Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Sohonos

Active ingredient: Palovarotene

Sponsor: Ipsen Pty Ltd

August 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADR	Adverse drug reaction
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
$AUC_{0-\infty}$	Area under the curve from time 0 extrapolated to infinite time
ACVR1	Activin A Receptor Type 1
CL/F	Apparent clearance
C_{max}	Maximum observed serum concentration
CMI	Consumer Medicines Information
DDI	Drug-drug interactions
DEXA	Dual-energy x-ray absorptiometry scan
DLP	Data lock point
FAS	Principal Full Analysis Set
FOP	Fibrodysplasia ossificans progressiva
HO	Heterotopic ossification
ITT	Intention to treat
NHS	Natural History Study
PBPK	Physiologically-based pharmacokinetic modelling
PD	Pharmacodynamics
PI	Product Information
PK	Pharmacokinetics
PPC	Premature physeal closure
PPS	Per-Protocol Set
PSUR	Periodic safety update report
PVO	Palovarotene
RAR	Retinoic acid receptor
RMP	Risk management plan
RXR	Retinoid X receptor
$T_{½}$	Terminal half-life
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration

Abbreviation	Meaning
T_{max}	Time to maximum concentration
Vss/F	Apparent volume of distribution at steady-state
WBCT	Whole body computed tomography
wLME	Weighted linear mixed-effects

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Sohonos
Active ingredient:	Palovarotene
Decision:	Approved
Date of decision:	27 November 2023
Date of entry onto ARTG:	28 November 2023
ARTG numbers:	393999, 394000, 394001, 394002, 394003
, *Black Triangle Scheme*	Yes
Sponsor's name and address:	Ipsen Pty Ltd, Level 5, 627 Chapel Street, South Yarra, VIC 3141
Dose form:	Hard capsule
Strengths:	1 mg, 1.5 mg, 2.5 mg, 5 mg, 10 mg
Container:	Blister pack
Pack size:	28
Approved therapeutic use for the current submission:	Sohonos is indicated to reduce the formation of heterotopic ossification (HO) in adults and children aged 8 years and above for females and 10 years and above for males with fibrodysplasia ossificans progressiva (FOP).
Route(s) of administration:	Oral
Dosage:	**Dosage in adults and children aged 14 years and over.** *Chronic treatment dose* Recommended dose: 5 mg once daily. *Flare-up treatment dose* Recommended dose: 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks for a total of 12 weeks (20/10 mg flare-up treatment) even if symptoms resolve earlier. In the presence of persistent flare-up symptoms, treatment may be extended in 4-week intervals with 10 mg Sohonos and continued until the flare-up symptoms resolve. 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, the flare-up 12-week treatment should be restarted. **Dose adjustment in children under 14 years of age** Sohonos dosing is weight-adjusted in patients under 14 years of age (Table 1). The physician should prescribe the most

appropriate dosage based on weight for children aged from 8 years (females) and 10 years (males) to less than 14 years.

Table 1*:* Weight-adjusted dosage for children < 14 years

Chronic Dosing	Chronic Dosing	Flare up (Weeks 1 to 4)	Flare up (Weeks 5 to 12)
≥60kg*	5 mg	20 mg	10 mg
40-<60kg	4 mg	15mg	7.5 mg
20-<40kg	3 mg	12.5 mg	6 mg
10-<20kg	2.5 mg	10 mg	5 mg

*All children ≥14 years of age and adults receive the dose in the ≥ 60 kg weight category

For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.

Pregnancy category:

Category X

Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Sohonos (palovarotene)

This AusPAR describes the submission by Ipsen Pty Ltd (the sponsor) to register Sohonos (palovarotene) 1 mg, 1.5 mg, 2.5 mg, 5 mg, 10 mg, hard capsule, blister pack, for the following proposed indication:[1]

> *Sohonos is indicated to reduce the formation of heterotopic ossification in adults and children aged 8 years and above for females and 10 years and above for males with fibrodysplasia ossificans progressiva (FOP).*

Fibrodysplasia ossificans progressiva (FOP)

Fibrodysplasia ossificans progressiva (FOP) (Münchmeyer disease) is a rare, genetic connective tissue disorder in which fibrous tissues (including muscles and tendons, but sparing certain muscles, such as cardiac smooth muscle) are gradually ossified (typically cumulative and

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

irreversible). This is caused by Activin A Receptor Type 1 (ACVR1) gene mutations responsible for changes in a bone morphogenetic protein receptor.

FOP is a highly penetrant congenital disease with early clinical onset, often causing severe deformity and disability during childhood in affected individuals. Flare-up episodes and HO formation typically begins at around 2 to 4 years of age, with the median age of FOP diagnosis of 5 years. Restricted mobility of the neck and shoulder, and spine immobility, are present by age 10; hip immobility is present by age 18; FOP patients are commonly confined to a wheelchair by age 24. The condition is also characterised by a weight loss, difficulty speaking and eating, and thoracic insufficiency syndrome. Trauma or other insults may lead to episodes of swelling and inflammation leading to ossification (known as 'flare-up').

Life-threatening complications result from cumulative HO in FOP including severe weight loss due to ankylosis of the jaw, and respiratory insufficiency due to ankylosis of the costovertebral joints, ossification of the intercostal and paravertebral muscles, and progressive spinal deformity including kyphoscoliosis or thoracic lordosis. Ankyloses of the temporomandibular joints result in severe tooth decay and malnutrition. Asymmetric HO in the rib cage and subsequent contralateral growth can lead to a rapid progression in spinal deformity and cause thoracic insufficiency.

Respiratory insufficiency causes complications such as pneumonia and right-sided heart failure, leading to a markedly shortened median survival of 56 years. Cardiac conduction abnormalities have been observed in 45% of baseline electrocardiograms recorded from patients participating in a natural history study of FOP. These abnormalities were not correlated with chest wall deformities, scoliosis, pulmonary tests, indicating potential elevated cardiovascular risk in patients with FOP.

The International FOP Association, a US-based patient group organisation, reports approximately 800 to 900 confirmed cases of FOP globally. The prevalence is estimated at approximately 1.36 per million individuals, with no geographic, ethnic, racial, or gender preference.

Current treatment options for FOP

- Currently, there are no effective medical treatment options to prevent flare-ups, HO, or disease progression in FOP.
- Current pharmacologic intervention for FOP is limited to palliative management and is not known to be disease modifying.
- Short course (4 days), high-dose corticosteroids administered within 24 to 48 hours of the onset of flare-up symptoms is typically used to reduced flare-up inflammation and tissue oedema in FOP.
- Presently there are medications available for use off-label, with theoretical or anecdotal support for beneficial effects in FOP that are used with caution, at the discretion of a treating physician. These include montelukast, a leukotriene inhibitor; cromolyn, a mast cell stabilizer; imatinib, a tyrosine kinase inhibitor; and amino-bisphosphonates such as pamidronate and zoledronate.
- Radiation therapy has been reported as helpful in impeding ossification in FOP, based on a single case study.

