared with untreated patients.

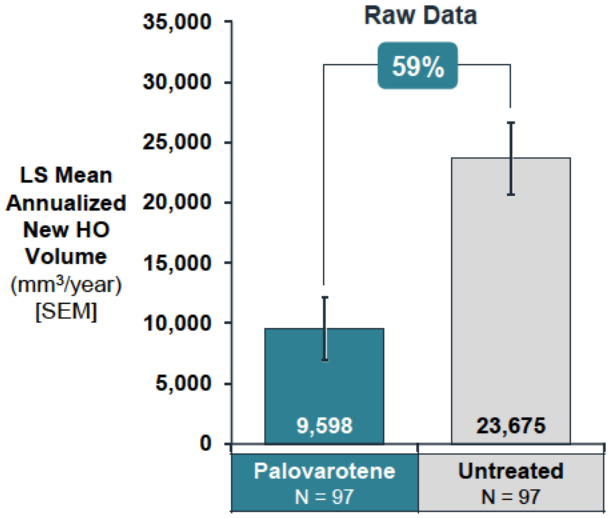
Figure 22: Annualized New HO Volume Using Bayesian Analyses (Square-Root Transformation) in Study 301 at IA2 (Principal FAS Population)



FAS=full analysis set; HO=heterotopic ossification

When the futility boundary was crossed at IA2, palovarotene dosing was paused, and the study data were unblinded. The raw data demonstrated a large effect of palovarotene – a 59% reduction in mean annualized new HO volume in palovarotene-treated patients compared with untreated patients (Figure 23). It was discovered that the results were primarily due to differences between WBCT visit schedules in NHS and Study 301 in conjunction with the square-root transformation, which biased the results against palovarotene due to more frequent assessments in Study 301.

Figure 23: Mean Annualized New HO Volume Using Raw Data in Study 301 at IA2 (Principal FAS Population)



HO=heterotopic ossification

Results from IA3 yielded findings consistent with those from IA2, with 24% longer total follow-up for palovarotene-treated patients. As such, the following sections present the data from IA3.

Assessment of the Impact of the Difference in WBCT Visit Schedules and Square Root Transformation

Table 4 shows the posterior probability of palovarotene efficacy (ie, Pr[γ < 1]) and median posterior γ when the first year of Study 301 new HO volume was collapsed into one 12-month interval, including all data obtained over that 12 months.

Table 4: Posterior γ Using the Data at Protocol-Specified Timepoints and When New HO was Collapsed Over 12 Month Interval in Study 301 With and Without Square Root (Principal FAS)

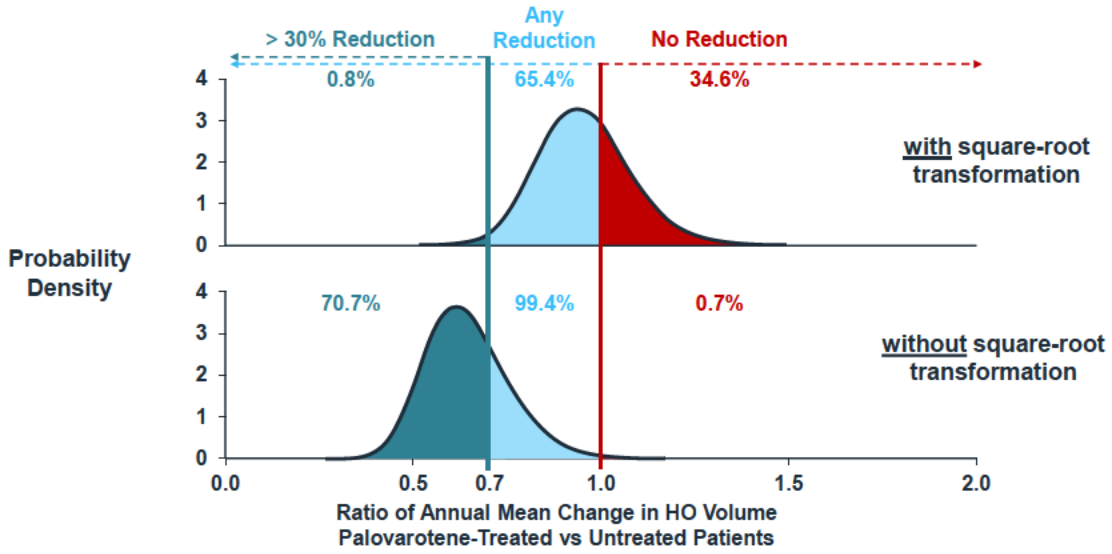
		Posterior Pr(γ < 1)	Median Posterior γ (95% Credible Interval)	% reduction on Sq-root scale	% reduction on Standard scale
Square-root transformation	Collapsed over 12-month interval	0.9065	0.84 (0.64, 1.09)	16%	**36%**
	Protocol-specified timepoints	0.6543	0.95 (0.74, 1.22)	5%	**31%**
No square-root transformation	Collapsed over 12-month interval	0.997	0.61 (0.42, 0.87)	-	**39%**
	Protocol-specified timepoints	0.9935	0.64 (0.45, 0.90)	-	**36%**

FAS=Full Analysis Set; HO=heterotopic ossification

Collapsing new HO in Study 301 for the first year over a 12-month interval when using the square-root transformation fitted an 36% reduction in new HO volume on the standard scale (16% reduction on the square-root scale). This analysis decreases γ, which results in a probability of efficacy (ie, Pr[γ < 1]) of 91%.

Another way to account for the bias of the visit schedule is to remove the square-root transformation in the pre-specified Bayesian analysis. This is presented in Table 4 above and Figure 24 below which shows the results of the primary efficacy endpoint with and without square-root transformation.

Figure 24: Annualized New HO Volume Using Bayesian Analyses in Study 301 at IA3



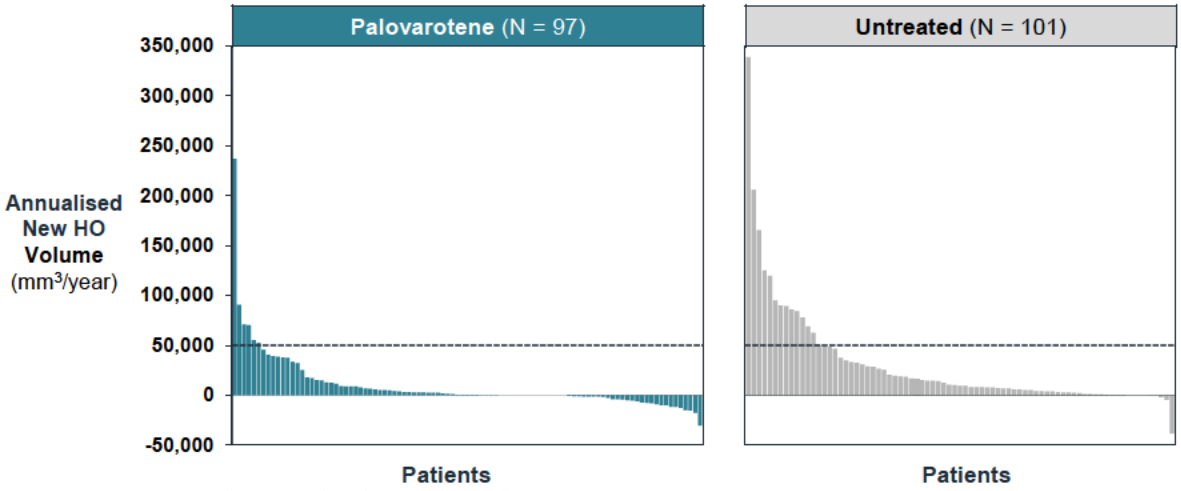
HO=heterotopic ossification

The analysis without the square-root transformation makes the difference in visit schedules no longer an important consideration, while still retaining the same pre-specified analytical approach. The findings presented above demonstrate the influence that the square-root transformation and visit schedule have on the interpretation of palovarotene treatment effect. After collapsing the dataset over 12-month intervals, the bias due to the difference in visit schedules and square-root transformation is reduced and the results are very similar with and without square-root transformation (36% reduction with square-root transformation when no longer on the square-root scale and 39% when the model is fitted on untransformed data) and probability of efficacy (91% with square-root transformation and > 99% without square-root transformation).

5.3.4.2 Negative New HO Volumes in Study 301 and the NHS

Given the variability in disease course among patients with FOP, individual patient-level data are important to the understanding of palovarotene's efficacy. Figure 25 shows mean annualized new HO volume for each individual patient treated with palovarotene in Study 301 and untreated patients from the NHS. While the majority of patients in both groups developed new HO, the overall annualized HO volume was lower in palovarotene-treated patients. Importantly, fewer patients treated with palovarotene had large volume increases in new HO compared with untreated patients. In addition, more palovarotene-treated patients also had negative HO volumes although the studies were not designed to characterize this phenomenon and it was not anticipated at the beginning of the trial that HO would decrease over time.

Figure 25: Annualized New HO Volume by Patient in Study 301 vs Untreated Patients in the NHS (Principal FAS Population)



FAS=Full Analysis Set; HO=heterotopic ossification

The literature provides support for this reduction in bone volume in both genetic and non-genetic forms of HO. In a retrospective review of radiographs, evaluations of 47 patients with FOP demonstrated remodelling of HO characterized by reductions in size and shape of heterotopic bone, with changes similar to what is seen post-fracture in normotopic bone. It was also noted that preosseous lesions may have spontaneous regression, which is more commonly seen in pediatric patients with FOP. The underlying mechanism for this observation is not understood, however once detectable ossification is seen on radiograph, complete resorption was not observed (Kaplan et al 1994).

Moreover, in non-genetic HO in paralyzed or bedridden patients, HO has been observed at different maturity on CT within one area, indicating different stages of bone formation. This allows qualitative grading of maturity as follows:

- Grade 1 – fluid attenuation without evidence of calcification
- Grade 2 – calcification of soft tissues without evidence of bone formation
- Grade 3 – immature bone formation
- Grade 4 – mature bone with cortical differentiation

Grade 1 describes immature HO with low fluid attenuation compared to muscle tissue but without evidence of calcification. As immature HO progressively accumulates calcium from Grade 2 through Grade 4 it mirrors radiographic evidence of bone formation (Ledermann et al 2002).

Progression of HO lesions from an amorphous soft tissue calcification, which may have a component of soft tissue oedema, to mature bone with cortical differentiation may result in overall smaller measurements of HO volume.

These data suggest that the observed reduction in HO volume likely represents maturation of emerging HO, which is not unexpected given that HO in patients with FOP is biochemically and histologically the same as normal skeletal bone. These learnings make the acceptability of manipulating the data by zeroing out negative values in order to utilize square-root transformation clinically unjustified.

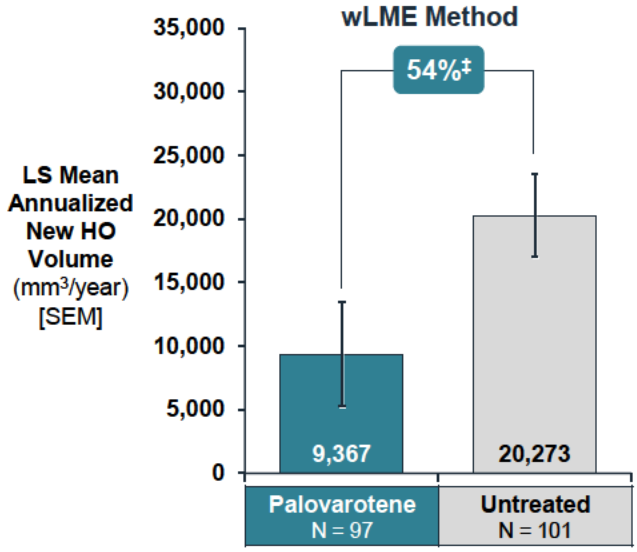
Although it is possible that these negative observations are due to heterotopic bone remodelling as described above, it is acknowledged that they may also be due to measurement variability in patients with negligible changes in HO. It is important to note, however, that the WBCT scans from the NHS and Study 301 were read simultaneously under the same Independent Review Charter in a blinded fashion, and as such any inherent shortcomings of the reads leading to measurement errors would have been applied to both arms. In the empirical data, reductions were noted in both treated and untreated patients alike. And, while we observed more negative values with palovarotene, this would be expected with a treatment that reduces new HO volumes.

As such, inclusion of negatives will not introduce bias but rather more accurately reflect the change in HO volume over time. The Bayesian compound Poisson models with and without square-root transformation require non-negative changes in HO volume for each patient for each region, and any apparent reductions in HO volume (ie, negative new HO volumes) must be "zeroed out." It is therefore appropriate that analyses which can accommodate the data as collected described below (including the wLME, the original pre-specified statistical model) be performed and duly considered in a comprehensive assessment of the efficacy of palovarotene. However, it is reassuring that there is consistent evidence of benefit with palovarotene even when negative values are zeroed out.

5.3.4.3 wLME and GEE Analyses Including All Observed Data

The assessment of mean annualized new HO volume at IA3 was conducted post hoc using a wLME model, without altering of the data; notably, this was the original primary efficacy analysis before the introduction of the Bayesian compound Poisson analysis with square-root transformation as the new primary analysis in Protocol Amendment 1. The wLME model, adjusting for baseline covariate of baseline total HO volume/baseline age (ie, average yearly HO volume prior to study participation) showed a mean reduction of 54% when comparing data from palovarotene-treated patients with untreated patients (nominal p=0.0392) (Figure 26).

Figure 26: Mean Annualized New HO Volume at IA3 (Principal FAS)



FAS=full analysis set; HO=heterotopic ossification; wLME=weighted linear mixed effects model; SEM=standard error of the mean; LS=least square
‡ Nominal p-value=0.0392

Using the GEE analysis method without weights, which was a pre-specified sensitivity analysis, the fitted mean annualized new HO volume was also reduced by 54% in palovarotene-treated patients (9,367 mm^3) as compared with untreated patients (20,273 mm^3) (nominal p=0.0106). The consistency with wLME and the stronger inference with GEE provide reassurance that the conclusions do not depend on the choice of regression method.

5.3.4.4 Sensitivity Analyses of the Primary Endpoint

Analysis with Adjustment for Additional Covariates

In the wLME analysis, the mean observed annualized new HO volumes with additional covariates included in the model was reduced by 56% (nominal wLME p=0.0314) in palovarotene-treated patients compared with untreated patients. The model includes baseline total HO volume divided by baseline age, baseline age, sex, baseline months since last flare-up, baseline CAJIS and treatment as covariates, noting that this analysis includes annualized HO volume for 4 fewer untreated patients than the original analysis due to missing data for the additional covariates.

Propensity Score Analysis

The mean observed annualized new HO volumes were compared using wLME analysis with propensity score quartile as a covariate. Similar to the analysis with the additional covariates, 4 untreated patients were omitted due to missing data in covariates. The wLME fitted mean annualized new HO volume was reduced by 57% in palovarotene-treated patients compared with untreated patients (nominal p=0.0264).

Note that propensity scores are also used in the matched pairs and propensity weighting analysis of patients who participated in either Study 301 or NHS (Section

5.3.4.6). In those analyses, propensity scores are used to create the matched pairs and weighting scores for use with the paired t-test.

Tipping Point Analysis

Table 5 presents the wLME analysis for annualized new HO volume (with no square-root transformation and negatives included) using a tipping point analysis for missing data through Month 18 in palovarotene-treated patients from Study 301. The data included in untreated patients from the NHS are unchanged from the wLME with no square-root transformation and negatives included; no imputation was performed for missing data in this population.

A total of 10 datasets were simulated per each scenario (0% to 100% effect retained) where missing HO volume data were multiply imputed. Of the expected 297 WBCT timepoints (99 patients with 3 post-baseline visits [Months 6, 12, and 18]), data are available from 250 (84%) timepoints:

- 63 patients had complete data at Months 6, 12, and 18.
- 36 patients had incomplete data, consisting of 44 missing data points (14%) and had their missing timepoints multiply imputed:
    - 2 patients with no data post-baseline (total of 6 missed visits),
    - 4 patients with only a Month 6 visit (total of 8 missed visits),
    - 30 patients with Months 6 and 12 visits (total of 30 missed visits).

In the first row in Table 5, the wLME LS mean annualized HO volume observed in Study 301 (ie, 9,367 mm^3 or equivalently 20,273 mm^3 [NHS] - 10,906 mm^3 [100% of treatment effect retained]), is assumed as the mean annualized HO volume in the intervals for which new HO volume was not available. This mean is used to multiply-impute (ie, impute multiple times) the new HO volume for the missing WBCT in order to analyze a ‘complete’ dataset (ie, with the full complement of 297 WBCT timepoints). In the second row in Table 5, 12,639 mm^3 (or equivalently 20,273 mm^3 [NHS] - 0.7*10906 mm^3 [70% of treatment effect retained]), is used in the multiple imputation. In the final row in Table 5, 31,179 mm^3 (or equivalently 20,273 mm^3 [NHS] - (-1)*10906 mm^3 [-100% of treatment effect retained]), is used in the multiple imputation.

The nominal p-value tips above 0.05 (p=0.0502) at a treatment effect of -100% (ie, the magnitude of the LS mean treatment effect estimate on top of the NHS LS mean annualized HO of 20,273 mm^3, or 31,179 mm^3), supporting the robustness of results to changes in missing data assumptions, including assumption of missingness not at random. The consistency of these results reflects the completeness of the Study 301 dataset through Month 18.

Table 5: wLME for Annualized New HO Volume (No Square-root Transformation and Negatives Included) in Tipping Point Analysis (Principal Enrolled Population)

% Observed Treatment Effect Retained	Number of Patients	LS Mean (SEM) mm^3 (NHS-301)	LS Mean % Reduction (NHS-301/NHS)	Treatment p-value
100%	99	-12577.9 (4615.5)	60.6	0.0064
70%	99	-12054.3 (4614.9)	58.0	0.0090
50%	99	-11705.5 (4615.3)	56.3	0.0112
20%	99	-11182.5 (4617.3)	53.8	0.0155
0%	99	-10833.9 (4619.5)	52.1	0.0190
-10%	99	-10659.6 (4620.8)	51.2	0.0211
-20%	99	-10485.4 (4622.4)	50.4	0.0233
-30%	99	-10311.2 (4624.0)	49.6	0.0258
-100%	99	-9091.7 (4641.1)	43.6	0.0502

HO=heterotopic ossification; LS mean=least squares mean; NHS=Natural History Study; SEM=standard error of the mean; wLME=weighted linear mixed effect model
Note: The annualized new HO wLME LS mean 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 patient effect. % reduction is average % reduction across the mixed effect models (10 datasets).
Note: The Principal Enrolled Population includes imputed data for 2 patients without post-baseline HO.

Assessment of the Impact of Extreme Values for Annualized New HO in Study 301 and the Natural History Study

To determine whether extreme values for annualized new HO volumes in Study 301 and the NHS unduly influence the described treatment effect, annualized new HO values > 100,000 mm^3 were set to 100,000 mm^3 (4 patients in the NHS and 1 patient in Study 301). The results of the wLME analysis are shown in Table 6.

Table 6: wLME for Annualized New HO Volume Truncating Values > 100,000 mm^3 in Study 301 (Principal FAS)

		Palovarotene (N=97)	Untreated (N=101)
New HO (mm^3)	Mean (SEM)	8016.7 (2195.3)	19194.4 (3014.6)
	% reduction (palovarotene vs untreated)	58.2%	
	LSmean (SEM)	8685.6 (2811.1)	17742.4 (2413.4)
	% reduction (palovarotene vs untreated)	51.0%	
		wLME estimate (95% CI)	p-value
	Intercept	14936.1 (8475.0, 21397.2)	< 0.0001
	Baseline total HO volume/baseline age	0.2 (-0.10, 0.48)	0.1863
	Treatment	-9056.8 (-15874.7, -2265.9)	0.0103

FAS=Full Analysis Set; HO=heterotopic ossification; LSmean=least square mean; SEM=standard error of the mean; wLME=weighted liner mixed effect
Note: Annualized new HO volume 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 volume/baseline age and a random subject effect.

The wLME fitted annualized new HO volume was significantly reduced by 51% in palovarotene-treated patients compared with untreated patients through Month 12 (nominal p=0.0103).

5.3.4.5 Patients Who Transitioned from the NHS to Study 301

An analysis was performed on the 39 untreated patients in the NHS who transitioned to palovarotene in Study 301 and contributed post-baseline data to both studies. This analysis is important as these patients serve as their own control, having provided data during standard of care treatment and during palovarotene in addition to standard of care treatment, providing further reassurance that observed efficacy is not due to confounding by differences between patients in each study.

Investigators were able to screen patients in the NHS who wished to participate in Study 301 and enroll those who met all inclusion/exclusion criteria. No proactive selection process occurred for patients in the NHS who were eligible to enroll into Study 301; information was available to all patients with FOP through clinicaltrials.gov and the International Fibrodysplasia Ossificans Progressiva Association website.

The demographics and baseline characteristics in the 39 patients who transitioned from the NHS to Study 301 at the NHS baseline and Study 301 baseline are shown in Table 7. Patients were older at Study 301 baseline (mean age 15.3 years) than the NHS baseline (mean age 13.1 years). Consistent with what would be expected for disease progression, patients also had higher total HO volume (259,186 mm^3 and 207,890 mm^3, respectively) and higher CAJIS and FOP-PFQ scores at Study 301 baseline compared with NHS baseline. The mean and median number of flare-ups within 12 months prior to study enrollment was 3.7 and 1.0 at the NHS baseline, respectively, and 1.1 and 0.5 at Study 301 baseline, respectively.

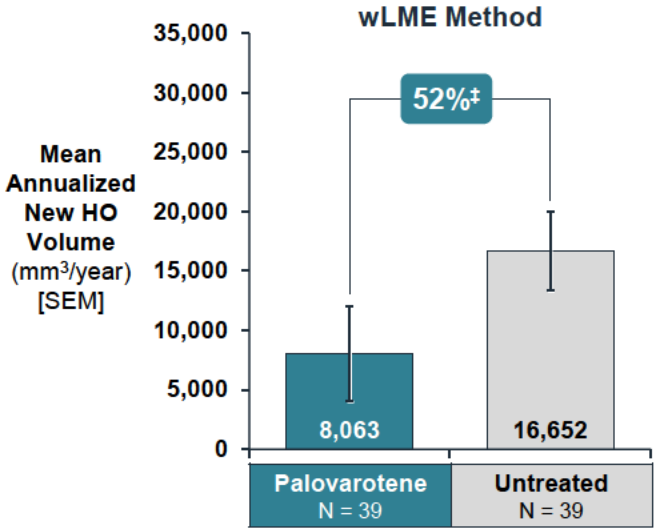
Table 7: Select Demographics and Baseline Characteristics in Patients who Transitioned from the NHS to Study 301 (Principal FAS)

	NHS Baseline (N=39)	Study 301 Baseline (N=39)
Age at enrollment, years		
Mean (SD)	13.1 (7.5)	15.3 (7.5)
Median	11.0	13.0
Range	4, 29	7, 32
Screening WBCT total HO volume, mm^3		
Mean (SD)	207890.3 (278910.5)	259186.4 (326642.9)
Median	114050.0	169240.0
Range	0, 1255360	0, 1335080
Baseline total number of regions with HO		
Mean (SD)	5.9 (2.4)	6.3 (2.1)
Median	6.0	6.0
Range	0, 9	0, 9
Number of flare-ups within 12 Months prior to enrollment		
Mean (SD)	3.7 (8.6)	1.1 (1.4)
Median	1.0	0.5
Range	0, 40	0, 5
Time since last flare-up, months		
Mean (SD)	16.76 (29.6)	16.96 (17.9)
Median	4.14	11.86
Range	0, 161.5	1.1, 84.7
Baseline total CAJIS score		
Mean (SD)	9.6 (6.7)	10.4 (5.9)
Median	7.0	9.0
Range	1, 25	1, 24
Baseline FOP-PFQ percent of worst score		
Mean (SD)	42.24 (23.2)	44.99 (24.9)
Median	45.54	46.2
Range	1.8, 92.0	1.8, 98.2

CAJIS= Cumulative Analogue Joint Involvement Scale; FAS=Full Analysis Set; FOP=fibrodysplasia ossificans progressiva; FOP-PFQ=FOP-Physical Function Questionnaire; HO=heterotopic ossification; NHS=Natural History Study; SD=standard deviation; WBCT=whole-body computed tomography
Note: Values included correspond to visits on or before 4 December 2019 for patients < 14 years of age (at date of visit) and on or before 24 January 2020 for patients ≥ 14 years of age; this logic is also used in most Study 301 efficacy tables in NDA.
Note: NHS flare-ups include telephone contact and in-clinic visit flare-ups. Only NHS data through Month 24 are included. Only Study 301 flare-ups reporting > 1 symptom are included.

Based on the wLME analysis in the 39 patients who transitioned from the NHS to Study 301, there was a 52% lower annualized new HO volume during palovarotene treatment in Study 301 compared with no treatment in the NHS (nominal p=0.0634) (Figure 27).

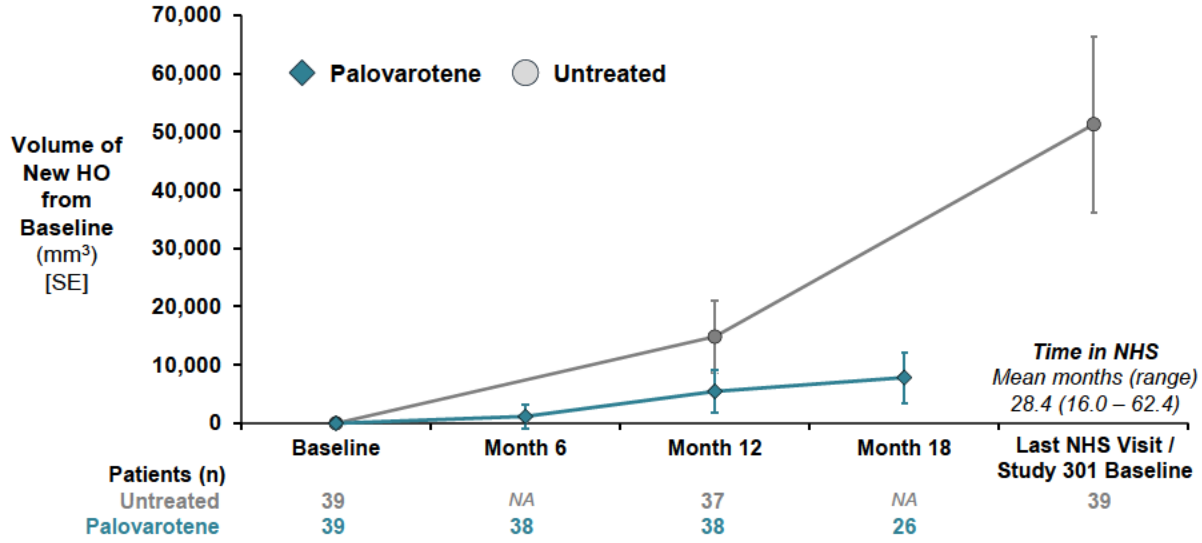
Figure 27: Mean Annualized New HO Volume in Patients who Transitioned from the NHS to Study 301 (Principal FAS)



FAS=Full Analysis Set; HO=heterotopic ossification; LS=least squares; SEM=standard error of the mean; wLME=weighted linear mixed effects model
‡ Nominal p-value=0.0634
Note: Post hoc wLME model (no square-root transformation, all observed data without alteration) in Principal FAS Population.

While WBCT was conducted at different time intervals between the studies, and the number of patients with long-term follow-up is limited, the trajectory of new HO volume while receiving palovarotene was minimized through 18 months of follow-up compared with the time in NHS (Figure 28).

Figure 28: Volume of New HO Over Time in Patients who Transitioned from the NHS to Study 301 (Principal FAS)



FAS=Full Analysis Set; HO=heterotopic ossification; NHS=Natural History Study; SE=standard error

5.3.4.6 Matched Pairs and Propensity Score Weighting Analysis of Patients in Study 301 vs Patients who Participated in the NHS Only

Matched Pairs Analysis

A matched pairs analysis was conducted on change in HO volume in palovarotene-treated and untreated patients using data from patients receiving palovarotene in Study 301 and patients in the NHS who did not go on to receive palovarotene in Study 301. All patients who crossed over from the NHS to Study 301 were excluded from the analysis. Baseline was defined as the baseline visit in Study 301 for palovarotene-treated patients and the first assessment in the NHS for untreated patients.

To assess the relationship between annualized new HO volume and treatment group, matching across groups was implemented based on propensity scores. Propensity scores were estimated based on a multivariable logistic regression model. Group membership (treated or untreated) served as the dependent variable; age-adjusted baseline HO volume, baseline age, sex, months since last flare-up, and baseline CAJIS served as independent variables. Model diagnostics included inspection of deviance residuals and assessment of calibration via the Hosmer and Lemeshow test.

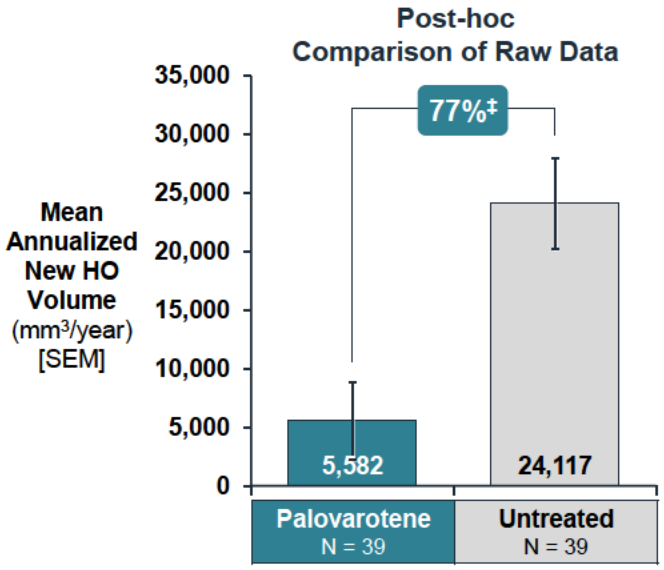
Each untreated patient was matched with a treated patient to the extent possible based on the distribution of propensity scores and a caliper matching algorithm with a tolerance of 0.2 standard deviations (SDs). Adequacy of the matching was further assessed in terms of summary statistics for baseline characteristics after matching, including standardized mean differences for continuous measures.

Two-sample t-tests were used to compare the mean annualized new HO volume across the matched treated and untreated patients. Sensitivity analyses were conducted with the square-root of HO volume reduction, and with reductions in new HO volume coded as zero change.

A total of 58 palovarotene-treated and 62 untreated patients were included in the analysis. Among these patients, 61 untreated patients were included in the propensity score analyses; 1 untreated patient was excluded due to a missing value for time since last flare-up. Overall, a total of 78 patients were successfully matched and had no significant differences in baseline characteristics (39 treated and 39 untreated patients).

The matched analysis of reduction in HO volume in palovarotene-treated and untreated patients is shown in Figure 29. In palovarotene-treated patients, the mean annualized new HO volume was 5,582 mm^3, compared with 24,117 mm^3 in untreated patients. The difference between the untreated and palovarotene groups, 18,534 mm^3, was statistically significant (nominal p-value < 0.05). This matched pairs analysis supports that efficacy is not an artifact of confounding of differences between patients in Study 301 and the NHS.

Figure 29: Matched Analysis of Reduction in New HO Volume Among Palovarotene-Treated (Study 301) and Untreated (NHS) Patients with FOP



FOP=Fibrodysplasia Ossificans Progressiva; HO=heterotopic ossification; SEM=standard error of the mean
‡ Two sample t-test p-value < 0.05

Propensity Score Weighting Analysis

An analysis was also performed using propensity score weighting of baseline characteristics. For the propensity score weighting analysis, both stabilized and unstabilized weighting methods were used, and each patient was assigned a weight based on their propensity score value. Unstabilized weights for treated and untreated patients were calculated as the inverse of the propensity score and the inverse of one minus the propensity score, respectively; stabilized weights were calculated by multiplying the unstabilized weights by the marginal probability of receiving treatment.

There was a nominally statistically significant difference in annualized new HO volume among treated and untreated patients when using both unstabilized and stabilized (Table 8) weights.

Table 8: Propensity Score Weighting Analysis of Reduction in New HO Volume in Study 301 and NHS Patients[a,b]

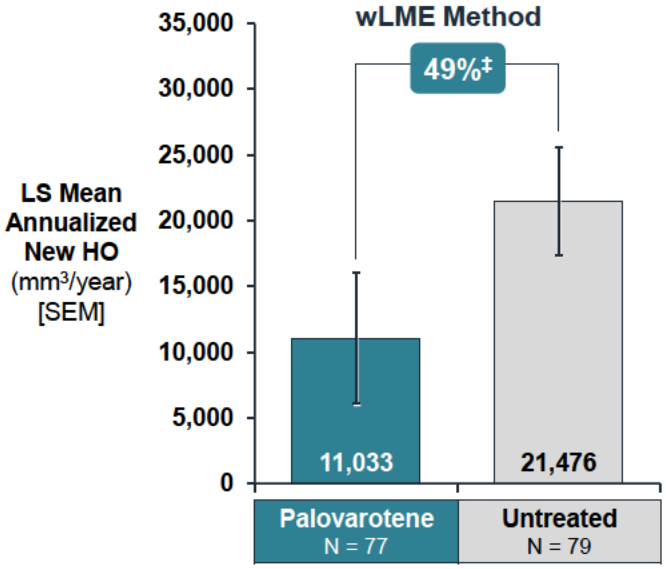
Analysis:	Palovarotene Study 301	Untreated NHS	Mean Difference (301-NHS)	p-value
Weighted analysis	**N=58**	**N=61**		
Stabilized weighting				
Annualized New HO Volume mm^3				
Mean ± SD	9,494.49 ± 33,033.78	28,924.87 ± 57,310.53	-19,430.38 ± 8,524.00	< 0.05
Median (range)	30.16 (-30,245.38, 236,803.75)	5,518.35 (-37,944.49, 339,328.08)	–	–
IQR	(-2,057.84, 8,806.47)	(0.00, 33,396.97)	–	–

HO=heterotopic ossification; IQR=interquartile range; NHS=Natural History Study; SD=standard deviation.
[a] Means and standard deviations are shown for continuous characteristics; counts and percentages are shown for categorical characteristics, unless otherwise noted.
[b] Statistical comparisons were assessed using 2 sample t-tests for continuous variables, and chi-squared tests for categorical variables.

5.3.4.7 *Analysis of Mean Annualized New HO Volume in Target Population*

Analysis of the annualized new HO volume in the target population (≥ 8/10) using the wLME model adjusting for baseline covariate of baseline total HO volume/baseline age showed a 49% reduction in palovarotene-treated patients compared with untreated patients (nominal p=0.1124) (Figure 30).

Figure 30: Mean Annualized New HO Volume for the Target Population in Study 301 at IA3 (Principal FAS Population)



FAS=full analysis set; HO=heterotopic ossification; LS=least squares; SEM=standard error of the mean; wLME=weighted linear mixed effects model
‡ Nominal p-value=0.1124
Note: Post hoc wLME model (no square-root transformation, all observed data without alteration) in Principal FAS population.

Overall, results from the primary endpoint demonstrate that palovarotene reduced the volume of new HO in patients with FOP, both in the FAS and target population. These results are expected to change the trajectory of the disease course over the lifetime of patients with FOP.

5.3.4.8 Other Subgroup Analyses

Palovarotene also demonstrated a reduction in new HO across patient subgroups, including age, sex, and race.

Palovarotene treatment was associated with a 58% reduction in new HO in patients ≥ 8/10 to < 14 years of age and a 44% reduction in patients ≥ 14 years of age. These data support the benefit of palovarotene across the age ranges included in the target population. While the mechanism of action of palovarotene would not be expected to be different across age categories, additional efficacy analyses by age subgroup were performed at the request of the FDA. Generally, the results show a consistent benefit of palovarotene across age categories; however, it is acknowledged that compared to the overall population, the treatment effect in adult patients ≥ 18 years of age was smaller (8,650 mm^3 in Study 301 vs. 10,650 mm^3 in NHS). Given the natural progression of disease, the accumulated burden of HO was lowest in older untreated patients in the NHS (Figure 12) – which makes it difficult to show a difference in older patients. As patients still form HO into adulthood, palovarotene's effect to reduce HO in this population is expected; even if the relative magnitude is smaller, the functional and quality of life impact may still be important for an individual patient.

Although male patients showed a greater percent mean reduction in annualized new HO volume than female patients (73% vs 26%, respectively; Table 9), there is no mechanistic reason that palovarotene would have a differential effect by sex. The natural history of FOP has not shown that sex is an important factor in HO progression, but rather that age is an important factor. In support of this, the annualized new HO volume was similar between palovarotene-treated male and female patients; however, untreated female patients formed less new HO compared with untreated male patients. The difference within untreated patients may be due to an older female patient population (mean age of female patients was 18.7 years compared with male patients 16.5 years). Additionally, treated female patients were younger than untreated female patients (13.6 years and 18.7 years, respectively). These differences would bias against palovarotene, as younger patients would be more likely to form greater volumes of new HO (Section 5.1).

There were no differences in reductions in annualized new HO volume when looking at race.

Table 9: Mean Annualized New HO Volume by Sex Subgroups (Principal FAS)

Subgroup		Annualized New HO Volume				% Reduction (palovarotene vs untreated)
		Palovarotene N=97		Untreated N=98		
		n	mm^3	n	mm^3	
Sex	Male	51	8,353	56	31,276	73%
	Female	46	10,618	45	14,317	26%

FAS=Full Analysis Set; HO=heterotopic ossification

5.3.5 Secondary Efficacy Endpoint Results

Study 301 pre-specified 2 secondary efficacy endpoints for evaluation:

- Proportion of patients with new HO at Month 12
- The flare-up rate per patient-month exposure through Month 24

In addition, exploratory endpoints included change from baseline in CAJIS score at Month 24 and change from baseline in FOP-PFQ worst score at Month 24. As established in the NHS, the CAJIS and FOP-PFQ are not sufficiently sensitive to demonstrate the loss of physical function in the timeframe of a clinical trial and were therefore included as exploratory only.

5.3.5.1 Proportion of Patients with New HO at Month 12

A similar proportion of palovarotene-treated and untreated patients had any new HO at 12 months, with similar mean number of body regions with new HO (Table 10). Month 12 was chosen for this analysis as it is the post-baseline timepoint with the most consistent amount of follow-up data per group. When interpreted within the context of the post hoc results for annualized new HO volume, these results suggest that while the percentage of patients forming any amount of new HO is similar between the groups, the mean volume of new HO formed by palovarotene-treated patients when there is new HO is less than the volume formed by untreated patients when there is new HO. These findings align with other analyses that have shown that palovarotene reduces new HO formation but does not prevent the accumulation of HO over time.

Table 10: Study 301: Proportion of Patients with Any New HO at Month 12

	Palovarotene N=97	Untreated N=101
Patients with new HO at Month 12, n/N (%)	59/92 (64.1)	56/90 (62.2)
Volume (mm^3) of new HO in patients with new HO at Month 12, Mean (SD)	17,722 (25,284)	40,120 (75,380)
Number of body regions with new HO at Month 12, mean (SD)	1.3 (1.4)	1.5 (1.6)

HO=heterotopic ossification; N=number of patients with assessments

5.3.5.2 Flare-up Rate Per Patient-month Exposure Through Month 24

The percentage of patients reporting at least 1 flare-up (defined as having at least 1 symptom) was 64.6% in palovarotene-treated patients in Study 301 and 54.1% in untreated patients. The flare-up rates (ie, ≥ 1 symptom) per patient-month of exposure were 0.15 (95% CI: 0.13, 0.17) in palovarotene-treated patients and 0.07 (95% CI: 0.06, 0.08) in untreated patients. The overall flare-up rate takes into account all reported flares, including the “index” flare-up (that which initiated palovarotene flare-up dosing in Study 301 or a new flare-up in the NHS) and any flare-up reported during flare-up dosing in Study 301 or the 12-week period after the index flare-up in NHS. The non-index flare-ups are defined as intercurrent or worsening flare-ups.

The overall intercurrent/worsening flare-up rate (95% CI) was 0.28 (0.23, 0.32) in Study 301 and 0.11 (0.08, 0.14) in the NHS. The majority of intercurrent flare-ups occurred within the first 12 weeks of an index flare-up in both studies. Flare-ups observed within the first 4 weeks of the index flare-up were possibly related to rebound of flare-up symptoms following the discontinuation of corticosteroids. The mean and median time between last dose of systemic corticosteroid and onset of the next new flare-up event within flare-up cycle in Study 301 were 22 days and 9 days, respectively, compared with 27 days and 14 days, respectively, in the NHS. In a retrospective flare-up survey of 500 participants reported by Pignolo et al (2016): “43% (126/293) of participants confirmed a rebound effect after completion of a course of steroids, with 65.1% (82/126) reporting the time to rebound being within 1 to 7 days.” Given median time since last systemic glucocorticoid in Study 301 (particularly in the “worsening” category), it is possible that many of these events were secondary to a rebound effect from glucocorticoids.