Clinical rationale for Sohonos use in FOP

Receptor-binding and transactivation assays indicate that palovarotene and its major metabolites are selective for retinoic acid receptor-γ (RARγ) over RARα or β. Retinoic acid receptors are transcription factors that are controlled by ligands that function together with retinoid X receptors (RXRs) as heterodimers to regulate various cellular processes, including growth, differentiation, survival, and cell death. Compared to other RARs, RARγ are highly and selectively expressed in chondrogenic cells and chondrocytes where they operate as unliganded transcriptional repressors. The rationale for testing retinoids as inhibitors of HO was based on the observation that retinoid signalling is a strong inhibitor of chondrogenesis and that unliganded RAR transcriptional repressor activity is needed for chondrogenic differentiation. The activities of the primary oxidative metabolites of palovarotene determined in a cell-based RARα, β, and γ transactivation assay ranged from 1.2% to 14% of the parent compound. RARγ agonist treatment inhibits BMP2-mediated Smad signalling in chondrogenic cells in addition to chondrogenic differentiation in both cell-based assays and a BMP-implant HO mouse model. Palovarotene inhibits BMP4-mediated Smad signalling in a human FOP fibroblast cell line carrying the overactive mutant ALK2.

Palovarotene was evaluated in distinct injury-based mouse models of HO and FOP. The results consistently demonstrated dose-dependent decreases of HO with palovarotene across the models and suggest that a human equivalent dose of 20 mg palovarotene should provide maximal inhibition of HO across all injury conditions. Palovarotene treatment was also observed to reduce aberrant inflammatory and fibroproliferative responses at the site of incipient HO. Furthermore, animals treated with palovarotene maintained joint mobility typically lost at the site of HO in vehicle-treated animals. In addition to the injury-based models, palovarotene was also effective in reducing HO in a mouse model of FOP that recapitulated many of the phenotypic features of FOP seen in patients, including spontaneous HO and malformed great toes.

Regulatory status

Australian regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

Foreign regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. Table 2 summarises these submissions and provides the indications where approved.

Table 2: International regulatory status at the time of product registration.

Region	Submission date	Status	Approved indications
Canada	23 April 2021	Approved 21 January 2022	Sohonos (palovarotene capsules) is indicated to reduce the formation of heterotopic ossification in adults and children aged 8 years and above for females and 10 years and above for males with Fibrodysplasia Ossificans Progressiva
United States of America	Initial submission: 31 March 2021 Withdrawn: August 2021 Resubmission: 29 April 2022	Approved 16 August 2023	Sohonos is indicated for the reduction in volume of new heterotopic ossification in adults and pediatric patients aged 8 years and older for females and 10 years and older for males with fibrodysplasia ossificans progressiva (FOP)
EU (Centralised Procedure)	Initial submission: 15 April 2021 CHMP negative opinion: 26 Jan 2023 Request for re-examination of CHMP opinion: 07 Feb 2023 Re-examination submission: 27 March 2023 CHMP negative opinion: 25 May 2023	Rejected 17 July 2023 (EC Decision date)	N/A
Switzerland	Initial submission: 13 April 2021 Withdrawn: November 2021 Resubmission: 16 June 2022	Withdrawn 23 October 2023	N/A

Registration timeline

Table 3 captures the key steps and dates for this submission.

The active ingredient with its proposed indication was given orphan drug designation.

Table 3: Timeline for Submission PM-2022-03518-1-5

Description	Date
Designation (Orphan)	13 July 2022
Submission dossier accepted and first round evaluation commenced	30 September 2022
First round evaluation completed	13 April 2023
Sponsor provides responses on questions raised in first round evaluation	23 April 2023
Second round evaluation completed	16 August 2023
Sponsor's notification to the TGA of errors/omissions in evaluation reports	3 August 2023
Delegate's[2] Overall benefit-risk assessment and request for Advisory Committee advice	6 September 2023
Sponsor's pre-Advisory Committee response	18 September 2023
Advisory Committee meeting	5-6 October 2023
Registration decision (Outcome)	27 November 2023
Administrative activities and registration in the ARTG completed	28 November 2023
Number of working days from submission dossier acceptance to registration decision*	202

*Statutory timeframe for standard submissions is 255 working days

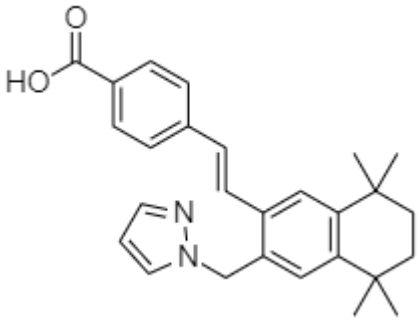
Submission overview and risk/benefit assessment

Quality

Palovarotene is a retinoid derived conceptually from retinoic acid with the addition of rigidifying aromatic rings and a pyrazolylmethyl substitutent. The principal mechanism of action is inhibition of RARγ.

[2] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who decided the submission under section 25 of the Act.

Figure 1: Structural formula of palovarotene.



The drug product is presented as white, opaque, elongated hard gelatin capsules containing a white to off white powder. The capsules are marked in black ink with a marking indicative of the strength. The product will be supplied in a 14-capsule blister pack. Two blister packs are further packaged into a cardboard carton. The proposed shelf life for the product is 36 months when stored below 25 °C and protected from light.

Approval for registration of the proposed product is acceptable from a pharmaceutical chemistry perspective.

Nonclinical

Non-clinical evaluation results were of high overall quality and adequate in scope, broadly consistent with ICH M3 (R2). All pivotal safety-related studies were Good Laboratory Practice-compliant.

Palovarotene is a RARγ selective agonist. *In vitro*, palovarotene was shown to bind to and activate RARγ with nanomolar affinity/potency and to inhibit the Smad signalling pathway that is aberrantly activated in FOP. Supporting utility for the proposed indication, inhibition of injury-induced and spontaneous heterotopic ossification was demonstrated with palovarotene in transgenic mouse models of FOP. Retention of joint mobility and reductions in mast cell infiltration and local fibroproliferative response were also found.

No notable secondary pharmacological targets were identified for palovarotene.

Safety pharmacology and other studies indicated no likely adverse effects on the central nervous system, cardiovascular, respiratory, renal or gastrointestinal function in patients.