A key consideration of the differences observed in flare-up rates between studies is the incongruence in the collection of flare-up assessments. The difference in flare-up rates may be due to the more frequent interactions the clinical sites had with the study participants in Study 301 compared with the untreated patients in the NHS. In Study 301, patients and/or their caregivers were asked to telephone site personnel to report potential flare-up symptoms. If a flare-up was confirmed, patients were initially assessed by remote visit at Flare-up Cycle Day 1 and every 4 weeks until the last flare-up in the cycle had resolved and flare-up treatment was completed. Starting with Protocol Amendment 2, all assessments after Week 4 occurred every 8 weeks, and starting with Protocol Amendment 3, assessments occurred every 12 weeks. If a patient experienced an intercurrent/worsening flare-up, or if the Investigator confirmed the presence of a substantial high-risk traumatic event likely to lead to a flare-up at any time during flare-up-based treatment, the 12-week dosing regimen was restarted. Regular contact was also made with the patients at baseline, Week 6, and every 3 months (either in-clinic or remotely). Additionally, patients were asked to document daily flare-up symptoms in a diary, and diaries were specifically reviewed to collect existing, worsening, and new flare-up information at every patient contact.

Compared with the monitoring in the Study 301, patients and/or their caregivers in the NHS were only asked to telephone the site at the time of any suspected flare-up for the duration of participation in the study. If a flare-up was confirmed by the Investigator, then information about the flare-up was recorded. During the 36-month observation period, up to 1 flare-up per year could be evaluated in-clinic on Days 1 and 84, with Day 48 as a clinic visit or telephone contact. Location of flare-up site was specifically captured during flare-up assessments; however, worsening of an existing flare-up was not. Contact was made with patients every 6 months; however, no specific questions were asked regarding occurrence of new-flare-ups during these protocol-specified contact points. Patient diaries to document flare-up symptoms were not used in the NHS.

The differences outlined in flare-up collection and documentation between the 2 studies likely contributed to under-reporting of flare-ups in the NHS. It is also possible that untreated patients in the NHS may have been less motivated to report flare-ups because flare-ups would not be treated. An analysis of patients who transitioned from the NHS to Study 301 showed that fewer flare-ups were reported prospectively during the last 12 months of the NHS (0.6 flare-ups) than retrospectively at Study 301 enrollment based on patient recall (1.1 flare-ups), even though these are the same time periods assessed. This explanation is further supported when comparing the overall flare-up rate in the NHS (0.07 flare-ups per patient-month or 0.84 flare-ups/year) to the reported flare-up rate in the literature (1.9 flare-ups in the preceding year) (Pignolo et al 2016). The reported flare-up rate in the literature is, however, consistent with the flare-up rate collected in Study 301 (0.15 flare-ups per patient-month or 1.8 flare-ups/year).

Additional potential explanations for the differences in flare-up rates were explored. While published literature connects systemic retinoids to inflammatory conditions including skin reactions, myopathies and myositis (Rivillas et al 2020), nonclinical data for palovarotene are conflicting, showing both pro-inflammatory and anti-inflammatory effects. Another possible explanation for the difference observed in the flare-up rate is that retinoid-associated musculoskeletal AEs such as arthralgia, joint swelling, and myalgia, which were commonly seen in the palovarotene clinical program, were misinterpreted and reported as flare-up symptoms. However, given that the flare-up rate in Study 301 is consistent with what has been reported in the literature, the differences in how flare-ups were captured between the studies are likely the largest contributing factor to the observed difference in flare-up rates.

5.3.6 Exploratory Efficacy Analyses

5.3.6.1 Functional Outcomes: CAJIS, FOP-PFQ, and PROMIS Results

Physicians and patients completed assessments of functional outcomes using the CAJIS, FOP-PFQ, and PROMIS. Overall, the results showed that these assessments were not sensitive enough measures to demonstrate the loss of physical function in untreated patients, even with a 3-year study duration.

Cross-sectional analysis of CAJIS score by age and FOP-PFQ by age from the NHS showed an estimated annual rate of change of 0.49 units (in scale 0–30 units) and 1.3% (in a scale 0%–100%), respectively.

Small changes from baseline on the PROMIS questionnaire through Month 24 were seen in palovarotene-treated patients at all post-baseline time points, and the results were similar to those reported in untreated patients.

It was understood prior to Study 301 that these functional assessments were not sufficiently sensitive to demonstrate disease progression over a period of 2 years and therefore were only used as exploratory endpoints.

5.4 Long-term Results

Given the prolonged interruption in dosing due to the partial clinical hold and crossing futility, the primary evidence of efficacy as described in the above sections is derived from the data collected up to the interruptions (pre-pause period). However, as the studies continued through completion, additional efficacy was collected both during off treatment as well as following restart of palovarotene until the time of Last-Patient-Last-Visit (September 2022). To understand HO progression during both on- and off-treatment time periods analyses were performed for distinct time periods defined as follows:

- “Intent-to-Treat (ITT)” period: analyses encompassing the overall ITT from screening through Last-Patient-Last-Visit. Note that this period spans time both on and off treatment and includes all patients regardless of whether they restarted palovarotene treatment or remained off treatment until study completion due to the partial clinical hold or other reason.
- “Post-pause treatment” (ie, post-restart) period for those patients who restarted palovarotene treatment: HO formation can be calculated if 2 or more WBCT scans were obtained during this period. All analyses that include this post-pause time period used the first scan obtained after palovarotene restart as post-pause baseline through to the last observation after palovarotene restart. This time period includes all patients that were on active treatment.
- “Post-off-treatment” period: period from first WBCT scan off treatment secondary to dosing interruption to Last-Patient-Last-Visit for patients who remained off treatment. This period represents therefore solely time off treatment.

Analyses were performed using the wLME as well as GEE modelling without weights, which was a pre-specified sensitivity analysis to confirm the results.

Study 301: ITT Period

Table 11 shows the analysis for annualized new HO volume in the ITT period (baseline to last visit) in Study 301 versus the NHS including the following covariates: baseline total HO, baseline age, sex, baseline months since last flare-up, and baseline CAJIS.

There was a 44% reduction in raw mean annualized new HO volume in palovarotene-treated patients in Study 301 (13,316 mm^3) compared with untreated patients in the NHS (23,656 mm^3). The wLME analysis showed a 46% reduction in the model-fitted mean annualized new HO volume in palovarotene-treated versus untreated patients (nominal p-value=0.0585). Additional analyses using GEE modelling without weights showed consistent results (48% reduction, nominal p-value=0.0477). During the ITT period, patients were on treatment with palovarotene for a mean (SD) of 25.4 (12.5) months and off treatment for 13.1 (9.3) months.

Table 11: wLME for Annualized New HO Volume (additional covariates): Study 301 and NHS ITT Treatment Period

		Palovarotene Study 301 (N=97)		Untreated (N=101)
New HO Volume (mm^3)	Mean (SEM)	13316.2 (3358.3)		23656.4 (4837.7)
	% reduction (palovarotene vs untreated)		43.7	
	wLME LSMean (SEM)	11230.9 (3254.8)		20942.7 (3689.1)
	% reduction (palovarotene vs untreated)		46.4	
	Treatment	wLME estimate (95% CI)		p-value
		-9711.82 (-19793.69, 370.06)		0.0585

HO=heterotopic ossification; N=number of patients with assessments; SEM=standard error of the mean; wLME=weighted linear mixed effects model.
Note: Linear Mixed Effects (LME) is modelled with weights.

Study 301: Post-restart Period

In the post-restart treatment period (ie, patients who restarted palovarotene and had at least 2 WBCT scans post-restart) the mean observed annualized new HO volume was 67% lower in palovarotene-treated patients in Study 301 (7,728 mm^3) than untreated patients in the NHS (23,656 mm^3) (Table 12). This represents an average time back on palovarotene of 14 months. The wLME analysis showed a 70% reduction in the model-fitted mean annualized new HO volume in palovarotene-treated vs untreated patients (nominal p-value=0.4069). Additional analyses using GEE modelling without weights showed consistent results (76% reduction, nominal p-value=0.0133).

Table 12: wLME for Annualized New HO Volume (Additional Covariates): Study 301 and NHS: Post-Restart Period

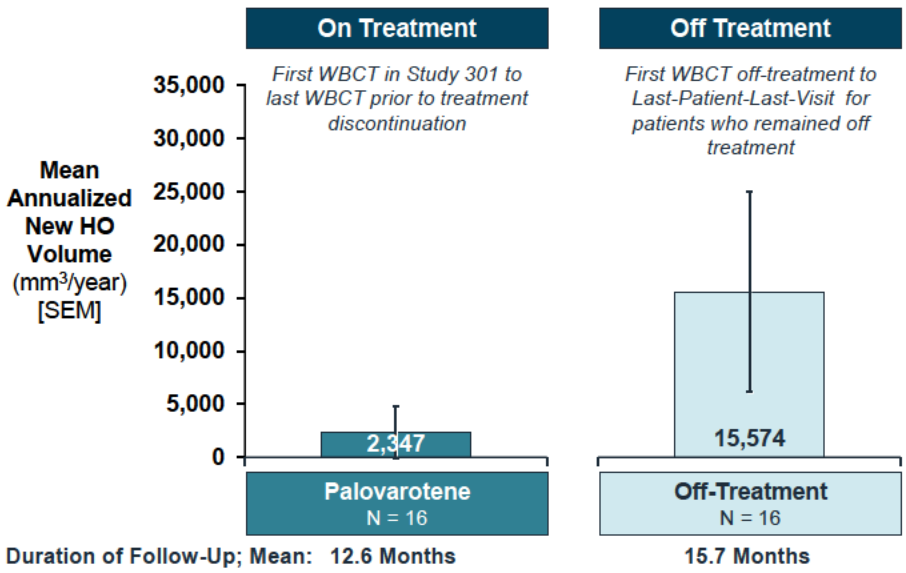
		Palovarotene Study 301 (N=17)	Untreated (N=101)
New HO Volume (mm^3)	Mean (SEM)	7728.1 (4968.4)	23656.4 (4837.7)
	% reduction (palovarotene vs untreated)	67.3	
	wLME LSMean (SEM)	5980.3 (12559.6)	19627.1 (3855.7)
	% reduction (palovarotene vs untreated)	69.5	
	Treatment	wLME estimate (95% CI)	p-value
		-13646.75 (-70002.97, 42709.47)	0.4069

HO=heterotopic ossification; N=number of patients with assessments; SEM=standard error of the mean; wLME=weighted linear mixed effects model.
Note: Linear Mixed Effects (LME) is modelled with weights.

Study 301: Post-Off-Treatment Period

Finally, an analysis was performed using data from the 16 patients from Study 301 who never restarted treatment (Figure 31). This "post-off-treatment period" includes data from first WBCT scan off treatment to Last-Patient-Last-Visit for those patients who remained off treatment, representing time entirely off treatment. As expected, given the time off treatment, mean annualized new HO volume for these 16 patients increased (15,574 mm^3) during this time compared with the mean annualized new HO volume for these same 16 patients during the pre-pause period while on treatment with palovarotene (2,347 mm^3). In addition, there is no evidence for a rebound or withdrawal effect, as the annualized new HO volume during the interruption period was not greater than that observed in the NHS.

Figure 31: Annualized New HO Volume (mm^3) at the Latest Post-Baseline Study 301 by Treatment Population in Patients Who Contributed Data to Both the Pre-Pause Time Period and Post-Off-Treatment Time Period (Principal FAS)



FAS=Full Analysis Set; HO=heterotopic ossification; SEM=standard error of the mean; WBCT=whole-body CT

5.5 Efficacy Conclusions

The efficacy of palovarotene in patients with FOP has been established based on findings from the NHS, Phase 2 Studies 201 and 202, and the pivotal Phase 3 Study 301. Findings from the NHS demonstrated a direct association between higher total body HO volume and worse physical function and supported the assessment of HO volume as the primary endpoint in Study 301. The NHS also served to provide information about flare-up outcomes at 12 weeks in untreated patients to supplement the findings from the Phase 2 studies. Together, the flare-up findings from these studies showed that HO formation may begin before clinical symptoms are present, supporting the use of chronic daily treatment with palovarotene, and suggested that higher flare-up dosing over a longer duration was required to maximally inhibit HO formation.

Efficacy assessments, including WBCT used for the primary efficacy endpoint of annualized change in new HO, were conducted every 6 months in Study 301 and every 12 months in the NHS. The pre-specified Bayesian analysis with square-root transformation introduced bias due to the different WBCT visit schedules in the NHS and Study 301 that inappropriately masked the treatment effect of palovarotene. When accounting for the different visit schedules, the pre-specified Bayesian model predicted a 91% probability that palovarotene would reduce mean annualized new HO compared with no treatment. Another way to account for this bias is to omit the square-root transformation, in which the model predicted a 99% probability that palovarotene would reduce annual mean new HO volume.

However, a major limitation of the Bayesian analysis is that it cannot accommodate negative values which were observed in both studies and should not be ignored when drawing efficacy conclusions. Such reductions were more common in palovarotene-treated patients. As reductions were noted in both treated and untreated patients alike, it is therefore appropriate that analyses which can accommodate the data as collected (including the wLME, which was the original pre-specified statistical model) be performed and duly considered in a comprehensive assessment of the efficacy of palovarotene. The wLME analysis showed a reduction of 54% in new HO volume in palovarotene-treated patients compared with untreated patients.

Furthermore, every additional analysis performed consistently demonstrates evidence of the beneficial effects of palovarotene in reducing new HO volume. The effect of palovarotene on formation of new HO was consistent in patients who transitioned from the NHS to Study 301 as well as those matched for baseline characteristics who did not transition compared with the overall study population. Together these analyses provide further reassurance that the observed efficacy is not due to confounding by differences between patients and support that the NHS is an adequate control for Study 301. A tipping point analysis showed that the missing follow-up annualized HO volume data from patients in Study 301 through Month 18 would need to be double that of the annualized new HO volume in untreated patients from the NHS to tip the p-value > 0.05. Additionally, assessment of the impact of extreme values for annualized new HO

volumes showed that the efficacy observed without square-root transformation and negatives included does not depend solely on the magnitude of the small number of patients with extremely large annualized new HO volume. Finally, the results in the target population were consistent with those in the overall population.

An analysis using the entire data set up to Last-Patient-Last-Visit (September 2022) also showed that annualized new HO volume was less with palovarotene treatment during Study 301 compared with no treatment in NHS. These analyses encompass the prolonged treatment interruption (due to the partial clinical hold and the initial finding of futility), as well as data both from patients that restarted treatment and those that remained off treatment. Overall, annualized new HO volume was less with palovarotene treatment during Study 301 compared with the NHS. This was evident in both the pre-pause and post-pause (restart) time periods. As expected, when dosing was interrupted, data from the entire ITT population (representing both time periods on and off treatment), demonstrated a greater volume of new HO than when data were analyzed in patients who were treated continuously with palovarotene. Despite including the treatment interruption period, annualized volume of new HO was still lower in Study 301 than what was observed in the NHS. Further support is seen in the 16 patients who contributed data both while on treatment and then subsequently entirely off treatment, which showed an increase in annualized volume of new HO during the off-treatment time period. In addition, there is no evidence for a rebound or withdrawal effect, as the annualized new HO volume during the off-treatment period was not greater than that observed in the NHS. In totality, the data summarized here are supportive of a palovarotene treatment effect of reducing new HO formation despite treatment interruption.

6 SAFETY FINDINGS

Summary

- Palovarotene has a well-established safety profile consistent with that of other retinoids based on data from 164 patients with FOP who received at least 1 dose of palovarotene in the FOP development program, as well as > 1000 patients from other indications and healthy participants.
- In the target FOP population, 33 patients (25%) taking palovarotene experienced ≥ 1 severe AE. A total of 57 patients (41%) taking palovarotene experienced ≥ 1 serious AE (SAE).
- The most common AEs were mucocutaneous, most of which were moderate in severity, manageable through dose modifications and supportive care, and reversible after discontinuation.
    - Dry skin, dry lips, alopecia, and pruritus were the most common AEs, affecting 81%, 58%, 42%, and 42% of patients, respectively.
- Dose reductions were often implemented to manage AEs, with 37% of palovarotene-treated patients reporting ≥ 1 AE leading to dose reduction, the majority of which were due to mucocutaneous events.
- Among the 12 patients who discontinued palovarotene due to an AE, dry skin was the only AE cited by more than 1 patient (n=2) as the reason for discontinuation.
- PPC is an important risk of palovarotene treatment and affected 13 out of 39 patients (33%) ages ≥ 8/10 to < 14 years at enrollment across the palovarotene treatment trials; no patients ≥ 14 years of age at enrollment had events of PPC.
- Teratogenicity is a known risk of retinoids which can cause cleft palate, misshapen skull bones, and shortening of long bones; pregnant and breastfeeding women should not take palovarotene.
- The proposed risk minimization measures will inform and guide patients and clinicians on the safe use of palovarotene.

6.1 Overview of Safety Analysis

The safety of palovarotene was extensively studied in nonclinical and clinical settings. The results of the nonclinical safety studies, including those in juvenile rats, suggest that potential adverse effects of administration of palovarotene in humans could include a subset of those produced by vitamin A and other retinoids; primarily mucocutaneous toxicity, skeletal effects resulting from palovarotene's intended inhibition of chondrogenesis, and teratogenicity. Details of the nonclinical safety findings are presented in Section 8.

In the clinical setting, safety data are available from 164 patients with FOP, as well as > 700 patients with multiple osteochondromas (MO) and chronic obstructive pulmonary disease (COPD) and > 300 healthy volunteers. The safety profile of palovarotene in the proposed indication is based on the assessment of 139 patients with FOP in the target population of females ≥ 8 and males ≥ 10 years of age who received chronic and/or flare-up treatment. Searches were performed for potential risks identified from literature outlining safety profiles of marketed oral systemic retinoids and ongoing safety monitoring from the palovarotene clinical development program. Findings on bone safety are provided in Section 6.5. A detailed presentation of additional safety evaluations of special interest is provided in Section 11.2.

All safety data are presented through the data cutoff date of January 2022.

6.2 Treatment Exposure

A total of 164 patients with FOP have received at least 1 dose of palovarotene across the development program, including 139 palovarotene-treated patients who represent the target patient population. Among this target population, mean exposure was approximately 3.5 years (184 weeks), and 78% of patients remained on treatment for more than 30 months (Table 13). Additionally, the safety of palovarotene has been evaluated in > 700 patients from other indications, as well as in > 300 healthy volunteers.

In the target population of females ≥ 8 and males ≥ 10 years of age with FOP, 270 flare-ups were treated in Phase 2 and Phase 3 studies. Most flare-ups were treated with the palovarotene 20/10 mg regimen (or weight-adjusted equivalent), indicating that the safety data described under flare-up dosing is derived primarily from the proposed flare-up treatment.

As no pharmacological intervention was applied to the NHS, only safety issues resulting from any study-related procedure were recorded as AEs; therefore, data are presented below for palovarotene-treated patients in the target population only.

Table 13: Exposure to Study Drug in Target Population (≥ 8/10 Years) Treated with Palovarotene

	Palovarotene N=139
Total exposure, mg	
Mean (SD)	5,781.5 (3,725.4)
Median (min – max)	5,067.0 (133–16,460)
Mean exposure, weeks (SD)	183.9 (82.0)
Total exposure by months, n (%)	
0 – 3 months	6 (4.3)
> 3 months – 6 months	1 (0.7)
> 6 months – 9 months	1 (0.7)
> 9 months – 12 months	1 (0.7)
> 12 months – 18 months	7 (5.0)
> 18 months – 24 months	12 (8.6)
> 24 months – 30 months	3 (2.2)
> 30 months	108 (77.7)

max=maximum; min=minimum; SD=standard deviation
Note: January 2022 cutoff date

6.3 Adverse Events

The safety profile of palovarotene is consistent with the well-established safety profiles reported with other systemic retinoids. While all palovarotene-treated patients experienced at least 1 AE, the majority were mild to moderate (Table 14). A total of 25% of patients experienced severe AEs. Dose modifications were made for 37% of patients, and 9% of patients discontinued treatment due to an AE. The incidence of SAEs was 41% in palovarotene-treated patients. Importantly, no deaths occurred across the entire palovarotene FOP development program, on study or within 30 days after discontinuation of therapy.