The pharmacokinetic profile of palovarotene in the key laboratory animal species used in the nonclinical program — rats and dogs — was characterised by rapid to moderately fast absorption after oral administration, low to moderate (rats) or high (dogs) bioavailability, and short plasma half-life. Plasma protein binding was high in all laboratory animal species, as in humans. No particular distribution of palovarotene into red blood cells was evident. Slow but wide tissue distribution of ^{14}C-palovarotene-derived radioactivity was demonstrated in rats, including ready penetration of the blood-brain barrier; there was no evidence of melanin binding.

Metabolism of palovarotene yields four major circulating metabolites in humans. These were also formed in laboratory animal species, but generally at lower levels relative to the parent *cf*. humans. CYP3A4 was identified as the major CYP isozyme involved in the metabolism of palovarotene, with an additional minor contribution by CYP2C19 and very minor contribution by CYP2C8. The metabolites retain only limited pharmacological activity. Excretion is primarily via the faeces, with biliary involvement.

Palovarotene was shown not to inhibit CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4; UGTs 1A1, 1A3, 1A4, 1A6, 1A9 and 2B7; or P-glycoprotein, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2-K at clinically relevant concentrations *in vitro*. Accordingly, interactions with other medicinal products caused through enzyme and transporter inhibition by palovarotene are not expected.

Palovarotene showed a low to moderate order of acute toxicity by the oral route in mice, rats and dogs.

Repeat-dose toxicity studies by the oral route were conducted in rats (up to 6 months duration), rabbits (4 weeks) and dogs (up to 9 months). To compensate for lower metabolite formation in animals, studies involving direct metabolite administration were additionally performed (up to 13 weeks duration in rats and dogs). Skin and skeleton were identified as the key targets for palovarotene toxicity, with the effects observed recognised as classic retinoid toxicities (*e.g.*, as in hypervitaminosis A) and to represent exaggerated pharmacology.

Studies in juvenile rats revealed more extensive skeletal effects *cf.* that seen in adult animals and indicate a risk of premature physeal closure in still growing children.

Palovarotene and its four major metabolites were not mutagenic in bacteria and not directly clastogenic in human lymphocytes *in vitro*. Negative results for clastogenicity were also obtained for palovarotene *in vivo* in the mouse bone marrow micronucleus test.

No carcinogenicity studies have been conducted with palovarotene, with the sponsor submitting a waiver request. Their absence is considered to be acceptable, but the most compelling justification for the absence of carcinogenicity studies was not identified by the sponsor: negative mouse and rat carcinogenicity studies with the existing RARγ-selective agonist, trifarotene.

Studies in rats identified no effects on male or female fertility at tolerable doses. Classic retinoid-type malformations (*e.g.*, cleft palate, misshapen skull bones, shortened long bones) were demonstrated with palovarotene in rats at doses yielding exposure well below that in patients. The findings justify assignment to Pregnancy Category X, and contraindication in women who are pregnant or may become pregnant, as the Sponsor proposes. Palovarotene and its major metabolites were shown to not be phototoxic in an in *vitro* assay.

There are no nonclinical objections to the registration of Sohonos for the proposed indication.

Clinical

Summary of clinical studies

Pharmacology studies

The clinical dossier consisted of 13 Phase 1 clinical pharmacology studies in healthy subjects and 4 population pharmacology studies. The efficacy and safety studies 201, 202, and 301 also provided pharmacokinetic (PK) data in the FOP population (Table 4).

- Study RB16327 (Report 1005298): a single ascending dose study (fed/fasted).
- Study RB16328 (Report 1006914): a multiple ascending dose study.
- Study NP17056 (Report 1016529): a [14C]-radiolabelled single-dose mass balance study.
- Study NP17584 (Report 1016091): a bioequivalence study (capsule vs. tablet formulation).

- Study NP17726 (Report 1016632): a single-dose age and sex study.
- Study 101 (PVO-1A-101): a single-dose bridging study in Japanese and non-Asian subjects.
- Study 102 (PVO-1A-102): a food-effect/mode of administration study (combined with a midazolam DDI study).
- Study 103 (PVO-1A-103): a thorough QT/QTc study.
- Study 104 (PVO-1A-104): a study evaluating the PK of palovarotene in seminal fluid.
- 5 drug-drug interaction (DDI) studies:
  - Study NP17041B (Report 1010705): DDI with ketoconazole (strong CYP3A4 inhibitor).
  - Study NP17040 (Report 1010704): DDI with rifampicin (strong CYP3A4 inducer).
  - Study NP17055 (Report 1015528): Effect (inhibition) of palovarotene on midazolam (CYP3A4 substrate).
  - Study 102 (PVO-1A-102): Effect (induction) of palovarotene on midazolam (CYP3A4 substrate).
  - Study NP21025 (Report 1026186): DDI with prednisone (weak CYP3A4 inhibitor).
- Population pharmacology studies:
  - Study PVO-PopPK-001: original population pharmacokinetics (PopPK) model.
  - Study PVO-PopPK-002 (Addenda 1 and 2 to PVO-PopPK-001: PopPK model refinement).
  - Study PVO-PopPK-003: PK in renal and hepatic impairment.
  - Study IPN-3B (with an ad hoc component for the FDA): Physiologically-based pharmacokinetic (PBPK) model for evaluation of CYP3A4, CYP2C8, and CYP2C19 DDI and PK in renal and hepatic impairment.

Efficacy and safety studies

To support the efficacy and safety, one pivotal phase 3 trial, two supportive phase 2 studies, and a Natural History Study (NHS) were submitted:

- Study 301 (PVO-1A-301): A pivotal phase 3, 24-month (with a 24 month extension), non-randomised, open-label, multi-centre, single-arm study with historical controls (from Study 001) to assess the efficacy and safety of oral palovarotene for the treatment of FOP (chronic and flare-up) in 107 treatment-naïve adult and paediatric patients aged ≥4 years.
- Study 201 (PVO-1A-201): Phase 2, multicentre, randomised, double-blind, placebo-controlled 12-week study (with open-label extension) in 40 female or male patients aged ≥6 years with FOP and an active flare-up.
- Study 202 (PVO-1A-202): Phase 2, multicentre, open-label, uncontrolled study in 40 (Part A) or 56 (Parts B) or 48 (Part C) male or female patients with FOP (chronic or flare-up) aged ≥6 years to investigate different dosing regimens of palovarotene.
- Study 101 (PVO-1A-101) Natural History Study (NHS): Multicentre, 3-year natural history, non-interventional (observational), longitudinal study.

FOP is an extremely rare disease, and thus patients have typically participated in more than one study. Study 203 (PVO-1A-203) has not been presented, as terminated early, and 5 of 6 participants were enrolled in Study 202.

Table 4. Overview of efficacy studies

Study Number (Phase)	Design	Population	Dose/Treatment	Number of Subjects per Dose
PVO-1A-301 (Phase 3) Ongoing	Multicenter, open-label study evaluating the efficacy and safety of PVO in decreasing HO in subjects with FOP versus untreated subjects in the NHS	Palovarotene treatment naïve FOP subjects with the R206H mutation (PEP) or other FOP mutations (SEP)	Oral 5 mg QD for up to 24 months, with dose escalation for flare-up treatment to 20 mg QD for 4 weeks, then 10 mg QD for 8 weeks (total of 12 weeks; may be extended by 4 week intervals until flare-ups (including intercurrent flare-ups) or major traumatic event(s) resolve	107 subjects (99 PEP and 8 SEP)
PVO-1A-201 (Phase 2) Completed	Multicenter, R, DB, PC adaptive dose finding/POC	Cohort 1: FOP subjects with active flare-ups; age ≥15 years Cohort 2: FOP subjects with active flare-ups age ≥6 years	Cohort 1: oral QD 10 mg for 2 weeks, then 5.0 mg for 4 weeks, or placebo Cohort 2: oral QD 10 mg for 2 weeks, then 5.0 mg for 4 weeks; oral QD 5 mg for 2 weeks, then 2.5 mg for 4 weeks; or placebo. Weight-based dosing implemented in Cohort 2 across three categories (20 to <40 kg, 40 to <60 kg, ≥60 kg)	Cohort 1: 12 active; 4 placebo Cohort 2: 18 active; 6 placebo Total of 40 subjects
PVO-1A-202/Part A (Phase 2) Completed	Multicenter, OLE of PVO-1A-201	FOP subjects who completed Study PVO-1A-201.	Oral QD 10 mg for 2 weeks, then 5 mg for 4 weeks for the next two subsequent treatment-qualifying flare-ups. Weight-based dosing when children 6+ years of age enrolled in Study PVO-1A-201.	40 subjects from PVO-1A-201
PVO-1A-202/Part B (Phase 2) Completed Corresponds to PVO-1A-204 in France	Multicenter, OLE of PVO-1A-201	FOP subjects from Part A and new FOP subjects with at least 90% skeletal maturity regardless of age.	Adult Cohort (chronic/PVO 20/10 mg): oral 5 mg QD for up to 24 months, with dose escalation for flare-up treatment to 20 mg QD for 4 weeks, then 10 mg QD for 8 weeks (total of 12 weeks; may be extended by 4 week intervals until flare-ups (including intercurrent flare-ups) or major traumatic event(s) resolve). Pediatric Cohort (flare-up only treatment): same as flare-up dosing in the Adult Cohort except dosing is weight-adjusted.	54 subjects: 36 subjects from Part A and 18 new Adult Cohort subjects (13 subjects from the NHS and five new subjects).

PVO-1A-202/Part C (Phase 2) Ongoing Corresponds to PVO-1A-204 in France	Multicenter, OLE of PVO-1A-201	FOP subjects from Study PVO-1A-202/Part B	All subjects (chronic/ PVO 20/10 mg treatment): oral QD administration 5 mg for up to 24 months, with dose escalation for flare-up treatment to oral QD 20 mg for 4 weeks, then 10 mg for 8 weeks (total of 12 weeks; may be extended by 4 week intervals until flare-ups (including intercurrent flare-ups) or major traumatic event(s) resolve). Dosing is weight-adjusted in skeletally immature subjects.	48 subjects from Part B
PVO-1A-001 Completed	Non-interventional natural history study	Subjects with the R206H mutation aged 0-65 years	NA (non-interventional study): 3-year follow-up.	114 subjects: 0 to <8 years (n=17) 8 to <15 years (n=36) 15 to <25 years (n=34) 25 to ≤65 years (n=27)

[1] PVO-1A-203 was terminated early; 5 of the 6 subjects enrolled were transferred to PVO-1A-202/Part B. The limited efficacy data from this study is not included in this integrated summary.
DB=double-blind; FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; HO=heterotopic ossification; IND=Investigational New Drug (application); NA=not applicable; OLE=open-label extension; PC=placebo-controlled; PEP=Principal Enrolled Population; POC= proof-of-concept; PVO=palovarotene; QD=once daily; R=randomized; SEP=Supplementary Enrolled Population

Pharmacology

Pharmacokinetics

An overview of PK parameters is presented in Table 5. The PK characteristics, as informed by PK studies are summarised below.

Table 5. Clinical pharmacology studies. Palovarotene PK parameters at steady state.

Study	Dose (mg)	Population	$C_{max,ss}$ (ng/mL)	$C_{min,ss}$ (ng/mL)	$AUC_{0-\tau}$ (ng•h/mL)	T_{max} (h)	$t_{½}$ (h)	CL/F (L/h)
RB16328	1	Healthy	7.1 (1.8)	–	46.3 (11.9)	5.2 (1.8)	7.0 (2.7)	21.0 (5.7)
MAD	5		27.8 (11.1)	–	212 (84.9)	7.3 (5.5)	11.1 (3.6)	25.2 (18.0)
	10		52.2 (12.7)	–	385 (73.3)	4.3 (2.4)	21.2 (19.3)	22.3 (6.3)
NP17040 DDI Rifampicin	1	Healthy	8.3 (2.6)	0.2 (0.1)	41.2 (12.1)	3.8 (1.0)	5.6 (0.7)	24.6 (5.0)
NP17041 DDI Ketoconazole	1	Healthy	10.5 (3.0)	0.3 (0.2)	52.7 (15.5)	2.5 (1.3)	6.0 (0.7)	19.7 (6.2)
NP17055 DDI Midazolam	1	Healthy	9.0 (3.0)	–	46.3 (13.6)	–	–	–
NP21025 DDI Prednisone	5	Healthy	43.7 (17.3)	2.0 (1.0)	304 (114)	3.7 (1.0)	–	18.8 (7.6)
PVO-1A-102 DDI Midazolam	20	Healthy	140 (53.0)	3.5 (2.1)	942 (361)	4.6 (0.7)	8.7 (2.4)	23.4 (6.7)
PVO-1A-104 Plasma and seminal fluid	20	Healthy	120 (30.4)[1]	–	876 (36.0)[1]	4 (1, 8)[2]	11.0 (2.2)	22.8 (36.0)[1]
NP17124 MAD	1	COPD	10.3 (3.6)	0.4 (0.3)	57.7 (12.6)	4.0 (2.4)	–	18.2 (4.4)
NB18332 MAD	2.5	COPD	27.9 (12.3)	1.7 (1.3)	200 (76)	3.4 (1.6)	–	14.6 (6.3)
	5		47.3 (30.9)	2.7 (2.0)	366 (267)	4.5 (2.0)	–	18.3 (10.2)
PVO-1A-201	2.5	FOP	19.0 (9.24)	0.614 (0.290)	143 (84.8)	3.9 (1.5)	4.5 (0.5)	19.5 (10.7)
	5		35.6 (19.9)	1.74 (0.96)	350 (182)	3.3 (1.5)	4.9 (1.2)	12.8 (4.1)
	5		45.5 (17.1)	3.88 (7.04)	311 (129)	3.2 (0.7)	4.4 (0.7)	17.7 (7.4)
	10		95.6 (30.3)	3.13 (2.36)	686 (247)	3.6 (1.3)	4.6 (1.1)	15.6 (7.0)
PVO-1A-202B	10	FOP	70.9 (27.2)	2.00 (1.67)	467 (194)	3.22 (0.86)	5.3 (2.6)	21.4 (11.6)
	20		153 (54.6)	3.19 (1.68)	1008 (325)	3.24 (0.96)	5.1 (1.8)	19.9 (7.53)
PVO-1A-202C	5	FOP	57.1 (23.1)	0.97 (0.37)	341 (111)	3.00 (0.25)	4.5 (1.3)	14.8 (4.6)
	10		104 (52.0)	1.82 (0.78)	651 (258)	3.09 (0.17)	4.0 (0.63)	16.3 (8.9)
	20[3]		166	3.00	978	2.83	4.1	20.5
PVO-1A-301	5	FOP	40.6 (16.2)	1.03 (0.71)	264 (98.4)	3.00 (2.67, 6.07)[2]	4.9 (1.4)	17.8 (8.64)
	10		78.4 (33.3)	1.86 (1.59)	540 (226)	3.00 (2.75, 10.0)[2]	4.3 (0.7)	17.0 (7.80)
	20		165 (72.7)	3.11 (2.47)	1060 (449)	3.00 (2.83, 10.0)[2]	4.4 (1.2)	16.5 (7.43)
PVO-2A-201	2.5	MO	18.0 (50.2)[1]	0.31 (86.1)[1]	112 (29.1)[1]	3.00 (2.47, 10.0)[2]	4.6 (15.4)[1]	13.2 (33.6)[1]
	5.0		34.9 (63.3)[1]	0.67 (83.3)[1]	241 (42.7)[1]	3.01 (2.42, 24.3)[2]	4.6 (20.6)[1]	12.4 (44.6)[1]