Table 14: Summary of Adverse Events in Target Population (≥ 8/10 Years) Treated with Palovarotene

Patients with AEs, n (%)	Palovarotene N=139
Any AE	139 (100)
Mild	24 (17.3)
Moderate	81 (58.3)
Severe	34 (24.5)
AEs leading to dose modification	52 (37.4)
AEs leading to dose interruption	40 (28.8)
AEs leading to study drug discontinuation	12 (8.6)
AEs leading to study discontinuation	4 (2.9)
SAEs	57 (41.0)
Deaths	0

AE=adverse event; SAE=serious adverse event
Note: January 2022 cutoff date

6.3.1 Common Adverse Events

The most frequently reported AEs in the palovarotene group (reported in ≥ 1/3 of patients) were mucocutaneous, consisting of dry skin (81%), dry lips (58%), alopecia (42%), pruritis (42%), and erythema (36%) (Table 28 in Section 11.1). Mucocutaneous events are defined as those involving the skin and mucous membranes. Other AEs reported in over one-third of palovarotene-treated patients were in the *Musculoskeletal and Connective Tissue Disorders* System Organ Class (SOC) and included arthralgia (50%) and extremity pain (42%). Musculoskeletal events (Section 11.2.1) are common in patients with FOP and are often associated with the natural progression of the disease.

6.3.1.1 Mucocutaneous Effects

Mucocutaneous effects, including skin and soft tissue infections, are an expected side effect of retinoids and were the most commonly reported AEs, affecting 99% of patients. The most common AEs observed in ≥ 30% of patients taking palovarotene included dry skin (81%), dry lips (58%), alopecia (42%), pruritus (42%), erythema (36%), rash (33%), generalized pruritus (31%), and skin exfoliation (32%). AEs were generally mild to moderate in severity.

To target uncommon and clinically significant mucocutaneous events, a broad Standardized Medical Dictionary for Regulatory Activities queries (SMQ) for the topic of severe cutaneous AEs was conducted. Based on this analysis, 53% of palovarotene-treated patients had severe mucocutaneous AEs. The most common severe mucocutaneous AEs reported in ≥ 5% of patients included skin exfoliation (32%), drug eruption (ie, retinoid dermatitis; 19%), and blister (7%; Table 15).

Table 15: Severe Mucocutaneous Adverse Events in Target Population (≥ 8/10 Years) Treated with Palovarotene

Preferred Term, n (%)	Palovarotene N=139
Patients with ≥ 1 severe mucocutaneous AE	73 (52.5)
Skin exfoliation	44 (31.7)
Drug eruption	27 (19.4)
Blister	10 (7.2)
Conjunctivitis	6 (4.3)
Stomatitis	5 (3.6)
Skin erosion	2 (1.4)
Bullous impetigo	1 (0.7)
Mouth ulceration	1 (0.7)
Lip exfoliation	1 (0.7)

AE=adverse event; FOP=fibrodysplasia ossificans progressiva
Note: January 2022 cutoff date

Mucocutaneous events were the most common reason for palovarotene dose reductions, which occurred more frequently during flare-up treatment with the 20/10 mg dosing regimen. Most events were manageable through dose modifications and supportive care. Specifically, prophylactic skin care was shown to aid in the management of areas affected by these events. The majority of patients were able to remain on treatment, with only 2 palovarotene-treated patients discontinuing due to a mucocutaneous event. Accordingly, prophylactic measures to minimize risk and/or treat the mucocutaneous effects are recommended in the label (eg, skin emollients, sunscreen, lip moisturizers, artificial tears, or other helpful treatments); a reduced dose may be necessary in the event of intolerable adverse effects.

6.3.2 Severe Adverse Events

Most AEs in the palovarotene group were mild or moderate in severity (17.3% and 58.3%, respectively). Severe events were reported in 24.5% of patients treated with palovarotene (Table 16). The overall incidence of severe AEs was low, with the most common occurring in 3 (2.2%) patients in the palovarotene group including dry skin and cellulitis.

Table 16: Most Common (≥ 2 Patients in the Palovarotene Total Group) Severe Adverse Events in Target Population (≥ 8/10 Years) Treated with Palovarotene

Preferred Term, n (%)	Palovarotene N=139
At least 1 severe AE	34 (24.5)
Dry skin	3 (2.2)
Cellulitis	3 (2.2)
Arthralgia	2 (1.4)
Epiphyses premature fusion	2 (1.4)
Erythema	2 (1.4)
Facial bones fracture	2 (1.4)
Fall	2 (1.4)
Pneumonia	2 (1.4)

AE=adverse event
Note: January 2022 cutoff date

6.3.3 Adverse Events Leading to Dose Reduction

Dose reductions were effective in managing AEs and allowed most patients to remain on treatment. AEs leading to dose reduction were reported in 37% of patients taking palovarotene (Table 17). The most common AEs leading to dose reduction in patients taking palovarotene were mucocutaneous in the SOC of *Skin and subcutaneous disorders*, including dry skin, drug eruption, and pruritis.

Table 17: Adverse Events Leading to Dose Reduction (> 1 Patient) in Target Population (≥ 8/10 Years) Treated with Palovarotene

System Organ Class Preferred Term, n (%)	Palovarotene N=139
Any AE	52 (37.4)
Skin and subcutaneous tissue disorders	**41 (29.5)**
Drug eruption	13 (9.4)
Dry skin	12 (8.6)
Pruritus	8 (5.8)
Pruritus generalized	7 (5.0)
Skin exfoliation	6 (4.3)
Erythema	4 (2.9)
Skin reaction	4 (2.9)
Rash	3 (2.2)
Alopecia	2 (1.4)
Cold sweat	2 (1.4)
Ingrowing nail	2 (1.4)
Swelling face	2 (1.4)
Injury, poisoning and procedural complications	**12 (8.6)**
Skin abrasion	4 (2.9)
Facial bones fracture	2 (1.4)
Eye disorders	**4 (2.9)**
Dry eye	2 (1.4)
Gastrointestinal disorders	**9 (6.5)**
Cheilitis	4 (2.9)
Lip dry	4 (2.9)
Chapped lips	2 (1.4)
Infections and infestations	**3 (2.2)**
Paronychia	2 (1.4)
Psychiatric disorders	**3 (2.2)**
Sleep disorder	2 (1.4)
Respiratory, thoracic, and mediastinal disorders	**2 (1.4)**
Nasal dryness	2 (1.4)

AE=adverse event
Note: January 2022 cutoff date

AEs leading to interruption of palovarotene occurred in 28.8% of palovarotene-treated patients (Table 29 in Section 11.1). The most common AE leading to dose interruption of palovarotene was rash (2.9%) and vomiting (2.9%).

6.3.4 Adverse Events Leading to Treatment Discontinuation

Most of the AEs were manageable with dose modification/interruption, which contributed to a low treatment discontinuation rate (Table 18). Altogether, 8.6% of patients discontinued palovarotene due to an AE, and dry skin was the only preferred term (PT) leading to discontinuation in > 1 patient (1.4%). The remaining AEs leading to discontinuation occurred due to a single AE in each patient. These data support that the safety profile of palovarotene is manageable through dose modifications, and that the majority of patients will be able to remain on treatment.

Table 18: Adverse Events Leading to Treatment Discontinuation in Target Population (≥ 8/10 Years) Treated with Palovarotene

System Organ Class Preferred Term, n (%)	Palovarotene N=139
Any AE	12 (8.6)
Infections and infestations	**4 (2.9)**
Cellulitis	1 (0.7)
Furuncle[1]	1 (0.7)
Localized infection	1 (0.7)
Hemophilus infection	1 (0.7)
Musculoskeletal and connective tissue disorders	**2 (1.4)**
Epiphyses premature fusion	1 (0.7)
Mobility decreased	1 (0.7)
Skin and subcutaneous tissue disorders	**2 (1.4)**
Dry skin	2 (1.4)
Erythema	1 (0.7)
Investigations	1 (0.7)
Amylase increased	1 (0.7)
Lipase increased	1 (0.7)
Metabolism and nutrition disorders	**1 (0.7)**
Malnutrition	1 (0.7)
Nervous system disorders	**1 (0.7)**
Myoclonus	1 (0.7)
Psychiatric disorders	**1 (0.7)**
Depression	1 (0.7)
Intentional self-injury	1 (0.7)

AE=adverse event
Note: January 2022 safety cutoff date

6.3.5 Serious Adverse Events

Serious adverse events occurred in 41% of palovarotene-treated patients (Table 19). The most common treatment-emergent SAEs were PPC (7%); coronavirus infection (8%), condition aggravated (3%), and pneumonia (3%); arthralgia, exposure to

communicable disease, pain in extremity, peripheral swelling, and cellulitis (2.2% each; note that condition aggravated is a manifestation of FOP); and abdominal pain, back pain, coronavirus test positive, pain, respiratory distress, syncope, and impacted tooth (1.4% each). PPC events were upgraded to "Serious" regardless of Investigator decision or criteria in order to ensure they were all comprehensively evaluated and followed. Notably, many of these SAEs were related to the progression of FOP. A detailed discussion of the PPC SAEs is found in Section 6.5.

The remainder of events occurred in single patients (Table 30 in Section 11.1). A medical review of the nature of these isolated events did not reveal any notable pattern of events.

Table 19: Serious Adverse Events (≥ 2 Patients) in Target Population (≥ 8/10 Years) Treated with Palovarotene

Preferred Term, n (%)	Palovarotene N=139
At least 1 SAE	57 (41.0)
Epiphyses premature fusion*	10 (7.2)
Coronavirus infection	11 (7.9)
Condition aggravated	4 (2.9)
Pneumonia	4 (2.9)
Arthralgia	3 (2.2)
Exposure to communicable disease	3 (2.2)
Pain in extremity	3 (2.2)
Peripheral swelling	3 (2.2)
Cellulitis	3 (2.2)
Abdominal pain	2 (1.4)
Back pain	2 (1.4)
Coronavirus test positive	2 (1.4)
Pain	2 (1.4)
Respiratory distress	2 (1.4)
Syncope	2 (1.4)
Tooth impacted	2 (1.4)

FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; SAE=serious adverse event
*4 events of PPC not included; 2 occurred post-treatment, 1 was incorrectly captured as a pre-treatment event, and 1 was incorrectly coded to epiphyseal injury.
Note: January 2022 cutoff date

6.4 Deaths

No deaths were reported during palovarotene treatment or for 30 days post-treatment. In Study 301, a 13-year-old patient with a history of restrictive lung disease died approximately 2.5 months after discontinuing palovarotene treatment and approximately 1.5 months after discontinuing study participation. During study participation, the patient experienced 4 flare-ups (right knee, right thigh, left elbow, right hip) and was treated with flare-up palovarotene dosing. The last flare-up of the hip was ongoing at the time of study discontinuation and at time of death. The patient discontinued study participation

citing disease progression and difficulty traveling. A post-mortem examination revealed the cause of death to be due to restrictive lung disease from complications of FOP.

In the NHS, there was 1 death reported in a 38-year-old female patient who died of cardiac arrest. The patient was diagnosed with FOP at approximately 3 years of age presenting with great toe malformation at birth. The patient had her first flare-up at 2 years of age and experienced 7 flare-ups in the 12 months prior to study enrollment. Medical history included recurring restricted chest expansion, locked jaw, uterine myoma, fractures, ear infections, irritable bowel syndrome, pneumonitis, gastro-esophageal reflux disease, and cholelithiasis. Physical examination at screening included cushingoid features, dental caries, scoliosis, scars on head, finger hypermobility, and inability to open mouth.

6.5 Bone Safety

Systemic retinoids have been associated with a variety of adverse effects on the musculoskeletal system, including PPC, osteoporosis, an increased risk for fracture, and hyperostotic changes or calcification of tendons and ligaments. For this reason, bone safety monitoring programs were implemented across palovarotene studies.

An extensive bone safety monitoring program covered all patients < 18 years of age to evaluate any potential adverse effects of palovarotene on the musculoskeletal system, and growth in patients from Study 301 was compared with untreated patients from the NHS as well as Study 202. These programs included linear and knee height assessments, regularly scheduled hand/wrist and knee radiographs, and WBCT scans, which assessed tibial length, femoral length, and growth plate abnormalities. All imaging was evaluated by 2 trained, independent radiologists, with a third adjudicator as needed. Additionally, the WBCT scans from the NHS, Study 202, and Study 301 were retrospectively reviewed to evaluate the potential impact of palovarotene treatment on the spine including bone density, strength, and bone mineral content (BMC) as well as spinal fracture analysis. This was done using new finite element analysis, a relatively new computational method because standard approaches like DEXA are uninterpretable in patients with FOP.

6.5.1 Premature Physeal Closure

The physeal plate is a ribbon of cartilage through each end of the long bones in children and adolescents where the bone adds length over time and is also referred to as the growth plate. Physeal plate closure is a natural process when growth is complete. If closed prematurely, the long bone cannot achieve mature length leading to shorter stature and potential deformity. The criteria by which the central imaging radiologists determined partial and closure of physeal growth plates at the hand/wrist and knee are as follows:

- Partial Closure: Growth plate has a definite disruption of portions of the adjacent outlines of the epiphyseal and metaphyseal, and

- Closure: Any portion of the growth plate with evidence of closure.

It is important to note that the identification of closure does not necessarily reflect actual 100% closure but spans the earliest sign of any portion of fusion through to full fusion of the epiphysis. Additionally, the determination of whether epiphyseal closure was premature was the responsibility of the Investigator, based on a comprehensive review of all available clinical data and radiographs for each patient. Absolute age criteria were not used to identify PPC.

All events of PPC (PT, epiphyses premature fusion) were categorized as SAEs as recommended by the Sponsor regardless of whether seriousness criteria were met, as shown in Table 20. As of the data cutoff date of January 2022, 27 patients (26.5%) < 18 years of age reported PPC, with all events happening among patients < 14 years of age at enrollment.

Table 20: Premature Physeal Closure in Children < 18 Years of age, by Age Group in Studies 301 and 202

	Palovarotene	
	n/N	%
Total PPC events	27/102	26.5
Ages < 8/10 years	14/25	56.0
Ages ≥ 8/10 to < 14 years	13/39	33.3
Ages ≥ 14 to < 18 years	0/38	0

N=number of assessments; PPC=premature physeal closure
Note: January 2022 cutoff date

A summary of locations of closure for patients with a PPC event as of the last safety update data cutoff date of January 2022 is provided in Table 21.

Table 21: Premature Physeal Closure Events in Children < 18 years of age, by Location in Studies 301 and 202

	PPC Events			
Patients with a PPC event, n	27			
	Radius	Ulna	Tibia	Femur
Patients (%) with status of location: Closed or Partially Closed, n (%)	4 (14.8)	2 (7.4)	16 (59.3)	20 (74.1)
Patients with status of Closed, n (%)	1 (3.7)	0	5 (18.5)	8 (29.6)
Patients with status of Partially Closed, n (%)	3 (11.1)	2 (7.4)	11 (40.7)	12 (44.4)

PPC=premature physeal closure
Note: January 2022 cutoff date

The majority of physes were identified as partially closed at all locations. The proportion of patients having closed or partially closed epiphyses was greatest for the knee (femur [74.1%] and tibia [59.3%]) compared with the wrist (ulna [7.4%], radius [14.8%]).

All events occurred with onset ranging between 6–30 months after treatment initiation. Two events occurred after discontinuation of palovarotene. Of note, 6 patients with PPC

had partial closure of at least at 1 physis at baseline, with subsequent progression of closure or identification of additional anatomical locations with closure, suggesting that the process of physiologic growth plate closure had already begun prior to palovarotene treatment. Consistent with the retinoid literature (Noyes et al 2016), all but one of the PPC SAEs was observed first in the knee, showing that PPC preferentially affects the lower extremities. When contralateral growth plate evaluations were available, growth plate closure was symmetric. When patients were informed of the findings of PPC, approximately half who were still receiving palovarotene decided to continue on treatment, with subsequent interruption at the time of the partial clinical hold.

6.5.1.1 Long-Term Assessment of PPC in the Target Population

To characterize the magnitude of the risk of PPC, the Sponsor has conducted a detailed review of the individual patient profiles, including radiologic and clinical assessments of growth for all 13 patients in the target population (> 8/10) who were diagnosed with PPC as well as the assessment of the leg length (a)symmetry. This assessment includes 1–3 years of off-treatment data for 8 patients, which provides a robust assessment of growth after treatment discontinuation and the potential long-term consequences of PPC.

Regarding concerns for patient growth, some key aspects to consider are listed below. Among the 13 patients diagnosed with PPC, 9 patients continued to grow after diagnosis, 2 patients had already achieved near adult height, 1 patient showed growth deceleration prior to palovarotene and 1 patient had moderate scoliosis develop by Month 12. Details of the clinical findings from the 13 patients diagnosed with PPC, including factors that could have contributed to their heights, are presented below (note that some patients may be contributing to multiple observations):

- 6 patients achieved a height within the normal adult range (≥ fifth percentile) by the last follow-up visit (average height z-score at last visit: 0.7)
    - 2 did not exhibit any detrimental effects on growth
    - 3 patients had moderate scoliosis that contributed to their height deceleration (2 showed signs of growth deceleration prior to the PPC diagnosis)
    - 1 patient was near adult height at the time of palovarotene initiation
- 7 patients had heights < fifth percentile for sex-matched adults at end of study (EOS) (average height z-score at last visit: -1.7)
    - 3 patients showed growth deceleration prior to initiating palovarotene
    - 6 patients showed growth deceleration after treatment initiation (of these, 4 showed growth deceleration prior to the diagnosis of PPC)
    - 1 patient was near adult height at the time of palovarotene initiation
    - 5 patients had moderate scoliosis and/or severe kyphosis (not related to palovarotene) that contributed to their height deceleration

- 2 patients had evidence of partial closure of at least 1 growth plate prior to PPC diagnosis
- 1 patient achieved growth stabilization following discontinuation of palovarotene

Individual patient profiles demonstrate that growth does not generally stop upon initiation of palovarotene or diagnosis of PPC. The difference between patients with PPC appearing to grow normally (average height z-score at last visit: 0.7) and those who had an impaired growth (average height z-score at last visit: -1.7) is likely multi-factorial including moderate/severe scoliosis and kyphosis, as well as a medical history of impaired growth. Additionally, patients often exhibited signs of growth disturbances (either observed through clinical height measurements or radiological assessments) prior to identification of PPC, suggesting that monitoring can help mitigate the real impact that PPC may have and inform risk-benefit early in the process.

Regarding leg length assessment and angular deformity, given that dedicated radiographic and CT were not performed to quantify these parameters, accurate measurements were often difficult due to uneven patient positioning. This applies to patients treated with palovarotene as well as those included in the NHS. Whether the mean or the median change from baseline of the absolute right-left difference in leg lengths are considered, patients who were reported as having experienced PPC did not display leg length asymmetry at Month 12 (mean of 0.1 cm and median of 0.3 cm). At the individual patient level, only one patient with PPC in the target population had a leg length discrepancy measurement just above the threshold of 1.5 cm (potentially clinically significant [PCS]), while 4 untreated patients and an additional 2 treated patients in the target population in the NHS also exceeded the 1.5 cm threshold for leg length discrepancy at Month 12.

Of the of the 13 patients diagnosed with PPC in the target population, none demonstrated a distal femoral angle post-baseline that would indicate angular deformity up to last assessment.

Whether mean or median change from baseline of the absolute right-left difference in leg lengths are considered (mean of 0.1 cm and median of 0.3 cm at Month 12), patients who were reported as having experienced PPC did not display leg length asymmetry. Based on data through the end of the interventional trials, only one patient with PPC in the target population had a leg length discrepancy measurement (PCS) just above the threshold of 1.5 cm. However, it is important to note that 4 untreated patients in the target population in the NHS also exceeded the 1.5 cm threshold for leg length discrepancy.

Consequently, none of the patients with FOP who experienced PPC displayed medically significant leg length discrepancy or angular deformity, and most patients displayed heights at the last visit within the normal adult range, while those who did not had confounding factors contributing to their decreased growth.

The clinical consequences of FOP and HO formation are severe, and thus for every growing patient, the potential risks of PPC need to be weighed against the benefits of reducing the volume of new HO formation and potential for preserved mobility. As a precautionary measure, the proposed risk minimization plan recommends radiologic monitoring and clinical assessment of growth every 6 to 12 months for growing patients receiving chronic therapy and every 3 months while patients are being treated for a flare-up.

Clinicians who care for these patients, such as pediatricians, are equipped to assess growing patients, in the context of PPC occurrence and impact, ensuring appropriate monitoring and informing clinical actions as applicable. The proposed assessments can be done with routine x-rays at any facility with radiologic capabilities and thus are feasible at smaller hospitals. Importantly, the proposed frequency of x-ray monitoring presents a low risk of radiation exposure. At maximal frequency of 4 x-rays per year, the radiation exposure is equivalent to about 2 days of environmental background radiation exposure (or ≤ 0.008 mSv), or approximately 15 times less than an airplane ride.

Lastly, to further mitigate the potential risk, the Sponsor has also proposed new language in the label and educational materials recommending that all growing patients have a consultation with an expert in growth (ie, pediatric endocrinologist) prior to starting palovarotene and ongoing as required.

PPC is an important risk associated with palovarotene treatment in pediatric patients with open growth plates. Although the potential consequences of PPC were not observed, occurrence of PPC must be carefully considered given that there are no available therapies to alter the unrelenting accumulation of irreversible disability in patients with FOP.

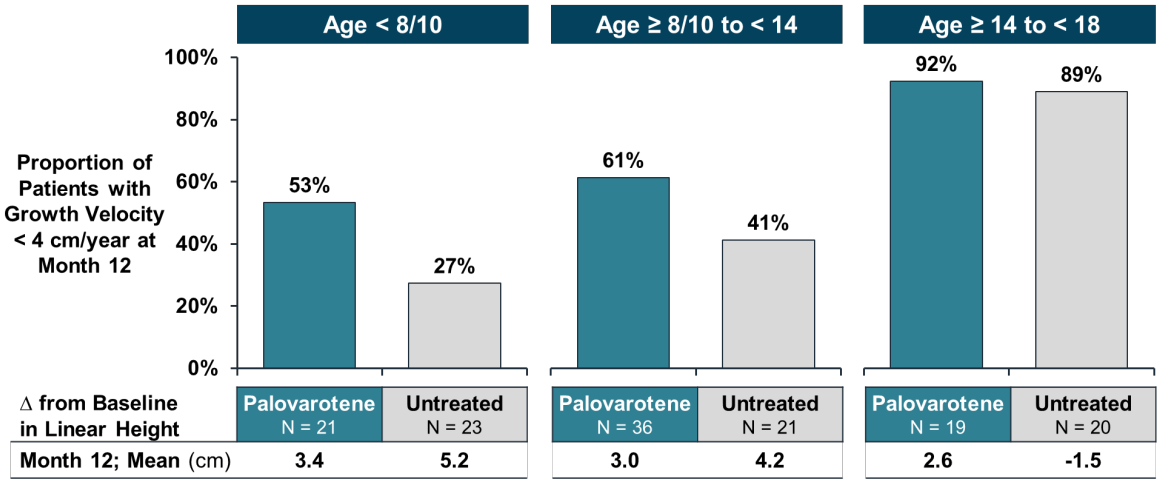
6.5.2 Linear Growth

Monitoring linear growth is challenging in the FOP population due to frequent spinal abnormalities and the apparent loss of height due to worsening scoliosis/kyphosis. Due to these limitations in the measure of linear height (by stadiometry in triplicate), several additional growth measurements were obtained to best understand the potential impact of palovarotene on growth including knee height (by knee caliper in triplicate) and femur and tibia length (by WBCT).

Growth Velocity

To better understand the rate of growth over time in different age categories, growth velocity was derived from linear height change over time. In patients < 14 years of age at Month 12, a greater proportion of palovarotene-treated patients had growth velocities of < 4 cm per year compared with untreated patients (Figure 32).

Figure 32: Study 301: Proportion of Patients with Growth Velocity < 4 cm/year at Month 12



Differences were also apparent when patients treated with palovarotene were grouped by PPC status (Table 22). In early adolescents, a higher percentage of patients with PPC had < 4 cm/year growth (88%) compared with palovarotene-treated patients without PPC (54%) and untreated patients (41%). In younger children (< 8/10 years), more palovarotene-treated patients, regardless of PPC status (with and without PPC; 55% and 50%, respectively), had a growth velocity < 4 cm/year compared with untreated patients (27%).

Table 22: Linear Height Change from Baseline and Growth Velocity at Month 12 by PPC Status in Study 301 and in Untreated Patients (FOP-FAS)

		With PPC		Without PPC		NHS (Untreated)	
		Age at First Entry, y		Age at First Entry, y		Age at First Entry, y	
Linear Height	Statistic	< 8/10 (N=12)	≥ 8/10 to < 14 (N=9)	< 8/10 (N=9)	≥ 8/10 to < 14 (N=27)	< 8/10 (N=23)	≥ 8/10 to < 14 (N=21)
Change from baseline at Month 12, cm	n	11	8	4	23	22	17
	Mean (SD)	3.4 (3.7)	1.2 (2.6)	3.6 (2.7)	3.6 (3.3)	5.2 (2.6)	4.2 (3.2)
	Median	3.3	0.8	3.4	3.9	5.8	4.5
	Min, max	-2.6, 9.9	-1.6, 5.9	0.8, 6.7	-4.0, 8.2	-1.9, 9.5	-4.9, 8.6
Growth velocity at Month 12, n (%)	< 4 cm/y	6 (54.5)	7 (87.5)	2 (50.0)	12 (54.2)	6 (27.3)	7 (41.2)
	≥ 4–5 cm/y	0	0	1 (25.0)	2 (8.7)	1 (4.5)	4 (23.5)
	> 5 cm/y	5 (45.5)	1 (12.5)	1 (25.0)	9 (39.1)	15 (68.2)	6 (35.3)
	Missing	1	1	5	4	1	4

FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; max=maximum; min=minimum; NHS=Natural History Study; PPC=premature physeal closure; SD=standard deviation; y=years
Note: FOP-FAS includes all patients enrolled or dosed in FOP clinical studies including the NHS

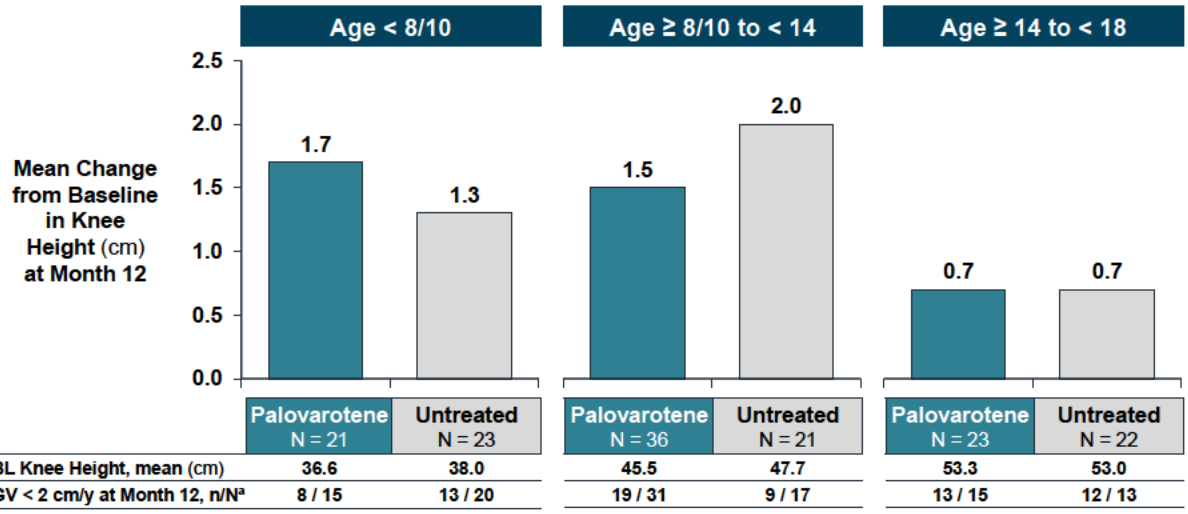
Knee Height

Change in knee height at Month 12 by age categories in Study 301 and the NHS is shown in Figure 33. In the FOP-FAS, mean knee height at baseline progressively increased from the < 8/10 years to ≥ 14 to < 18 years age categories in both the palovarotene and untreated (NHS) groups. At Month 12 across treated and untreated patients, mean changes from baseline in knee height and knee growth velocities did not markedly differ across age categories.

In the FOP-FAS, treated and untreated patients in the ≥ 14 to < 18 years age category had the highest proportion of patients with growth velocities < 2 cm/year. Normative data for knee height reference ranges in typically growing children are sparse, and thus it is not possible to provide data on knee height Z-scores. However, a recent study showed that knee height increased rapidly before age 13 years in males and before age 11 years in females at an average rate of about 2–2.5 cm/year before plateauing (Ruiz Brunner et al 2020).

In the ≥ 8/10 to < 14 years age category, the proportion of patients with growth velocities < 2 cm/year was 61.3% in the palovarotene groups and 52.9% in untreated patients. However, patients with negative knee height gains likely represent measurement error for patients who have difficulty remaining in a seated position.

Figure 33: Mean Change from Baseline in Knee Height at Month 12



[a] N does not include missing values

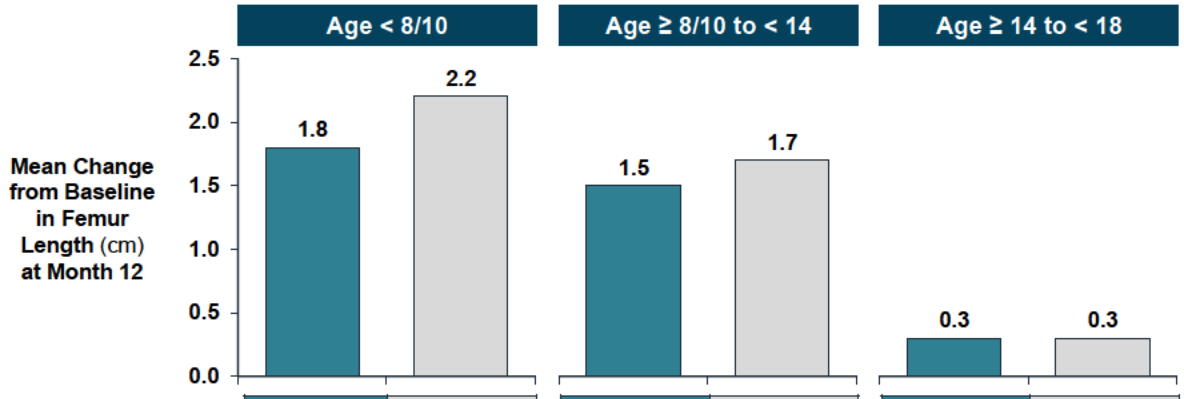
Femur Length

Change in femur length at Month 12 by age categories in Study 301 and the NHS is shown in Figure 34. In the FOP-FAS, mean femur lengths increased similarly across palovarotene-treated and untreated patients and pediatric age categories. Across treated and untreated patients, the mean change from baseline in femur length decreased with increasing age. Negative changes in femur length may also represent

measurement errors due to the difficulty in measuring length from WBCT scans in patients with hip and/or knee ankyloses.

In the FOP-FAS, a higher percentage of patients in the < 8/10 years of age palovarotene group had growth velocities < 2 cm/year compared with untreated (NHS) patients, which was the only notable difference between age categories across treated and untreated patients. These data suggest that slower femur growth may occur within the first 12 months of initiating treatment in younger children.

Figure 34: Mean Change from Baseline in Femur Length at Month 12



[a] N does not include missing values

These data also suggest that in the younger children (< 8/10 years of age), palovarotene may affect growth regardless of radiographic evidence of PPC; in older children, the effect on growth is most evident in those with PPC. Given the difficulties in measurements in patients with FOP discussed above, careful assessment of spinal anatomy for evidence of kyphosis and/or scoliosis should be included and considered when assessing linear height measurements over time.

6.5.3 Bone Mineral Density and Fracture

Given previously known class effects of retinoids and toxicology findings in juvenile rats related to the potential for skeletal risks and decreased areal bone mineral density (BMD), BMD was monitored with dual-energy x-ray absorptiometry (DXA) in a palovarotene study for another indication. In this study, a dose-dependent trend of reduction in BMC accrual was observed in the palovarotene groups relative to placebo. Therefore, a retrospective assessment of WBCT scans was performed to assess the risk in the FOP population.

Further characterization of bone parameters in the spine including BMD, bone strength, and BMC, and fracture analysis were performed retrospectively utilizing WBCT scans from the NHS, Study 202, and Study 301 to evaluate the potential impact of palovarotene treatment. These assessments were not conducted at the beginning of the

clinical development program due to limitations of imaging to accurately characterize measurements. Although DXA is the established standard for measuring BMD (particularly for osteoporosis), its use in patients with FOP is limited because it is not an accurate method of measuring BMD given the excess of bone from HO formation and ankylosis throughout the skeleton in patients with FOP. As such, biomechanical computed tomography (BCT) using finite element analysis and vertebral fracture assessment (VFA) utilizing semi-quantitative methods were used for assessments because of the many advantages over standard bone densitometry techniques for measuring bone health (especially for pediatric patients who already had scans at various timepoints in the FOP studies). These advantages include:

- In the evaluation of pediatric bone health, unlike DXA, BCT is not influenced by size artifacts.
- BCT can use previously taken CT scans, without requiring any change to how those CT scans are originally acquired, through phantomless calibration.

Assessment of VFA was performed using the VirtuOst VFA software (version 2.0), which is the only VFA software for use on CT scans that is a validated tool used for radiologic vertebral fracture risk assessment and diagnostic purposes.

The preliminary review of the WBCT scans from BCT and VFA using descriptive analyses revealed a trend of low BMC accrual in palovarotene-treated compared with untreated pediatric patients and a higher prevalence of new-onset radiologic vertebral fractures in both adult and pediatric treated patients.

Analysis of change from baseline in patients < 18 years of age at enrollment in BMD, vertebral strength, and BMC showed a similar change from baseline in BMD in palovarotene-treated and untreated patients, and a greater decrease in vertebral strength and BMC in palovarotene-treated patients than untreated patients (Table 23).

Table 23: Retrospective Analysis of Change from Baseline in Bone Health Parameters in Study 301 Patients < 18 years of age

	Palovarotene			Untreated		
Values Mean (SD)	**Baseline N=67**	**Month 12 N=58**	**Δ from Baseline**	**Baseline N=61**	**Month 12 N=53**	**Δ from Baseline**
Midvertebral bone mineral density (mg/cm^3)	117 (35)	105 (32)	-5.7% (15.4)	112 (31)	108 (31)	-4.9% (11.8)
Vertebral strength (newtons)	4290 (1596)	4188 (1598)	-3.2% (12.3)	4276 (1509)	4214 (1358)	-0.7% (11.3)
Vertebral bone mineral content (grams)	3.7 (1.7)	3.8 (1.8)	-0.5% (10.2)	3.8 (2.0)	3.8 (1.8)	5.6% (10.4)

At baseline in the target population, 23% of untreated and 22% of treated patients had at least 1 radiological vertebral fracture all of which were clinically silent. Twenty four percent (24%) of palovarotene-treated patients had a new-onset radiological vertebral

fracture at 12 months compared with 12% in untreated patients, which were also asymptomatic.

Unadjusted and Adjusted Regression Model Analysis

Further statistical analyses using unadjusted and adjusted regression models assessed the relationship between each continuous bone safety outcome (mid-vertebral bone strength, BMC, BMD) and treatment in Study 301 compared with the NHS. For each year since baseline, treatment with palovarotene was associated with a 154 newton decrease in vertebral body strength, a 0.16 g decrease in entire vertebral body BMC, and a 3.36 mg/cm^3 decrease in mid-vertebral (trabecular) density relative to untreated patients in the target (≥ 8/10) population. An age indicator for patients ≥ 18 years of age did not have a significant association with bone outcomes in any model. The results of this analysis support that palovarotene has an effect on decreases in vertebral bone strength, BMC, and BMD compared with no treatment in the NHS.

Unadjusted and adjusted Poisson regression models were used to assess the relationship between the number of vertebral fractures and palovarotene treatment in Study 301 compared with the NHS. The increased risk of radiological vertebral fractures was 2.98 times higher in palovarotene-treated patients in the target population (patients aged ≥ 8/10 years of age) compared with untreated patients, suggesting a causal association between exposure to palovarotene and the occurrence of radiological vertebral fractures. When considering only moderate/severe radiological vertebral fractures, the association between exposure to palovarotene was not statistically significant but demonstrated a consistent effect. These findings were still evident when adjusted for potential confounders (age, glucocorticoid use, etc.) with no notable evidence of interaction of the effect of palovarotene with age.

Although certain confounding factors were accounted for during data analysis using the modelling approach, it is recognized that patients with FOP may be predisposed to low bone density due to their underlying disease and frequent use of glucocorticoids. In fact, 36% of patients reported a history of fracture at baseline of the NHS. Across the palovarotene program, fractures as reported AEs (search under the MedDRA high-level group term of fracture, bone and joint injuries, muscle disorders, and bone disorders excluding congenital/fractures) occurred in 11.6% of patients in the FOP-FAS while, 7.9% of untreated patients in the NHS had additional fractures over 3 years of observation. Therefore, there is a high prevalence of fractures in patients with FOP, and the incidence of clinically reported fractures was similar between treated and untreated patients.

6.5.4 Bone Safety Conclusions

Based on the totality of evidence, PPC is an important, identified, and irreversible risk associated with palovarotene treatment. Consistent with the proposed indication, palovarotene is not recommended for pediatric patients aged < 8/10 years of age. In the target population (patients aged ≥ 8/10 years of age), monitoring for the risk of PPC is

recommended every 6 to 12 months during chronic treatment and every 3 months in case of flare-up dosing until patients achieve skeletal maturity. Treatment interruption or discontinuation may be required if clinically meaningful consequences are observed. The long-term clinical meaning of the bone parameter findings and radiological vertebral fractures is not known; it is important to note that these findings are based on a novel method, applied to a unique population in which there are no validation data. Given the causal association, radiological vertebral fractures are considered a risk of palovarotene. As such, appropriate risk management activities are proposed (see Section 6.7). Treatment decisions should be based on an individual benefit-risk determination for each patient.

6.6 Other Safety Assessments

Additional safety assessments including physical examinations, Columbia-Suicide Severity Rating Scale (C-SSRS), safety laboratory tests, vital signs, and electrocardiograms (ECGs) were included in all clinical studies with palovarotene. Due to the known association between systemic retinoid use and teratogenicity, pregnancy testing for all females of child-bearing potential was protocol specified.

Results of the C-SSRS suggest there was not an effect of palovarotene on psychiatric disorders including suicidal ideation and behavior.

There were no clinically meaningful changes from baseline in mean or median chemistry, hematology, lipids, or urinalysis parameters.

In palovarotene-treated patients across analysis sets, there were no consistent or clinically meaningful changes from baseline in mean vital sign values (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature).

There were no substantive differences between palovarotene-treated patients and placebo/untreated patients in most ECG changes from baseline, QTc values, ECG abnormalities or SMQ findings. Additionally, a thorough QT (TQT) study evaluated the effect of therapeutic and supratherapeutic doses of palovarotene on ECG parameters. Palovarotene groups across analysis sets did not have clinically meaningful changes in cardiac intervals (PR, RR, QRS, QT, QTcF, and QTcB), incidences of PCS values, ECG interpretation abnormalities, QTc analysis, or SMQ findings, suggesting there were no cardiac effects of palovarotene and no safety concerns with respect to ECG safety endpoints.

Results of these assessments are provided in Section 11.2.

6.7 Risk Minimization Plan

The Sponsor has assessed the safety profile of palovarotene with the proposed regimen and an FOP population in clinical studies. Adverse drug reactions associated with palovarotene including mucocutaneous events and radiological vertebral fractures have been identified and are included in the proposed label. The risks deemed most

important are teratogenicity and PPC. These risks are highlighted in the proposed product label with a box warning. The guidance for management of these events is presented in the proposed label under Warnings and Precautions, and these events are characterized under the Undesirable Effects section.

The Sponsor will continue to assess the emerging safety data from routine pharmacovigilance in the post-marketing setting and through a post-approval registry study.

Teratogenicity

While there were no pregnancies observed in the NHS or Study 301, the proposed label states that medically documented pregnancy tests in all females of child-bearing potential are recommended prior to palovarotene initiation, monthly during treatment, and 1 month after discontinuation. Healthcare professionals (HCPs) and patients will be informed that at least 1 highly effective method of contraception (ie, intrauterine device) or 2 effective methods (ie, combined hormonal contraception in combination with another method of contraception such as a barrier method) is recommended during treatment with palovarotene. Patients receiving only palovarotene flare-up treatment should continue to use effective contraception even during time periods when palovarotene is not being taken, as the timing of a flare-up is not predictable. These conditions also concern patients who are not currently sexually active unless the prescriber attests that there is no risk of pregnancy.