1 GeoMean (CV%)

2 Median (minimum, maximum).

3 n=1.

$AUC_{0-\tau}$=area under the plasma concentration versus time curve over a dosing interval at steady state; CL/F=apparent total body clearance; $C_{max,ss}$=maximum observed concentration at steady state; $C_{min,ss}$=minimum observed concentration at steady state; COPD=chronic obstructive pulmonary disease; CV%=percent coefficient of variation; DDI=drug-drug interaction; FOP= fibrodysplasia ossificans progressive; GeoMean=geometric mean; MAD=multiple ascending dose; MO= multiple osteochondromas; PK=pharmacokinetics; SD=standard deviation; T=apparent terminal elimination half-life; T_{max}=time of maximum observed concentration

Absorption

After fed administration of 20 mg palovarotene once daily for 14 days in healthy subjects, the median T_{max} was 4.6 hours, the mean C_{max} was 140 ng/mL, and the average $AUC_{0-\tau}$ was 942 ng*hr/mL.

Administration of a 20 mg single dose after a high-fat, high-calorie meal increased the mean $AUC_{0-\infty}$ by 40% and the mean C_{max} by 16% compared with administration under fasting conditions. T_{max} increased from approx. 2 to 4 hours.

From a population PK analysis, derived $AUC_{0-\tau}$ and $C_{max,ss}$ were 37% and 32% higher, respectively, under fed conditions compared to fasted conditions for a typical adult.

Distribution

Palovarotene is highly bound (ranging from 97.9 to 99.6%) to human plasma proteins (*in vitro* data). The mean apparent volume of distribution at steady-state (Vd_{ss}/F) is 319 L following 20 mg once daily doses.

Metabolism

Palovarotene is extensively metabolised by primarily CYP3A4 and to a minor extent by CYP2C8 and CYP2C19 *in vitro*.

Five metabolites were observed: M1 (6,7-dihydroxy), M2 (6-hydroxy), M3 (7-hydroxy), M4a (6-oxo), and M4b (7-oxo) which reached steady-state by Day 4 with a large plasma concentration variability. M3 was the major metabolite based on AUC (50% to 60% of parent AUC) and with approx. 2% activity of the parent drug based on an *in vitro* transactivation assay.

Following administration of [^{14}C]-radiolabelled palovarotene, the contribution of palovarotene and its major metabolites (M2, M3, M4a, and M4b) collectively represented 40% of the total plasma exposure.

In vitro data suggest that palovarotene is not a significant substrate of any of the uridine 5'-diphospho-glucuronosyltransferases (UGTs).

Excretion and elimination

Palovarotene has a terminal half-life (T½) of approx. 8-13 hours and an estimated apparent clearance (CL/F) of 19.9 L/h. The hepatic extraction ratio of palovarotene appears to be <30%.

Dose proportionality

Following oral administration under fed conditions, palovarotene appeared to exhibit linear PK with dose-proportional increases in plasma exposure from doses of 0.02 to 50 mg (single dose), and 0.1 to 10 mg (multiple doses) in healthy volunteers. In the FOP studies, the range was 2.5 to 20 mg. In the target population, dose proportionality was observed following chronic (5 mg) and flare-up (20 mg and 10 mg) dosing.

Excretion

Following administration of [^{14}C]-radiolabelled palovarotene (54.5 µCi/mg), 97.1% of the dose was recovered in the faeces and 3.2% in the urine. Palovarotene and its four known major metabolites accounted for 67.2% of the dose in faeces and six other unidentified metabolites accounted for 28.4%. More than 92% of the dose was recovered in the first 6 days post-dose and mass balance was achieved with 100% of the dose recovered by Day 14.

Little or no accumulation was observed following once daily dosing. The mean steady-state trough plasma concentration was 3.5 ng/mL after once daily 20 mg palovarotene.

Interactions

In vitro, palovarotene did not significantly inhibit CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. *In vitro*, palovarotene did not significantly inhibit UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, or UGT2B7.

Palovarotene appears not to be a substrate of P-gp, BCRP, OATP1B1, OATP1B3, or OCT1; or to be an inhibitor of P-gp, OAT1, OAT3, OCT2, MATE1, or MATE2-K.

A clinical DDI evaluation for CYP2B6 was not conducted, as the sponsor considered the risk of induction low. Palovarotene appears not to have a clinically significant effect regarding the induction of CYP1A2, CYP2C8, CYP2C9, or CYP2C19.

Clinical drug-drug interaction (DDI) study results:

- DDI with ketoconazole (strong CYP3A4 inhibitor): Strong CYP3A4 inhibitors increase the systemic exposure of palovarotene (2-to 3-fold based on C_{max} and AUC). Concomitant use with strong CYP3A4 inhibitors should be avoided.
- DDI with erythromycin (moderate CYP3A4 inhibitor) (simulated PBPK model): A moderate inhibition (AUC GMR ≥2 and <5) was observed in the simulation. Concomitant use with moderate CYP3A4 inhibitors should be avoided.
- DDI with prednisone (weak CYP3A4 inhibitor): In the presence of prednisone, mean palovarotene $C_{max,ss}$ and $AUC_{0-\tau}$ were both reduced by approximately 14% (not considered clinically significant).
- DDI with rifampicin (strong CYP3A4 inducer): Co-administration of palovarotene with rifampicin decreased the exposure of palovarotene approximately 10-fold. Concomitant use with strong CYP3A4 inducers should be avoided.
- DDI with efavirenz (moderate CYP3A4 inducer) (simulated PBPK model): A moderate induction (AUC GMR ≤0.5 and >0.2) was observed in the simulation. Concomitant use with moderate CYP3A4 inducers should be avoided.
- DDI with midazolam (CYP3A4 substrate): Co-administration with multiple doses of palovarotene resulted in less than 15% decrease in midazolam exposure. Palovarotene did not significantly induce CYP3A4 in healthy subjects.
- Smoking appeared to have no significant effect on the PK.

Intra- and inter-individual variability

Following single-dose fed administration conditions in healthy subjects, inter-individual variability (%CV) for AUC and C_{max} was low to moderate (typically 30% to 40%). High inter-individual variability appears to have been observed in the Population PK simulations. Intra-individual variability appears not to have been considered.

Special populations

Effect of hepatic impairment: In a PopPK covariate analysis (PVO-PopPK-003) (n=701), there was no evidence that mild hepatic impairment (n=47, 6.7%) affected palovarotene PK and did not suggest that moderate hepatic impairment affected the PK, noting that the number of patients with hepatic impairment was low (e.g., n=2 for moderate impairment), and did not include severe impairment.

Simulation results from a PBPK model suggested that patients with Child-Pugh classifications A, B, and C had an $AUC_{0-\tau}$ which was 1.10, 1.61-, and 1.85-fold greater, respectively, and a C_{max} which was 1.07-, 1.42-, and 1.53-fold greater, respectively, compared to healthy subjects.

No dose adjustment is required in patients with mild hepatic impairment. The use in moderate and severe hepatic impairment has not been specifically studied. Palovarotene may be used with caution in moderate hepatic impairment, and but should not be used in severe hepatic impairment.

Effect of renal impairment: Palovarotene is not mainly renally eliminated. In a PopPK covariate analysis (PVO-PopPK-003) (n=701), there was no evidence that that mild (n=158, 22.5%) or moderate (n=24, 3.4%) renal impairment clinically affected palovarotene PK, and no dose adjustment is needed. Use in severe renal impairment is not recommended.

Population PK (popPK) and PBPK data

This consisted of: Population pharmacology studies PVO-PopPK-001 (original analysis), PVO-PopPK-002 (Addenda 1 and 2 of PVO-PopPK-001), PVO-PopPK-003, and Study IPN-3B (PBPK).

Methods

PK clinical data source: 15 studies, including 8 studies in healthy volunteers, 3 studies in patients with symptomatic emphysema secondary to COPD (NA17598 (Tier 2), NP17124 and NB18332), 3 studies in patients with FOP (201, 202 and 301) and 1 study in patients with multiple osteochondromas (MO) (Study PVO-2A-201).

PVO-PopPK-002 included 9088 concentrations from 701 subjects, of which 184 (26%) were aged <18y. This generated the final model (run 082) that was also used for Study PVO-PopPK-003, and Study IPN-3B.

Model: The following covariates were evaluated for their impact on the palovarotene PK: age, body weight, biological sex, race, smoking status, health status, administration with food, formulation, method of administration (sprinkled on food or swallowed whole), administration of prednisone, albumin, ALT, AST, ALP, creatinine, and bilirubin.

The evaluation used nonlinear mixed effects modelling with a Monte Carlo Importance Sampling Expectation Maximization method implemented in NONMEM (v.7.30. and 7.4.3).

The population PK models were evaluated using a prediction corrected visual predictive check (pc-VPC) method. The final model was used to perform simulations in adults, and subsequently in skeletally immature children (250 males and 250 females were simulated using CDC growth chart data) to assess the proposed weight-based dosing.

The weight-adjusted equivalent doses used in the simulation for skeletally immature subjects were:

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

For each subject, a 24-hour steady-state concentration-time profile was simulated following a once daily dose of 5, 10, and 20 mg (or weight-adjusted equivalent). Steady-state peak concentration (C_{max}), trough concentration (C_{min}) and area under the curve (AUC) were calculated using non-compartmental methods and compared by weight group.

Results and conclusions

Model: The final PK model (run067 (original analysis), run080 (Addendum 1) and run082 (Addendum 2)) was a two-compartment lagged model with first-order absorption (six transit compartments were used to describe the delay in absorption) and first-order elimination. VPCs

confirmed the predictive capability of the model and showed good agreement between observations and model predictions over the range of the data.

The PK model development process was rigorous and the final PK model was robust and adequately described the PK data collected in 16 studies in healthy subjects and patients with COPD, FOP and MO. The predictive performance of the model was adequate to predict exposures in a paediatric population.

Dose-proportionality: The model supported palovarotene PK dose-proportionality for the dose range tested (0.02 to 50 mg).

Covariate modelling: Population PK parameter estimates are summarised in Table 6.

Table 6. Population PK Study PVO-PopPK-002 (Addendum 2). Parameter Estimates of Final PopPK Model (run082)

$CL/F = 19.9 \times (WT/70)^{0.499}$
$Q/F = 4.17 \times (WT/70)^{1.07}$
$Vc/F = 36.2 \times (WT/70)^{0.899}$
$Vp/F = 77.3 \times (WT/70)^{0.812}$
$Ka = 0.396$
$MTT = 1.12 \times 0.357^{fasted} \times 0.267^{sprinkled}$
$F=1 \times 0.768^{fasted}$