Premature Physeal Closure

Concerning the risk of PPC, the proposed label ensures that HCPs are informed of baseline clinical and radiological assessment recommendations (ie, skeletal maturity as assessed by hand/wrist and knee radiographs, growth measurements, and pubertal staging). The recommendations include continued clinical monitoring until skeletal maturity or final adult height is reached. The HCP, in consultation with the patient and family, should make individual treatment decisions regarding the use of palovarotene based on the patient-level benefit-risk assessment.

The indication statement also contributes to the management of the risk of PPC. Given that the highest incidence of PPC occurred in the youngest patients with FOP, who have the greatest long-term potential sequelae of PPC, the proposed target population was chosen based on the average ages at which pediatric female and male patients achieve approximately 80% of their adult height (ie, at 8 and 10 years of age, respectively). As such, should PPC occur in skeletally immature children in the proposed target population, the potential longer-term sequelae of PPC are minimized.

Pharmacovigilance and Educational Program

The proposed risk minimization activities include an educational program for prescribing HCPs, pharmacists, caregivers, and patients informing them of the risk and potential consequences of palovarotene treatment. The educational program will include a pregnancy prevention program that accounts for the specificities of the FOP patient

population. The proposed pharmacovigilance activities based on a post-marketing registry study will also allow further characterization of the longer-term safety of palovarotene including the risk of PPC and the collection and follow-up of any pregnancies and their outcome. As part of the Warnings and Precautions, it is recommended that periodic spinal x-rays be performed to assess for symptomatic or asymptomatic vertebral fractures. Such assessments will be characterized as part of the patient registry. A palovarotene educational program will include key elements to further inform stakeholders and provide guidance on the important risk of PPC and avoidance of pregnancy. The educational programs may include, but are not limited to the following:

- Communication and outreach: Information about the palovarotene educational program and an overview of the educational messages will be sent to HCPs and pharmacists who are likely to treat patients with FOP. Given the rarity of FOP, treatment is likely to be initiated by specialists. However, general HCPs in the community may subsequently assume the patient's care locally. Palovarotene will be distributed through an exclusive US specialty pharmacy whose staff have been trained on the Prescribing Information, the educational program overview, and the educational materials. Each potential prescriber will receive an introductory letter describing the program and a set of comprehensive educational materials for review prior to prescribing palovarotene.
- Educational Program Materials: Educational program materials will be made available to HCPs, pharmacists, and patients and their caregivers through the exclusive US specialty pharmacy, by calling the Ipsen Medical Information line, and on the healthcare provider section of the product website. Healthcare professionals should review the palovarotene educational program and the educational materials before prescribing palovarotene. Prescribers and pharmacists will have educational resources as described below to counsel patients and caregivers as appropriate. Content will be customized by risk and by the target audience (prescriber, patient/caregiver) and based on the product label, including the following:
    - A Guide for Prescribers and Pharmacists
    - A Guide for Patients and Their Caregivers
    - A Guide for Females
    - A Caregiver Guide for Growing Pediatric Patients

Post-Approval Registry

The Sponsor is also planning an observational, prospective, post-approval registry targeting to enroll at least 80% of patients treated with palovarotene in countries willing to participate and where palovarotene is registered/marketed at the time of the study. The primary aim of the post-approval registry is to collect and assess real-world safety data, with specific safety endpoints focused on pregnancy outcomes, PPC, and

fractures (including vertebral fractures). The study will also aim to further characterize the effectiveness of palovarotene, including its effect on physical function (eg, CAJIS, FOP-PFQ, use of assistive devices/adaptations for daily living). Although this post-approval registry is a real-world study, sites will be selected and staff will be educated and trained on the importance of enrolling patients to ensure robust data collection. After palovarotene has been prescribed as per the label, patients will be enrolled at a clinic visit, but follow-up visits could occur on site or remotely according to routine clinical practice in order to limit additional burden to patients and clinicians. Importantly, this study will follow patients for up to approximately 10 years.

7 BENEFIT-RISK SUMMARY

7.1 Therapeutic Context

FOP is an ultra-rare, genetic, severely disabling condition associated with significant morbidity and premature mortality due to progressive HO. HO is cumulative throughout life, resulting in segments, sheets, and ribbons of extra bone developing throughout the body and across joints, progressively restricting movement.

FOP has early clinical onset, often causing severe deformity and disability during childhood in affected individuals (Cohen et al 1993; Morales-Piga et al 2012; Pignolo et al 2016; Smith et al 1996). On average, restricted mobility of the neck and shoulder, and spine immobility, are present by 10 years of age; hip immobility is present by 18 years of age; and patients with FOP are commonly confined to a wheelchair by 25 years of age (Baujat et al 2017; Cohen et al 1993; Kaplan et al 2010; Kitterman et al 2005; Pignolo et al 2016; Pignolo et al 2020; Pignolo et al 2011).

Patients with FOP typically experience an average of 2 flare-up episodes per year (Pignolo et al 2019). Flare-ups can occur spontaneously or can be induced by traumatic events and influenza-like viral infections (Scarlett et al 2004). In most cases, flare-ups resolve spontaneously within a few weeks or months but can result in the formation of heterotopic bone.

It is a certainty that HO formation is cumulative and increasing HO burden is associated with greater physical function disability as determined by the physician and by the patient.

Currently, there are no FDA-approved treatment options to prevent flare-ups, HO, or to slow disease progression in FOP. Surgical resection of heterotopic bone is not recommended as it can exacerbate flare-ups and incite further HO formation. Current pharmacologic intervention for FOP is limited to palliative management and is not known to be disease modifying.

Due to the ultra-rare nature of FOP, enrolling patients into a clinical development program is challenging. Given the many uncertainties associated with developing a potential therapeutic in FOP, the palovarotene development program was designed based on emerging nonclinical and clinical data.

The data from untreated patients in the NHS were used as a comparison to a single, chronic/flare-up dosing regimen of palovarotene in Study 301. While these studies did not have randomization of parallel groups, HO is an objective assessment that was performed in a blinded manner, and the NHS has many characteristics that support its use as a comparator (Section 5.3.1.3).

7.2 Analysis of Benefits

Taken together, the data presented in the preceding sections support the efficacy of palovarotene in reducing the volume of new HO in patients with FOP.

Study 301 is the largest and first prospective longitudinal study evaluating a potential therapeutic in this ultra-rare disease. Along with the NHS, the total number of individuals contributing data represents approximately 20% of the world's known population with FOP. The NHS provides a unique and valuable dataset. Recognising the challenges of relying on a natural history comparator, several important characteristics make the NHS an appropriate control group for Study 301. The data were collected in a robust, consistent, and highly standardized manner, including use of detailed image acquisition and independent read charters. Enrolment in the pivotal Phase 3 study completely reached planned sample size. The length of study duration presented up to treatment interruption spanned a period of time on study of approximately 18 months, representing the longest duration for a Phase 3 study conducted with an investigational product in patients with FOP.

Although the futility boundary for Study 301 was crossed at IA2, this was primarily due to differences between WBCT visit schedules in the NHS and Study 301, which, in combination with the application of a square-root transformation to the data, inappropriately biased the results against palovarotene, masking the treatment effect. When accounting for the bias through adjustment of the visit schedules, the pre-specified Bayesian model predicted a 91% probability that palovarotene would reduce mean annualised new HO volume, compared with no treatment. When accounting for the bias by removing the square-root transformation, the model predicted a 99.4% probability that palovarotene would reduce any new HO compared with no treatment. Furthermore, every additional analysis performed provides confirmation of the beneficial effects of palovarotene in reducing new HO volume. The confidence to rely on these post-hoc analyses is derived from their comprehensiveness and the strength of the data, which consistently demonstrate benefit.

In addition, the analysis looking at the longer-term data through to study completion demonstrated that annualised new HO volume was reduced with palovarotene treatment during Study 301 compared with the NHS. Similar to the pre-pause treatment period, the highest reduction was seen when subjects were actively treated after post treatment re-start.

Additional supportive evidence of the efficacy of palovarotene is derived from mechanism of action of palovarotene, nonclinical pharmacology data in relevant animal models of FOP, Phase 2 flare-up new HO outcome data, and WBCT new HO data.

Collectively, these findings would be expected to change the trajectory of disease course over the lifetime of patients with FOP.

7.3 Analysis of Risk

The risks of palovarotene treatment are consistent with other known systemic retinoids including teratogenicity as well as mucocutaneous (eg, dry skin, dry lips, and alopecia) and musculoskeletal AEs (eg, PPC). The Sponsor has assessed the safety profile of palovarotene with the proposed dosing regimen and in the FOP population in the clinical

study setting. Teratogenicity and PPC are important risks associated with palovarotene treatment that will be included in the product label with a box warning.

Teratogenicity is a risk in the palovarotene clinical program and a well-known class effect of systemic retinoids (Brecher and Orlow 2003). Pregnant and breastfeeding females were excluded from all palovarotene clinical studies, and no pregnancies occurred. The Sponsor has proposed additional pharmacovigilance and risk minimization measures for this risk.

PPC was reported in 26.5% of treated pediatric patients (< 18 years of age) and in 33.3% of the patients (≥ 8/10 to < 14 years) of the proposed target population. In light of the incidence of PPC, the Sponsor has proposed an indication for patients ≥ 8/10 years of age and routine labeling as well as additional pharmacovigilance and risk minimization measures including a boxed warning, recommended monitoring, and an educational program. The detailed nature, severity, and incidence of PPC will continue to be assessed.

7.4 Analysis of Benefit-Risk Profile

FOP is an ultra-rare disease leading to progressive HO of muscles, tendons, and ligaments. HO is irreversible and cumulative throughout life, resulting in segments, sheets, and ribbons of extra bone developing throughout the body and across joints, progressively restricting movement. The consequences of HO are often severe and life threatening and they include skin breakdown and pressure sores from increased pressure over heterotopic or normotopic bone, increased skin infections due to creation of difficult to reach body folds, spontaneous or post-traumatic ankylosis of the temporomandibular joints leading to severe disability and resultant difficulties in eating and poor oral hygiene, severe scoliosis and thoracic insufficiency syndrome with life-threatening complications (Kaplan 2022).

The comprehensive assessment of the Phase 3 data showed a reduction in annualized new HO in the overall population and the proposed target population, with supportive data derived from mechanistic evidence of benefit in nonclinical models and findings from Phase 2 Studies 201 and 202. Overall, the multiple statistical methodologies employed to analyze the new HO volume data in Study 301 and the NHS in conjunction with the comparable data from Phase 2 studies are consistent in their conclusion of efficacy.

The AE profile of palovarotene in the FOP trials is consistent with other known systemic retinoids consisting mainly of mucocutaneous and musculoskeletal AEs, including PPC.

As HO is cumulative, minimizing the annual amount of new HO year over year is expected to extend function and delay the progression of disability over the lifetime of individuals with FOP. Palovarotene has been shown to decrease annualized new HO volume across all pediatric age groups. Published data reflect that preventing HO at the earliest age possible could limit functional disability (Pignolo et al 2016). Although palovarotene has shown efficacy in all pediatric subgroups, it is understood that the

youngest patients are at the highest risk of developing PPC. Due to the risk of PPC, palovarotene is not recommended in females < 8 years of age and males < 10 years of age. The specific age cutoffs were chosen based on the average ages at which pediatric female and male patients achieve approximately 80% of their adult height (ie, at 8 and 10 years of age, respectively) to mitigate the potential consequences of the PPC in the youngest of patients, while still being able to intervene at the median age of onset of large joint immobility such as the shoulders, hips, and knees, which is a critical time for disease progression.

In conclusion, the data support the use of the chronic/flare-up palovarotene treatment regimen in adults and children (aged 8 years and older for females and 10 years and older for males) with FOP to reduce annual new HO formation. As HO is cumulative with irreversible consequences, minimizing the amount of new HO should maintain function over time. Not only is it important to intervene as early as possible in childhood to preserve function but also in adulthood when preventing even small amounts of new HO can be life altering.

SUPPLEMENTAL INFORMATION

8 NONCLINICAL FINDINGS

8.1 Pharmacodynamics

8.1.1 Receptor Binding Activity and In Vitro Assays

Receptor binding affinity and transactivation activity assays show that palovarotene and its major oxidative metabolites (M2, M3, M4a, and M4b) are selective for RARγ, over retinoic acid receptor alpha (RARα) and retinoic acid receptor beta (RARβ). Specifically, palovarotene binding to the RARγ was 10-fold greater than RARα and 6-fold greater than RARβ, based on half-maximal inhibitory concentration values (RARγ=450nM, RARα=4,700nM, and RARβ=2,900nM).

Palovarotene inhibited BMP4-mediated SMAD signaling in a human FOP fibroblast cell line carrying the *ACVR1/ALK2 R206H* variant.

8.1.2 Efficacy in Animal Models

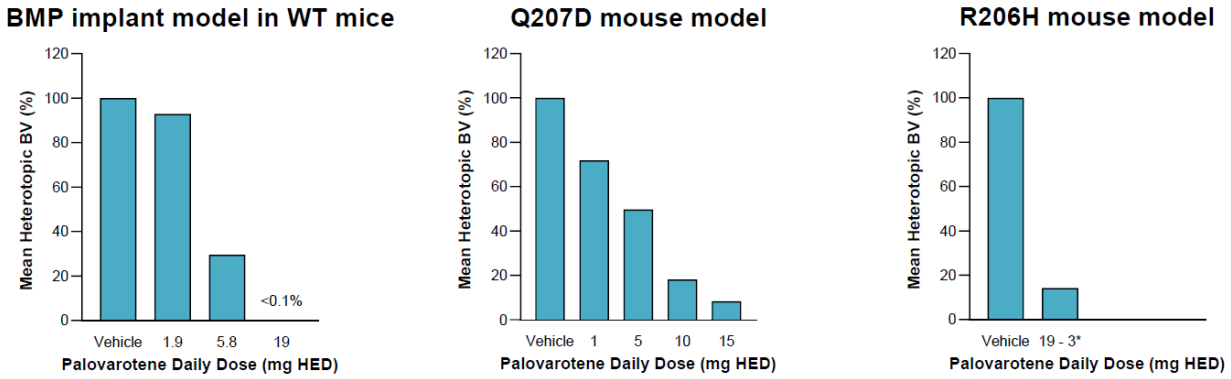
In animals, Palovarotene was shown to reduce HO in both traumatic HO and FOP animal models.

Injury-induced studies in HO and FOP mouse models consistently demonstrate palovarotene decreases HO accumulation in a dose-dependent manner compared with vehicle-treated controls (Figure 35). Palovarotene treatment reduced inflammatory and fibroproliferative responses at the site of injury compared with vehicle-treated controls. Similarly, animals treated with palovarotene maintained more joint mobility at the site of HO that was typically lost in vehicle-treated controls. Palovarotene was also effective in reducing HO in a mouse model of FOP that recapitulates many phenotypic features

seen in patients with FOP, including spontaneous HO and malformed great toes (Chakkalakal et al 2012; Shimono et al 2011).

Palovarotene also outperformed corticosteroids in preventing HO in an FOP animal model. Dexamethasone treatment of 4.4 mg/kg/day for 4 days (maximum clinical equivalent of prednisone) had no statistically significant effect on heterotopic bone volume, which was at 94% relative to vehicle control after 4 days of daily administration in FOP mice. Palovarotene reduced HO volume 30% relative to vehicle control after 15 days of daily administration at 10 mg human equivalent dose (HED).

Figure 35: Microcomputed Tomography Analysis 2 Weeks Post-Muscle Injury in Three Animal Models of FOP

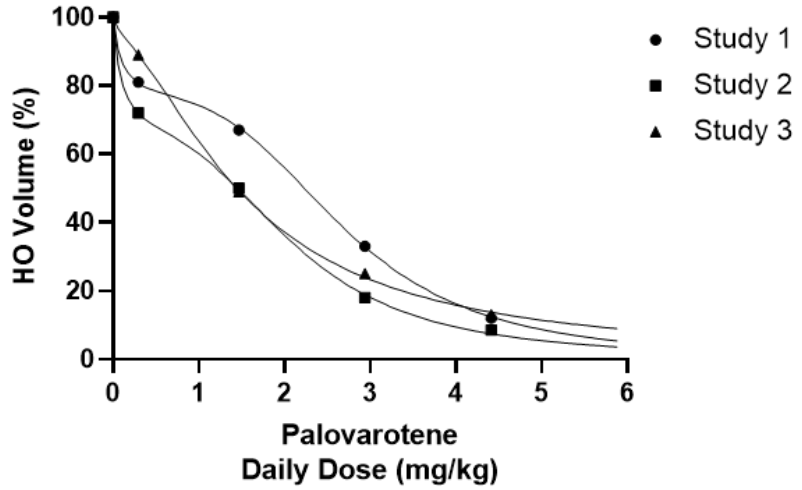


BMP=bone morphogenetic protein; FOP=fibrodysplasia ossificans progressiva; HED=human equivalent dose; WT=wild-type
*=19 mg HED for 3 days followed by 3 mg HED for 11 days

The 20/10 mg flare-up dose was used as the flare-up component of the palovarotene chronic/flare-up regimen first in Study 202B and subsequently in Study 301 based on the nonclinical observations described below.

The data from 3 independent studies demonstrated a clear dose-response relationship in which higher doses of palovarotene resulted in less HO in this injury based Q207D mouse model of FOP. These data were also used to develop a dose-response model (dual site E_{max} model with an estimated dose at half-maximum response at approximately 2 mg/kg/day or 7 mg/day HED) that suggests that a dose of ~6 mg/kg or 20 mg HED once daily may provide greater efficacy in inhibiting HO in this FOP mouse model (Figure 36).

Figure 36: Dose-Response of Palovarotene to Inhibit HO Inhibition in Q207D Mice



8.2 Nonclinical Safety Findings

The toxicology of palovarotene was extensively characterized in nonclinical studies, including single-dose, repeat-dose (sub-chronic and chronic), reproductive toxicity, genotoxicity, and phototoxicity studies. Toxicity studies of 4 metabolites of palovarotene were also performed. A juvenile toxicology program was conducted by the Sponsor, which included a 3-week dose range-finding study and a 6-week Good Laboratory Practice study in juvenile rats. Relevant findings from nonclinical studies are provided below.

8.2.1 Nonclinical Bone Safety

Long-term use of systemic retinoids in humans affects the musculoskeletal system in several ways, including PPC, osteoporosis, increased risk of fracture, and hyperostotic changes or calcification of tendons and ligaments; these effects are also seen in hypervitaminosis A syndrome (Armstrong et al 1994). Therefore, the skeletal effects of palovarotene in pediatric patients are presumed to be a direct reflection of palovarotene's pharmacologic activity, which prevents HO by inhibiting chondrogenesis. At the doses and systemic exposures necessary to prevent HO, palovarotene also inhibits chondrogenesis in growth plates. Although this is irrelevant for adult patients, in whom growth plates have closed, it has implications for pediatric patients and should be closely monitored.

The potential effects of chronic administration of palovarotene in pediatric patients were investigated in juvenile rats given daily doses of palovarotene at 0.1, 0.5, or 1.2 mg/kg throughout the period of skeletal growth (from weaning through puberty). Palovarotene produced dose-dependent effects on bone size, shape, and mass and/or geometry, all of which appeared to result from impaired physeal cartilage maturation/differentiation.

For example, physes in long bones and vertebrae exhibited a range of findings that included widening (sometimes accompanied by dysplasia), narrowing, or partial-to-complete closure. In the proximal femur, narrowing/closure of the physis resulted in changes in femoral head shape and (at the highest dose) avascular necrosis of the femoral head. These changes were accompanied by microfracture of trabeculae in a few rats. There also were fibula fractures in 2 high-dose females. In vertebrae, palovarotene completely inhibited the endochondral ossification that normally occurs in the hyaline cartilage at the end of the vertebral body. Effects on bone mass and/or geometry showed evidence of reversibility after discontinuation at lower doses (0.5 mg/kg/day) but not at the highest dose (1.2 mg/kg/day). During the recovery, differences in proximal tibial physis thickness measured by histomorphometry partially or completely resolved at ≥ 0.5 mg/kg/day. No recovery for effects on thinning/closure of the physis, chondrodysplasia or bone size were observed at ≥ 0.5 mg/kg/day. The limited reversibility may have been partly due to the fact that the majority of skeletal growth and development had already taken place by the time rats entered the recovery period at 9 weeks of age. At 0.5 mg/kg/day, skeletal effects were mild to moderate and did not affect overall body growth; at 1.2 mg/kg/day, effects were severe and associated with stunted growth.