Parameter	Units	NONMEM Estimates					MCMC BAYES Estimates[e]
		Estimate[a]	%RSE[b]	95% CI[a]	IIV CV%[c] (%RSE)	IOV CV% (%RSE)	Median [95% CI]
CL/F	L/hr	19.9	1.51	19.3-20.5	34.1 (6.49)	-	19.8 [19.3 to 20.4]
Vc/F	L	36.2	6.52	31.9-41.2	90.1 (12.4)	-	37.7 [32.1 to 43.3]
Q/F	L/hr	4.17	4.69	3.80-4.57	106 (9.65)	-	4.17 [3.82 to 4.60]
Vp/F	L	77.3	4.59	70.7-84.6	89.0 (9.23)	-	76.7 [70.2 to 84.2]
Ka	hr^{-1}	0.396	3.31	0.371-0.423	19.9 (49.7)	43.7 (13.3)	0.414 [0.385 to 0.448]
MTT	hr	1.12	4.45	1.02-1.22	84.2 (9.61)	44.6 (16.4)	1.10 [0.999 to 1.21]
F~fasted	unitless	0.768	2.68	0.727-0.808	-	-	0.782 [0.739 to 0.824]
MTT~fasted	unitless	0.357	13.3	0.264-0.450	-	-	0.361 [0.269 to 0.457]
CL/F~weight	unitless	0.499	6.82	0.432-0.565	-	-	0.522 [0.445 to 0.589]
Vc/F~weight	unitless	0.899	11.3	0.700-1.10	-	-	1.10 [0.891 to 1.33]
Q/F~weight	unitless	1.07	9.00	0.883-1.26	-	-	0.866 [0.678 to 1.06]
Vp/F~weight	unitless	0.812	13.3	0.601-1.02	-	-	0.780 [0.578 to 0.970]
MTT~sprinkled	unitless	0.267	15.7	0.185-0.349	-	-	0.192 [0.138 to 0.297]
$\sigma^2_{prop\ TAD > 4\ hr\ HV}$	unitless	0.0851	3.02	0.0800-0.0901	29.2%[d]	-	0.0850 [0.0801 to 0.0904]
$\sigma^2_{prop\ TAD \leq 4\ hr\ HV}$	unitless	0.164	3.79	0.152-0.176	40.5%[d]	-	0.164 [0.152 to 0.177]
$\sigma^2_{prop\ Patients}$	unitless	0.166	3.18	0.156-0.176	40.8%[d]	-	0.166 [0.156 to 0.177]

[a] Back-transformed from natural log scale (except for σ^2, F~fasted, MTT~fasted, CL/F~ weight, Vc/F~weight, Q/F~weight, Vp/F~weight, MTT~sprinkled)

[b] RSE=SE.100 (except for σ^2, F~fasted, MTT~fasted, CL/F~ weight, Vc/F~weight, Q/F~weight, Vp/F~weight, MTT~sprinkled). RSE for σ^2, F~fasted, MTT~fasted, CL/F~ weight, Vc/F~weight, Q/F~weight, Vp/F~weight, MTT~sprinkled =SE(θ)/θ.100

[c] CV for IIV calculated as $CV_{TVP}=\sqrt{e^{\omega^2_P}}\cdot 100$ if $\omega^2_p \leq 0.15$, else $CV_{TV_p} = \sqrt{e^{\omega^2_P} - 1}\cdot 100$

[d] Proportional residual error expressed as CV.

[e] From 1,000 iterations in which every 10th iteration from a total of 10,000 was sampled.

Abbreviations: CL/F = apparent total clearance, Vc/F = apparent volume of central compartment, Vp/F = apparent volume of peripheral compartment, Q/F = inter compartment clearance between central and peripheral compartments, Ka=first order absorption, MTT=mean transit time, F=bioavailability, IIV = inter-subject variability, CI=confidence interval, RSE=relative standard error, CV=coefficient of variation, σ^2_{prop} = proportional residual error, TAD=time after dose, HV=healthy volunteers

The reference population is a 70 kg subject administered palovarotene in the fed state and swallowed whole.

CL/F, Vc/F, Q/F and Vp/F all increased with weight, with estimated allometric scalars. The MTT and relative bioavailability were decreased in the fasted state (64% shorter and 23% lower, respectively, compared to fed). Sprinkling (vs. swallowing the capsule whole) had little impact on palovarotene exposure (C_{max} or AUC) (12-15% lower).

After inclusion of the investigated covariate effects, graphical evaluations showed no residual trends with other covariates, suggesting no effect of, age, biological sex, race, smoking status, health status, administration of prednisone, albumin, ALT, AST, ALP, creatinine or bilirubin on palovarotene PK.

Weight covariate: Body weight had a significant impact on PK (increasing exposure with decreasing body weight at the same dose). In adult simulations, derived $AUC_{24,ss}$ and $C_{max,ss}$ were 8% and 12% greater for a 51-kg (5^{th} percentile) adult, and 18% and 26% lower for a 98-kg adult (95^{th} percentile), respectively, compared to a typical 70-kg subject.

Weight-based paediatric dosing: Although C_{max} was higher and C_{min} was lower for paediatric subjects <20 kg, the overall exposure (AUC) was comparable between the weight groups and the proposed paediatric weight-based dosing scheme was considered appropriate. Consistent results were obtained across the successive analyses.

The sponsor proposes weight-adjusted dosing in patients aged ≤14y (with <90% skeletal maturity), but not in adults or skeletally mature children, in order to provide the highest tolerated dose to minimise HO formation. But dose adjustments may occur based on clinical tolerability.

Effects in patients with reduced renal or hepatic function.

At baseline, the study included:

- 519 (74%), 158 (23%) and 24 (3%) subjects with normal renal function, mild renal impairment and moderate renal impairment, respectively
- 652 (93%) and 47 (7%) subjects with normal hepatic function and mild hepatic impairment, respectively.

Based on the renal and hepatic function groups represented in the study:

- There was no apparent effect of mild renal impairment or moderate renal impairment on palovarotene clearance.
- There was no apparent effect of mild hepatic impairment on palovarotene clearance.

Pharmacodynamics

Mechanism of action

Palovarotene is a selective retinoic-acid receptor gamma agonist that inhibits heterotopic ossification.

Pharmacodynamic variables

Exposure-efficacy analyses: Using data from Studies PVO-1A-001, 201, and 202, no consistent ER trends for response measures vs exposure metrics could be found.

Using pivotal phase 3 data in FOP patients, the sponsor claims that there was a statistically significant relationship between change from baseline in HO volume and cumulative AUC at Month 12 (but not at Week 12).

Exposure-safety analyses: No data available.

Efficacy

Study 301 (PVO-1A-301) (MOVE study) (pivotal phase 3 study)

Design

A pivotal, 24-month (Part A) (with a 24 month extension (Part B)), phase 3, non-randomised, open-label, multi-centre (16 centres in 11 countries), single-arm study with historical controls

(from Study 101) to assess the efficacy and safety of oral palovarotene for the treatment of FOP (chronic and flare-up) in 107 treatment-naïve adult and paediatric patients aged ≥4 years.

The study evaluated the efficacy and safety of the chronic/flare-up regimen on annualised change in new HO as assessed by WBCT compared to the external control group of 'untreated' subjects from Study 001.