8.2.2 Teratogenicity

Like other retinoids, palovarotene can impair embryonic and fetal development when taken during pregnancy. Studies in pregnant rats showed that palovarotene administration during embryonic organ development (organogenesis) caused fetal malformations typical of retinoids (eg, cleft palate, misshapen skull bones, and shortening of long bones). Palovarotene can be excreted in breast milk, and women who are breastfeeding should not take palovarotene.

8.2.3 Mucocutaneous Effects

Mucocutaneous effects, such as erythema, edema, epithelial hyperplasia, hyperkeratosis, and/or hypergranulosis in the epidermis were the most commonly noted events in nonclinical studies. Incidence and intensity increased with dosing and duration of exposure. Additionally, lesions affected the squamous epithelium of other tissues, such as nonglandular mucosa of the stomach (forestomach, rodent-specific), esophagus (rabbits only, non-adverse), and conjunctivae of the eye and surface of inner ear (dogs only). The changes identified in the esophagus of rabbits did not compromise the integrity of the esophageal mucosa or the health of the animal and were not interpreted to be toxicologically significant. Mucocutaneous effects reversed when dosing stopped. No palovarotene-related findings were observed in non-squamous mucosae, such as the mucosa of glandular stomach, esophagus, or intestinal tissues in rats, dogs, or rabbits, suggesting that the potential for gastrointestinal toxicity is low.

9 CLINICAL PHARMACOLOGY

9.1 Pharmacokinetics

The pharmacokinetics (PK) of palovarotene after oral administration have been well characterized from single- and multiple-dose studies in healthy volunteers and in patients with COPD, FOP, and MO. Oral absorption of palovarotene is increased when given with food. For this reason, palovarotene should be taken with food.

Following single-dose administration (5–20 mg) under the fed condition, the plasma concentration-time profile of palovarotene in healthy individuals is characterized by a moderate absorption rate (Tmax of approximately 4 hours) followed by a biphasic decline with a mean apparent terminal elimination half-life ranging from 7.3 to 14 hours. Following oral administration under fed conditions, palovarotene exhibited linear PK with dose-proportional increases in plasma exposure from 0.02 to 50 mg. Co-administration of 20 mg palovarotene with food increased mean exposure by 40% and mean maximum concentration by 16%, compared with administration under fasting conditions.

A Population Pharmacokinetics (PopPK) model was developed to describe the time course of palovarotene in plasma in healthy volunteers and patients with COPD, FOP, and MO. The pharmacokinetics (PK) of palovarotene following oral administration in healthy volunteers and patients with COPD, FOP, and MO were adequately described by a 2-compartment model with first-order elimination and first-order absorption with 6 transit compartments. There was a total of 9,088 concentration records from 701 participants in the final PopPK model. The PK of palovarotene was dose-proportional across the doses (0.02–50 mg) in this analysis and there was no evidence of non-linearity. Administration of palovarotene in the fasted state had a significant effect on palovarotene PK (derived steady-state exposures and maximum steady-state concentrations were 37% and 32% higher, respectively, under fed conditions, compared with fasted conditions for a typical adult). The population PK model demonstrated that body weight was found to have a significant impact on palovarotene PK, resulting in increasing exposure with decreasing weight at the same dose.

Palovarotene is highly bound to human plasma proteins based on in vitro data. The mean blood-to-plasma ratios of palovarotene in humans indicates that palovarotene did not partition into erythrocytes. Following administration of [^{14}C] radiolabeled palovarotene, 97.1% of the dose was recovered in the feces and 3.2% in the urine.

Several human cytochrome P450 (CYP) enzymes (3A4, 2C8, and 2C19) contribute to metabolization of palovarotene, with CYP3A4 being the major enzyme responsible for palovarotene biotransformation. Palovarotene does not pose a clinically relevant risk with respect to the induction of CYP1A2, CYP2C8, CYP2C9, or CYP2C19, or the inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. In a clinical drug-drug interaction study, palovarotene has been shown not to induce CYP3A4. For CYP2B6, the risk assessment of all available data suggests that the likelihood of palovarotene inducing CYP2B6 in vivo is negligible.

Palovarotene inhibits several transporters, including breast cancer resistance protein, organic anion transporting polypeptides B1 and B3, organic cation transporter 1, and bile salt export pump transporter. However, these inhibitions do not pose a clinically relevant risk with respect to the inhibition of any of these transporters.

9.2 Drug-Drug Interactions

In the presence of a strong CYP3A4 inhibitor, ketoconazole, the systemic exposure to palovarotene increased 2- to 3-fold relative to treatment with palovarotene alone. Concomitant use of strong and moderate CYP3A4 inhibitors should be avoided with palovarotene. Grapefruit or grapefruit juice, which are known to inhibit CYP3A4, should also be avoided during palovarotene treatment. In addition, in the presence of a strong CYP3A4 inducer, rifampicin, the systemic exposure of palovarotene decreased 5-to-10-fold relative to palovarotene treatment alone. Concomitant use of strong and moderate CYP3A4 inducers should be avoided with palovarotene.

Clinically significant interaction of palovarotene with other drugs is unlikely.

9.3 Dosing

9.3.1 Dosing in Adults, Adolescents and Children

Palovarotene should be taken with food, preferably at the same time each day. Palovarotene may be swallowed whole, or if needed, the capsules may be opened, and the contents emptied onto a teaspoon of soft food and consumed immediately. If a dose of palovarotene is missed, the patient should take the missed dose as soon as possible. If the dose has been missed by more than 6 hours, the patient should be instructed to skip the missed dose and continue with the next scheduled dose. The patient should be instructed not to take 2 doses at the same time or in the same day.

The recommended chronic/flare-up treatment regimen consists of dual approach that combines chronic dosing of 5 mg palovarotene once daily (chronic regimen) with an increased dosage at the onset of a flare-up. During flare-ups, patients will take 20 mg palovarotene once daily for 4 weeks, followed by 10 mg once daily for 8 weeks for a total of 12 weeks, even if symptoms resolve earlier (20/10 mg flare-up regimen).

In the event that flare-up symptoms persist beyond the recommended 12-week 20/10 mg treatment cycle, flare-up treatment may be extended in 4-week intervals of 10 mg per day and continued until the flare-up symptoms resolve. Should the patient experience another flare-up — either in a new location or a marked worsening of the original site, at any time during flare-up treatment, the 12-week flare-up treatment should be restarted. This may result in patients receiving 20 mg once daily for longer than a 4-week interval.

Flare-up treatment should be initiated at the time of any substantially traumatic events such as surgery, intramuscular immunization, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, falls, or influenza-like viral illnesses.

All female patients ≥ 8 years of age and male patients ages ≥ 10 years of age are eligible as appropriate candidates for the chronic/flare-up treatment regimen.

The population pharmacokinetic (PK) analysis revealed a significant impact of body weight on the PK characteristics 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.

To ensure optimal dosing, the dosing of palovarotene will be adjusted based on body weight for all patients, including adults, adolescents, and children (Table 24).

Table 24: Weight-Adjusted Dosage for all female patients ≥ 8 years of age and male patients ages ≥ 10 years

Weight range category	20-mg Equivalent	10-mg Equivalent	5-mg Equivalent
< 20 kg	10 mg	5 mg	2.5 mg
20 to < 40 kg	12.5 mg	6 mg	3 mg
40 to < 60 kg	15 mg	7.5 mg	4 mg
≥ 60 kg	20 mg	10 mg	5 mg

The use of palovarotene in female patients < 8 years of age and male patients < 10 years of age is not recommended.

9.3.2 Dose Reductions/Flare-up Only Dosing for Intolerability

In the event of intolerable AEs during chronic or flare-up palovarotene treatment, the daily dose should be reduced to the next lower dosage, as shown in Table 25. Additional dose reduction should occur if adverse reactions continue to be intolerable.

Table 25: Palovarotene Dose Reductions

Dose Prescribed	Reduced Dose
20 mg	15 mg
15 mg	12.5 mg
12.5 mg	10 mg
10 mg	7.5 mg
7.5 mg	5 mg
6 mg	4 mg
5 mg	2.5 mg
4 mg	2 mg
3 mg	1.5 mg
2.5 mg	1 mg

If patients cannot tolerate the 5 mg (or weight-adjusted equivalent) daily chronic regimen after attempted dose reductions, all patients in the target population — both

pediatric and adult — remain candidates for the flare-up only treatment regimen. This is a stand-alone treatment approach that reserves palovarotene therapy for intervention only during flare-up episodes to minimize HO accumulated during these periods of heightened disease activity. Dosing for the flare-up only regimen mirrors the 20/10 mg flare-up regimen described in Sections 9.3.1.

10 ADDITIONAL EFFICACY INFORMATION

10.1 Inclusion and Exclusion Criteria

Natural History Study

Patients were required to meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Written, signed, and dated informed consent or age-appropriate patient assent (performed according to local regulations).
2. Male or female ≥ 18 years of age for Part A and male or female ≤ 65 years of age for Part B.
3. Clinically diagnosed with FOP with documented *ACVR1/ALK2 R206H* variant or believed to carry the *ACVR1/ALK2 R206H* variant.

Patients meeting any of the following exclusion criteria were not enrolled into the study:

1. Unable or unwilling to complete the study or all study-related procedures, including the radiographic assessments.
2. Participation in an interventional clinical research study within the 4 weeks prior to enrollment.

Study 301

Patients were required to meet all of the following inclusion criteria to be eligible for enrollment:

1. Written, signed, and dated informed patient/parent consent; and for patients who are minors, age-appropriate assent (performed according to local regulations).
2. Male or female at least 4 years of age.
3. Previous participation in the NHS; or clinically diagnosed with FOP, with the *ACVR1/ALK2 R206H* variant or other FOP variants reported to be associated with progressive HO; or participants in Study 202 or Study 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 study.
4. No flare-up symptoms within the past 4 weeks, including at the time of enrollment.

5. 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 female of child-bearing potential patients must agree to remain abstinent from heterosexual sex during treatment and for 1 month after treatment or, if sexually active, to use 2 effective methods of birth control during and for 1 month after treatment. Additionally, sexually active female of child-bearing potential patients must already be using 2 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 2 effective methods of birth control will be clearly defined in the informed consent and the patient or legally authorized representatives (eg, parents, caregivers, or legal guardians) must specifically sign this section.
6. Must be accessible for treatment and follow-up and be able to undergo all study procedures. Patients 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. Patients must be able to undergo low-dose WBCT (excluding head) without sedation.

Patients with any of the following exclusion criteria were not eligible for enrollment:

1. Weight < 10 kg.
2. 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.
3. Exposure to synthetic oral retinoids other than palovarotene within 4 weeks prior to screening.
4. Concurrent treatment with tetracycline or any tetracycline derivatives due to the potential increased risk of pseudotumor cerebri.
5. History of allergy or hypersensitivity to retinoids, gelatin, or lactose (note that lactose intolerance is not exclusionary).
6. Concomitant medications that are strong inhibitors or inducers of CYP450 3A4 activity; or kinase inhibitors such as imatinib.
7. Amylase or lipase > 2x above the upper limit of normal (ULN) or with a history of chronic pancreatitis.
8. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5x ULN.
9. Fasting triglycerides > 400 mg/dL with or without therapy.
10. Female patients who are breastfeeding.

11. Patients with uncontrolled cardiovascular, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease.
12. Patients experiencing suicidal ideation (Type 4 or 5) or any suicidal behavior within the past month as defined by the C-SSRS.
13. Simultaneous participation in another interventional clinical research study (other than palovarotene studies) within 4 weeks prior to screening; or within 5 half-lives of the investigational agent, whichever is longer.
14. Any reason that, in the opinion of the Investigator, would lead to the inability of the patient and/or family to comply with the protocol.

10.2 WBCT Scan Read Process

The NHS began collecting low-dose WBCT scans in 2014. These assessments occurred yearly for up to 3 years for each patient and initial scans were interpreted by a single radiologist. Study 301 began in 2017 with the primary objective of evaluating the efficacy of palovarotene in preventing new HO formation in adult and pediatric patients with FOP as assessed by WBCT (excluding head) compared with no treatment in the NHS. As such, in order to ensure assessment objectivity and limit potential bias, a new read paradigm was developed to assess all scans in both studies per a new independent read charter. Per this charter, any initial WBCT scans from the NHS that had been reviewed previously, as well as any new scans being obtained in the NHS and Study 301, were read according to the same procedures. The scans were assigned to each independent reviewer by the central imaging lab operations group (who were not involved with the interpretation or adjudication process), with scans from NHS interspersed with scans from Study 301 in a blinded manner. Each participant had a patient blinding number automatically generated by the central imaging vendor's image management and review system. This patient blinding number had no study-specific, patient, or post-baseline timepoint information associated with it and could not be unblinded by the independent reviewer. Specifically, independent reviewers were blinded to the protocol number a given patient was enrolled in, patient number, patient name, patient initials, patient date of birth, patient sex, exam date, visit name, total number of imaging timepoints, Investigator site identifiers, site assessments, and reason for exam (ie, scheduled versus unscheduled). WBCT scans for both studies were read in chronological order timepoint by timepoint with radiologist having access to historical patient imaging.

10.3 Concomitant Medications

The most common prior medications (excluding corticosteroids) reported at baseline during Study 301 are presented in Table 26.

Table 26: Most Common Ongoing Prior Medications (≥ 3% of Patients) Reported at Baseline in Study 301 (Principal Safety Set)

Anatomic Therapeutic Class Preferred Term[1]	Palovarotene (N=99) n (%)
Other systemic drugs for obstructive airway diseases	27 (27.3)
Montelukast	18 (18.2)
Montelukast Sodium	9 (9.1)
Anti-inflammatory and antirheumatic products, non-steroids	25 (25.3)
Celecoxib	9 (9.1)
Ibuprofen	9 (9.1)
Naproxen	3 (3.0)
Vitamin A and D, incl. combinations of the 2	12 (12.1)
Vitamin D NOS	8 (8.1)
Colecalciferol	4 (4.0)
Drugs for peptic ulcer and gastro-esophageal reflux disease (GERD)	10 (10.1)
Omeprazole	6 (6.1)
Other analgesics and antipyretics	10 (10.1)
Paracetamol	8 (8.1)
Intestinal anti-inflammatory agents	9 (9.1)
Cromoglicic Acid	7 (7.1)
Topical products for joint and muscular pain	9 (9.1)
Ketoprofen	5 (5.1)
Emollients and protectives	6 (6.1)
Other Emollients and Protectives	3 (3.0)
Antipruritics, including antihistamines, anesthetics, etc.	5 (5.1)
EMLA	5 (5.1)
Ascorbic acid (Vitamin C), including combinations	4 (4.0)
Ascorbic Acid	3 (3.0)

EMLA= Eutectic Mixture of Local Anesthetics; NOS=not otherwise specified
[1] excluding systemic (oral) corticosteroids.
Note: The Principal Safety Set included all enrolled patients with the *ACVR1/ALK2 R206H* variant receiving ≥ 1 dose of palovarotene.

New-onset medications (excluding corticosteroids) during treatment and new-onset corticosteroids during chronic and flare-up treatment in Study 301 are presented in Table 27.

Table 27: Most Common New-Onset Medications (≥ 10% of Patients Overall) in Study 301 and the NHS (Principal Safety Set)

Anatomic Therapeutic Class Preferred Term	Study 301 Palovarotene			NHS (Untreated)
	Chronic Treatment (N=99) n (%)	Flare-up Treatment (N=70) n (%)	Overall (N=99) n (%)	(N=111) n (%)
Emollients and protectives	72 (72.7)	38 (54.3)	87 (87.9)	
Other emollients and protectives	35 (35.4)	22 (31.4)	52 (52.5)	
Soft paraffin and fat products montelukast	35 (35.4)	9 (12.9)	39 (39.4)	
Dimeticone	10 (10.1)	4 (5.7)	14 (14.1)	
Corticosteroids for systemic use, plain	38 (38.4)	54 (77.1)	64 (64.6)	80 (72.1)
Prednisone	28 (28.3)	41 (58.6)	47 (47.5)	
Prednisolone	10 (10.1)	14 (20.0)	18 (18.2)	
Corticosteroids, plain	36 (36.4)	31 (44.3)	58 (58.6)	1 (0.9)
Hydrocortisone	21 (21.2)	10 (14.3)	29 (29.3)	
Triamcinolone	6 (6.1)	9 (12.9)	11 (11.1)	
Anti-inflammatory and antirheumatic products, non-steroids	35 (35.4)	28 (40.0)	53 (53.5)	57 (51.4)
Ibuprofen	25 (25.3)	16 (22.9)	35 (35.4)	
Antihistamines for systemic use	28 (28.3)	32 (45.7)	48 (48.5)	
Desloratadine	8 (8.1)	9 (12.9)	13 (13.1)	
Cetirizine	4 (4.0)	9 (12.9)	12 (12.1)	
Other analgesics and antipyretics	30 (30.3)	18 (25.7)	41 (41.4)	33 (29.7)
Paracetamol	25 (25.3)	17 (24.3)	35 (35.4)	
Unspecified herbal and traditional medicine	26 (26.3)	13 (18.6)	35 (35.4)	1 (0.9)
Avena sativa fluid extract	11 (11.1)	5 (7.1)	16 (16.2)	
Unspecified herbal and traditional medicine	10 (10.1)	4 (5.7)	12 (12.1)	
Beta-lactam antibacterials, penicillins	20 (20.2)	20 (28.6)	33 (33.3)	19 (17.1)
Amoxi-clavulanico	9 (9.1)	8 (11.4)	16 (16.2)	
Amoxicillin	8 (8.1)	8 (11.4)	13 (13.1)	
Protectives against UV radiation	24 (24.2)	4 (5.7)	28 (28.3)	
Protectives against UV radiation for topical	16 (16.2)	4 (5.7)	20 (20.2)	
Other dermatological preparations	21 (21.2)	6 (8.6)	27 (27.3)	1 (0.9)
Vanicream	7 (7.1)	3 (4.3)	10 (10.1)	
Antibiotics for topical use	9 (9.1)	16 (22.9)	24 (24.2)	1 (0.9)
Mupirocin	3 (3.0)	9 (12.9)	12 (12.1)	

Anatomic Therapeutic Class Preferred Term	Study 301 Palovarotene			NHS (Untreated)
	Chronic Treatment (N=99) n (%)	Flare-up Treatment (N=70) n (%)	Overall (N=99) n (%)	(N=111) n (%)
Drugs for peptic ulcer and gastro-esophageal reflux disease (GERD)	9 (9.1)	13 (18.6)	21 (21.2)	19 (17.1)
Omeprazole	4 (4.0)	8 (11.4)	11 (11.1)	
Topical products for joint and muscular pain	5 (5.1)	8 (11.4)	13 (13.1)	16 (14.4)
Other beta-lactam antibacterials	10 (10.1)	5 (5.7)	14 (14.1)	5 (4.5)
Anti-infectives	7 (7.1)	6 (8.6)	12 (12.1)	6 (5.4)
Opioids	6 (6.1)	8 (11.4)	13 (13.1)	3 (2.7)

GERD=gastro-esophageal reflux disease; UV=ultraviolet
Note: The Principal Safety Set included all enrolled patients with the *ACVR1/ALK2 R206H* variant receiving ≥ 1 dose of palovarotene. For safety comparisons, the Principal Safety Set also included enrolled patients from the NHS with available post-baseline follow-up.

10.4 Bayesian Compound Poisson Analyses

10.4.1 With Square-Root Transformation

Primary Analysis

The primary efficacy endpoint is the annualized new HO volume (as assessed by WBCT). The new HO volume is calculated by summing the increase in HO volume across all body regions for which new HO has occurred where the increase in HO volume per region is defined as the square-root of the volumetric increase in that region. The square-root transformation is used to reduce the influence of outliers. Transformation of volumetric changes has been used in related contexts. For example, a log transformation has been used to model volumetric increases in the kidneys of patients with autosomal dominant polycystic kidney disease. The new HO volume is modelled using a Bayesian compound Poisson distribution. The Bayesian compound Poisson distribution assumes that the new HO volume can be modelled as a compound distribution of the number of body regions with new HO, K, and the new HO volume per region where new HO has occurred, Z. The number of body regions with new HO in patient i for WBCT scan j with duration w_{ij} (the time between scan j and the previous scan) is distributed as:

$$K_{ij} \sim Pois\left(\lambda_{i,j} * w_{ij} * \theta_{1,t(ij)}\right);$$

$$\log\left(\lambda_{i,j}\right) = \log(\lambda_i) + \beta_1 X_{1,i} + \beta_2 X_{2,i,j}$$

The patient-level rate λ_i follows a gamma distribution and accounts for potential correlation in measurements from the same patient; $t(ij)$ is an indicator function equal to 1 if the patient was on treatment at the time of the jth WBCT scan and 0 if the patient

was not on treatment. Therefore, the marginal distribution of the number of body regions with new HO follows a negative binomial distribution, which requires much less restrictive assumptions than a Poisson distribution and does not tend to result in an underestimate of the variance.

Letting $\theta_{1,0} = 1$, the variable $\theta_{1,1}$ is the multiplicative effect of palovarotene treatment on the rate of body regions with new HO. Covariates are included in the analysis of the number of body regions with new HO to adjust for potential explained differences in the rate of new HO based on the patient's sex, $X_{1,i}$, and age at time of scan, $X_{2,i,j.}$ Age at the time of scan is represented as a factor variable with 0 for < 18 years of age and 1 for ≥ 18 years of age. 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 patient *i* in scan *j* is assumed to be distributed as:

$$\sqrt{Z_{ijr}}/1000 \sim N\left(\alpha * \alpha_r * \theta_{2,t(ij)}, \frac{\alpha_r^2}{\tau_{t(ij)}}\right).$$

The scale of new HO volume is modelled in the thousands. Letting $\theta_{2,0} = 1$, 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 restrictions α_r=$\alpha_{r'}$, where r and r' are a left and right region pair are included (ie, right chest and left chest, right arm and left arm, right hip and left hip, and right lower leg and left lower leg). The precision variables, τ_0 and τ_1, introduce flexibility by allowing variability to differ between new HO volume in treated patients and untreated patients.

The prior distributions for the variables in the Bayesian compound Poisson distribution are the following:

$$\begin{array}{ccc} \lambda_i & \sim & Gamma(a, \text{scale} = b) \\ \beta_1, \beta_2 & \sim & N(0, 2^2) \\ a, b & \sim & Gamma(1,1) \\ \alpha & \sim & N(0,1) \\ \alpha_r & \sim & Unif(0,4) \\ \tau_0, \tau_1 & \sim & Gamma(1, 0.01) \\ \theta_{1,1}, \theta_{2,1} & \sim & Unif(0,2). \end{array}$$

All gamma distributions are parameterized as the shape and rate, except as noted for λ_i. The primary efficacy analysis comparing the annualized new HO volume between patients treated with palovarotene and untreated patients is performed by calculating the ratio of the annual mean change in HO volume in palovarotene-treated patients to untreated patients using the Principal FAS and assuming missing at random.

Using the Bayesian compound Poisson model described above, the efficacy ratio γ is calculated as the treatment effect on the mean number of body regions with new HO, $\theta_{1,1}$, multiplied by the treatment effect on new HO volume conditional on new HO occurring, $\theta_{2,1}$, expressed as $\gamma = \theta_{1,1} * \theta_{2,1}$. Random samples generated via Gibbs sampling from the posterior distribution of $\theta_{1,1}$ and $\theta_{2,1}$ were used to compute the posterior probability that $\gamma < 1$ to determine statistical significance.

10.4.2 Without Square-Root Transformation

When performed without the square-root transformation, the new HO volume in region r, Z_{ijr}, where new HO has occurred for patient *i* in scan *j* is assumed to be distributed as:

$$Z_{ijr}/1000 \sim N\left(\alpha * \alpha_r * \theta_{2,t(ij)}, \frac{\alpha_r^2}{\tau_{t(ij)}}\right).$$

The prior distributions for the variables in this Bayesian compound Poisson distribution are the following:

$$\begin{array}{ccc} \lambda_i & \sim & Gamma(a, \text{scale} = b) \\ \beta_1, \beta_2 & \sim & N(0, 2^2) \\ a, b & \sim & Gamma(1,1) \\ \alpha & \sim & N(0, 10^2) \\ \alpha_r & \sim & Unif(0, 4) \\ \tau_0, \tau_1 & \sim & Gamma(1,100) \\ \theta_{1,1}, \theta_{2,1} & \sim & Unif(0, 2). \end{array}$$

The Bayesian compound Poisson model were fitted using the R statistical computing language and environment. The R programs were run using v3.5.0 or later.

11 ADDITIONAL SAFETY INFORMATION

11.1 Additional Safety Tables

Table 28: Most Common Adverse Events Occurring in ≥ 10% of Patients (FOP-FAS)

System Organ Class Preferred Term, n (%)	Palovarotene N=139
Any AE	139 (100)
Skin and subcutaneous tissue disorders	**137 (98.6)**
Dry skin	112 (80.6)
Alopecia	59 (42.4)
Pruritus	59 (42.4)
Erythema	50 (36.0)
Rash	46 (33.1)
Pruritus generalized	43 (30.9)
Skin exfoliation	44 (31.7)
Drug eruption	27 (19.4)
Eczema	25 (18.0)
Skin irritation	15 (10.8)
Gastrointestinal disorders	**121 (87.1)**
Lip dry	80 (57.6)
Nausea	34 (24.5)
Vomiting	33 (23.7)
Chapped lips	25 (18.0)
Abdominal pain	24 (17.3)
Diarrhea	21 (15.1)
Dry mouth	19 (13.7)
Cheilitis	15 (10.8)
Infections and infestations	**115 (82.7)**
Upper respiratory tract infection	37 (26.6)
Nasopharyngitis	34 (24.5)
Paronychia	22 (15.8)
Ear infection	16 (11.5)
Musculoskeletal and connective tissue disorders	**113 (81.3)**
Arthralgia	69 (49.6)
Pain in extremity	58 (41.7)
Back pain	29 (20.9)
Musculoskeletal pain	31 (22.3)
Joint swelling	29 (20.9)
Neck pain	23 (16.5)

System Organ Class Preferred Term, n (%)	Palovarotene N=139
Myalgia	19 (13.7)
Musculoskeletal chest pain	17 (12.2)
Joint range of motion decreased	15 (10.8)
Pain in jaw	14 (10.1)
Injury, poisoning and procedural complications	**96 (69.1)**
Skin abrasion	34 (24.5)
Fall	24 (17.3)
Contusion	20 (14.4)
General disorders and administration site conditions	**67 (48.2)**
Pyrexia	22 (15.8)
Peripheral swelling	25 (18.0)
Fatigue	16 (11.5)
Swelling	15 (10.8)
Condition aggravated	4 (2.9)
Respiratory, thoracic, and mediastinal disorders	**67 (48.2)**
Cough	26 (18.7)
Epistaxis	21 (15.1)
Oropharyngeal pain	18 (12.9)
Nervous system disorders	**62 (44.6)**
Headache	40 (28.8)
Dizziness	15 (10.8)
Eye disorders	**49 (35.3)**
Dry eye	37 (26.6)
Metabolism and nutrition disorders	**40 (28.8)**
Decreased appetite	17 (12.2)

AE=adverse event; FAS=full analysis set; FOP=fibrodysplasia ossificans progressive
Note: The age at first entry of 8/10 years indicates 8 years of age for female patients and 10 years of age for male patients.
Note: January 2022 cutoff date

Table 29: Adverse Events Leading to Dose Interruption in > 1 Patient (FOP-FAS)

System Organ Class Preferred Term, n (%)	≥ 8/10 Palovarotene N=139 n (%)
Any AE Leading to Dose Interruption	40 (28.8)
Skin and subcutaneous tissue disorders	**15 (10.8)**
Rash	4 (2.9)
Decubitus ulcer	3 (2.2)
Drug eruption	2 (1.4)
Dry skin	2 (1.4)
Erythema	2 (1.4)
Pruritus generalized	2 (1.4)
Infections and Infestations	**12 (8.6)**
Coronavirus infection	2 (1.4)
Paronychia	2 (1.4)
Gastrointestinal disorders	**10 (7.2)**
Vomiting	4 (2.9)
Abdominal pain	2 (1.4)
Nausea	2 (1.4)
Musculoskeletal and connective tissue disorders	**5 (3.6)**
Epiphyses premature fusion	2 (1.4)
Pain in extremity	2 (1.4)
Investigations	**3 (2.2)**
Lipase increased	3 (2.2)
Renal and urinary disorders	**2 (1.4)**
Hematuria	2 (1.4)

AE=adverse event; FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva
Note: January 2022 cutoff date

Table 30: Serious Adverse Events in Target Population in Patients Treated with Palovarotene (FOP-FAS)

System Organ Class Preferred Term, n (%)	Palovarotene N=139
At least 1 SAE	57 (41.0)
Infections and infestations	**20 (14.4)**
Corona virus infection	11 (7.9)
Pneumonia	4 (2.9)
Cellulitis	3 (2.2)
Appendicitis	1 (0.7)
Bacterial sepsis	1 (0.7)
Escherichia sepsis	1 (0.7)
Gastroenteritis	1 (0.7)

System Organ Class Preferred Term, n (%)	Palovarotene N=139
Hemophilus infection	1 (0.7)
Influenza	1 (0.7)
Klebsiella bacteremia	1 (0.7)
Mycoplasma infection	1 (0.7)
Staphylococcal sepsis	1 (0.7)
Urosepsis	1 (0.7)
Musculoskeletal and connective tissue disorders	**20 (14.4)**
Epiphyses premature fusion	10 (7.2)
Arthralgia	3 (2.2)
Pain in extremity	3 (2.2)
Back pain	2 (1.4)
Aneurysmal bone cyst	1 (0.7)
Epiphyseal disorder	1 (0.7)
Mobility decreased	1 (0.7)
Muscle tightness	1 (0.7)
Neck pain	1 (0.7)
General disorders and administration site conditions	**10 (7.2)**
Condition aggravated	4 (2.9)
Peripheral swelling	3 (2.2)
Pain	2 (1.4)
Oedema peripheral	1 (0.7)
Vessel puncture site pain	1 (0.7)
Gastrointestinal disorders	**9 (6.5)**
Abdominal pain	2 (1.4)
Tooth impacted	2 (1.4)
Diarrhea	1 (0.7)
Dysphagia	1 (0.7)
Incarcerated inguinal hernia	1 (0.7)
Mallory-Weiss syndrome	1 (0.7)
Esophageal stenosis	1 (0.7)
Small intestinal obstruction	1 (0.7)
Tooth disorder	1 (0.7)
Vomiting	1 (0.7)
Injury, poisoning and procedural complications	**9 (6.5)**
Exposure to communicable disease	3 (2.2)
Ankle fracture	1 (0.7)
Extraskeletal ossification	1 (0.7)
Femur fracture	1 (0.7)
Fracture	1 (0.7)
Humerus fracture	1 (0.7)
Radius fracture	1 (0.7)
Post-procedural hematoma	1 (0.7)
Skull fracture	1 (0.7)

System Organ Class Preferred Term, n (%)	Palovarotene N=139
Subdural hemorrhage	1 (0.7)
Traumatic fracture	1 (0.7)
Nervous system disorders	**5 (3.6)**
Syncope	2 (1.4)
Epilepsy	1 (0.7)
Generalized tonic-clonic seizure	1 (0.7)
Myoclonus	1 (0.7)
Seizure	1 (0.7)
Respiratory, thoracic and mediastinal disorders	**4 (2.9)**
Respiratory distress	2 (1.4)
Asthma	1 (0.7)
Dyspnea	1 (0.7)
Hypoxia	1 (0.7)
Renal and urinary disorders	**3 (2.2)**
Hematuria	1 (0.7)
Adrenal insufficiency*	1 (0.7)
Urinary retention	1 (0.7)
Investigations	2 (1.4)
Coronavirus test positive	2 (1.4)
Blood and lymphatic system disorders	**1 (0.7)**
Anemia	1 (0.7)
Metabolism and nutrition disorders	**1 (0.7)**
Malnutrition	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.7)**
Uterine leiomyoma	1 (0.7)
Psychiatric disorders	**1 (0.7)**
Drug dependence	1 (0.7)
Vascular disorders	1 (0.7)
Lymphoedema	1 (0.7)

FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; SAE=serious adverse event

* Adrenal Insufficiency was erroneously re-coded to PT Renal Failure

Note: January 2022 cutoff date

11.2 Additional Safety Evaluations of Special Interest

11.2.1 Musculoskeletal Events

Musculoskeletal events are common in patients with FOP and are often associated with the natural progression of the disease. Importantly, most musculoskeletal AEs were mild to moderate and did not lead to treatment discontinuation. There was no dose-dependent increase in the rate of musculoskeletal events, and AEs occurred at a similar rate during chronic and flare-up treatment periods. Arthralgia was the most common musculoskeletal AE, occurring in 50% of palovarotene-treated patients (Table 31).

Table 31: Musculoskeletal Adverse Events Occurring in ≥ 5% of Patients (FOP-FAS)

Preferred Term, n (%)	Palovarotene N=139
Any Musculoskeletal AE	107 (77.0)
Arthralgia	69 (49.6)
Joint swelling	29 (20.9)
Neck pain	23 (16.5)
Myalgia	19 (13.7)
Joint range of motion decreased	15 (10.8)
Pain in jaw	14 (10.1)
Joint stiffness	12 (8.6)
Epiphyses premature fusion	10 (7.2)
Muscle spasms	9 (6.5)
Musculoskeletal stiffness	8 (5.8)

AE=adverse event; FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; ROM=range of motion
Note: January 2022 cutoff date

11.2.2 Psychiatric Effects

The SMQ for psychiatric disorders identified 19% of patients with associated AEs (Table 32). Other psychiatric disorder AEs seen in this group included depressed mood (9%), suicidal ideation (4%), and depression (5%). Many of these events were considered at least possibly related to the study drug and most were considered mild to moderate in severity. Notably, 9.4% of patients had a history of depression.

Table 32: Psychiatric Disorder Adverse Events in Target Population (FOP-FAS)

Preferred Term, n (%)	Palovarotene N=139
Patients with ≥ 1 AE	26 (18.7)
Depressed mood	12 (8.6)
Suicidal ideation	6 (4.3)
Depression	7 (5.0)
Mood altered	2 (1.4)
Mood swings	2 (1.4)
Memory impairment	2 (1.4)
Drug dependence	1 (0.7)
Intentional self-injury	1 (0.7)
Disturbance in attention	1 (0.7)

AE=adverse event; FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; SMQ=standardized Medical Dictionary for Regulatory Activities query
Psychiatric disorder AEs were obtained from a broad and narrow SMQ for active depression and suicide/self-injury.
Note: January 2022 cutoff date

There was no treatment-related increase in suicide ideation or suicidal behavior observed in the FOP-FAS as assessed by the C-SSRS. Moreover, at baseline, placebo/untreated patients had a slightly higher incidence of more severe (Type 3 to Type 5) suicidal ideation.

Overall, the assessments of psychiatric medical history in the FOP-FAS (including comparisons with untreated patients from the NHS), the SMQ for psychiatric disorders (such as depression), and results of the C-SSRS suggest there was not an effect of palovarotene on psychiatric disorders including suicidal ideation and behavior; findings may be due to the underlying chronic disease of FOP. Of note, montelukast was common concomitant medication in the ≥ 8/10 years palovarotene group, which may have contributed to the risk of depression and suicidal ideation.

The incidence of suicidal ideation in treated and untreated patients with FOP was higher than the estimated 12-month average of 2.0% for suicidal ideation reported from the World Health Organization World Mental Health Surveys conducted from 2001–2007 (Borges et al 2010). Kaplan and colleagues noted that if a clinical evaluation of a patient with FOP suggests depression, psychological support is recommended. Treatment of depression may further provide pain relief separate from correction of the mood disorder, which is important given that chronic pain is correlated with a higher prevalence of suicide (Petrosky et al 2018). As such, access to mental health treatment when appropriate may be an important component to the overall care of FOP patients.

11.2.3 Teratogenicity

Teratogenicity is a known and serious risk of retinoids, and nonclinical findings showed that palovarotene administration during embryonic organ development (organogenesis) caused fetal malformations typical of retinoids (details in Section 8.2.2). Teratogenicity AEs during and post-treatment were obtained from a narrow SMQ for normal pregnancy conditions and outcomes. There were no pregnancies observed in Study 301; accordingly, the SMQ identified no teratogenicity AEs in the FOP-FAS ≥ 8/10 years palovarotene group.

11.2.4 Clinical Laboratory Evaluations and Additional Safety Evaluations

Elevations in plasma lipids, particularly triglycerides, and elevations of transaminases have been reported with systemic retinoids, occurring relatively early after initiation of treatment (in the first 2 to 4 weeks) (Brecher and Orlow 2003). Elevated triglycerides generally resolve within 8 weeks after drug discontinuation and transaminases usually resolve within 2 to 4 weeks despite continuation of drug treatment.

Based on the safety profile of other systemic retinoids, ALT, AST, total bilirubin, triglycerides, total cholesterol, thyroxine, amylase, and lipase were analyzed. Of note, blood alkaline phosphatase was bone specific and not hepatic.

11.2.4.1 Pancreatic and Hepatobiliary Events

No AEs of pancreatitis were identified in any palovarotene group with the exception of a healthy volunteer with a drug/drug interaction of pancreatitis from palovarotene and ketoconazole, which was classified as a mild SAE. The Sponsor's assessment indicated a possible contribution of ketoconazole by way of increasing palovarotene plasma concentrations.

Instances of asymptomatic, transient elevations of lipase in FOP-FAS generally recovered despite continuation of palovarotene treatment. These findings imply that palovarotene is unlikely to increase risk of pancreatitis.

No hepatotoxicity AEs other than elevated liver enzymes and bilirubin were identified from the SMQ for severe drug-related hepatic disorders and liver-related investigations signs and symptoms. However, as no patients in the ≥ 8/10 years palovarotene group had PCS liver transaminases elevations (AST, ALT) or AST/ALT values > 3×ULN and total bilirubin values > 2×ULN, these AEs were not considered clinically significant. These results suggest that palovarotene is unlikely to increase the risk of hepatotoxicity or cause elevations in liver enzymes and bilirubin.

11.2.4.2 Clinical Laboratory Evaluations

The mean and median changes from baseline in clinical laboratory values were similar between palovarotene and placebo groups. In addition, the mean changes from baseline over time for each parameter were small and not deemed clinically meaningful for palovarotene-treated patients.

Laboratory abnormalities occurring in patients treated with palovarotene included isolated instances of elevations of lipase and triglycerides. These laboratory abnormalities were usually transient, recovered while remaining on palovarotene and not accompanied by clinical symptoms.

In summary, changes from baseline in clinical safety laboratory parameters (hematology, chemistry, lipid, urinalysis) and incidences of PCS values did not identify clinically meaningful safety concerns related to clinical laboratory endpoints.

11.2.5 Vital Sign Parameters

The incidence of new-onset PCS vital sign parameters was similar between the palovarotene and placebo groups with the exception of a higher incidence of new-onset PCS decreased heart rate in the ≥ 8/10 years palovarotene group compared with placebo/untreated patients in the FOP-FAS. In almost all cases, decreased heart rates meeting new-onset PCS criteria represented decreases of 20 bpm or more from baseline rather than heart rates below 55 bpm with actual heart rates remaining in the normal range, suggesting this was not a clinically meaningful finding. Decreases in heart rate in pediatric patients in the FOP-FAS (≥ 8/10 to < 18 and the ≥ 12 to < 17 years) suggest that changes may be due to, in part, normal physiologic decreases in heart rate that occur during the transition from younger ages to adolescence.

In the palovarotene group, there were no consistent or clinically meaningful changes from baseline in mean vital sign values including systolic and diastolic blood pressure, heart rate, respiratory rate, weight, BMI, and body temperature. There was not a clinically meaningful safety concern related to vital sign safety endpoints.

11.2.6 Cardiac Safety

The cardiac safety of palovarotene was assessed through a TQT study in healthy volunteers that evaluated the effect of therapeutic and supratherapeutic doses of palovarotene on the QTcF.

The TQT study in healthy volunteers evaluated the effect of therapeutic (20 mg) and supratherapeutic (50 mg) daily doses of palovarotene on the QTcF. The mean ΔQTcF at therapeutic and supratherapeutic doses did not notably differ from placebo. There were no participants who received palovarotene 50 mg with post-baseline QTcB > 480 ms and no participants with QTcF > 450 ms. Based on a plasma concentration-QTc analysis, an effect on ΔΔQTcF exceeding 10 ms was not observed within the range of palovarotene plasma concentrations up to approximately 500 ng/mL. Palovarotene at the doses studied had no clinically relevant effects on the TQT ECG parameters.

The results demonstrated that palovarotene chronic and flare-up treatment and palovarotene at supratherapeutic doses did not lead to clinically significant cardiac safety findings. Cardiac abnormalities such as intraventricular conduction delay and right bundle branch block are consistent with cardiac abnormalities in patients with FOP (Kou et al 2020).

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