The study period commenced on 30 November 2017 (first subject signed informed consent form) with 28 February 2020 being the data cut-off for the interim CSR. The study was completed in September 2022.

Based on the serious identified risk of premature physeal closure (PPC), a partial clinical hold was implemented on subjects aged <14 years. At the time of this report, the partial clinical hold remained in place for subjects <14 years of age.

Interim analyses assessed annualised new HO volume in the chronic/flare-up regimen in Study 301 and compared them with those from untreated subjects in Study 001 (as external control).

Primary efficacy objective

- To evaluate the efficacy of palovarotene in decreasing heterotopic ossification (HO) in adult and paediatric subjects with FOP as assessed by low-dose whole body computed tomography (WBCT), excluding head, as compared to untreated subjects (in Study 001).
- To evaluate the safety of palovarotene in adult and paediatric subjects with FOP.

Secondary efficacy objectives

- To evaluate the effect of palovarotene on flare-up rate and proportion of subjects reporting at least one flare-up.
- To evaluate the effect of palovarotene on range of motion (ROM) as assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP.
- To evaluate the effect of palovarotene on physical function using age-appropriate forms of the FOP-Physical Function Questionnaire (FOP-PFQ).
- To evaluate the effect of palovarotene on physical and mental health using age-appropriate forms of the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale.

Inclusion criteria included

- FOP diagnosis:
    1. subjects from Study 001.
    2. clinical FOP diagnosis with the R206H activin receptor type IA (ACVR1) mutation or other FOP variants reported to be associated with progressive HO.
    3. subjects from Study 202/204 who could not receive the chronic/flare-up regimen in the Phase 2 trial (due to practical reasons).
- Other criteria: Age ≥4 years; no flare-up symptoms within the past 4 weeks; negative pregnancy test; abstinence from heterosexual sex or use of two effective birth control methods during and for one month before/after treatment; ability to undergo low-dose WBCT without sedation.

Up to a maximum of 110 subjects were to be enrolled (up to 99 with a R206H mutation and no previous palovarotene exposure, and up to 11 with other mutations or previous participation in the Phase 2 trials).

Exclusion criteria included (full list in Table 22): weight <10 kg; exposure to synthetic oral retinoids (except palovarotene) 4 weeks prior to screening; concurrent treatment with tetracycline or its derivatives; concomitant use of strong CYP3A4 inhibitors or inducers; amylase or lipase >2x ULN or history of chronic pancreatitis; AST or ALT >2.5x ULN; fasting triglycerides >400 mg/dL; breastfeeding; uncontrolled cardiovascular, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease; suicidal ideation (Type 4 or 5)/suicidal behaviour within the past month (C-SSRS definition).

Treatments

- Dosing:
  - Chronic treatment: Palovarotene 5 mg daily (or weight-adjusted) for up to 24 months.
  - Flare-up treatment (12 weeks):
    - Palovarotene 20 mg daily (or weight-adjusted) for 4 weeks; then
    - Palovarotene 10 mg daily (or weight-adjusted) for 8 weeks.
- Flare-up treatment triggers:
  - Flare-up symptoms (only one symptom needed) including pain, swelling, redness, decreased range of motion, stiffness, and warmth; or
  - Substantial high-risk traumatic events including surgery, intramuscular immunisations, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, falls, or influenza-like viral illnesses.
- Flare-up treatment duration: a 12 week cycle but could be extended in 4-week intervals. Once all flare-ups/traumatic events had been resolved and flare-up-based treatment completed, the chronic treatment dosing regimen was resumed. Another flare-up/event prior to resolution of a previous event could restart a flare-up treatment cycle.
- Weight adjustment dosing in <18 years with <90% skeletal maturity on hand-wrist radiography at Screening (ceased once growth plate 100% closed at both knee and hand-wrist locations):

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

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

- Adverse effect dose adjustment: reduction to the next lower dose, or if on the lowest dose, discontinuation.

Baseline characteristics

39 patients from the NHS transitioned to Study 301 (i.e., they were part of the treatment and the historical control group, but at different ages).

- Patient demographics are summarised in Table 7. Both groups were reasonably balanced except for age category. In Study 301, 75.8% were <18y compared to 59.5% in the control group. The patients age ranged between 4 and 61 years with a median of 13.0 and 15.0 years, respectively.

Table 7. Study 301. Baseline Demographic Characteristics (Principal Safety Set).

	Study PVO-1A-301 Palovarotene (N = 99)	Study PVO-1A-001 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)
Black or African American	1 (1.0)	0
Asian	9 (9.1)	9 (8.1)
American Indian or Alaska Native	0	1 (0.9)
Native Hawaiian or other Pacific Islander	1 (1.0)	1 (0.9)
Multiple	6 (6.1)	1 (0.9)
Other	1 (1.0)	2 (1.8)
Unknown	11 (11.1)	16 (14.4)
Ethnicity, n (%)		
Hispanic or Latino	19 (19.2)	23 (20.7)
Not Hispanic or Latino	69 (69.7)	72 (64.9)
Not reported[1]	11 (11.1)	16 (14.4)

Disease characteristics are summarised in Table 8 and Table 9: Both groups were generally balanced regarding FOP history. In both groups, nearly all patients were born with great toe malformation (not surgically repaired in most). Approximately half had thumb malformations and cervical spine malformations. Osteochondromas of the tibia were present in 38% and 36% of active and control group patients, respectively. Almost all patients had experienced a flare-up. In the treatment group, the most common (>10%) last flare-up location was head/neck, upper back, hip, lower spine/abdomen, or shoulder. In the control group, this was the upper back, elbow, hip, or shoulder. The cause of last flare-up was unknown in 75% vs. 48%.

Table 8. Study 301. Baseline Disease Characteristics (Principal Safety Set).

	Study PVO-1A-301 Palovarotene (N = 99)	Study PVO-1A-001 Untreated (N = 111)
Age at FOP diagnosis (years)		
n	98	111
Mean (SD)	5.8 (4.74)	6.6 (5.11)
Median (min, max)	4.1 (0; 20)	5.1 (0; 23)
Time from FOP diagnosis to enrollment (years)		
n	99	110
Mean (SD)	9.8 (9.27)	11.4 (9.45)
Median (min, max)	7.8 (0; 56)	8.2 (0; 43)
Clinical/phenotypic features of FOP:		
Great toe malformations		
Yes	98 (99.0)	111 (100)
No	1 (1.0)	0
If yes, when noted:		
Birth	93 (93.9)	95 (85.6)
Other	5 (5.1)	16 (14.4)
Surgically repaired?		
Yes	19 (19.2)	20 (18.0)
No	79 (79.8)	91 (82.0)
Other Associated Clinical Findings		
Cervical Spine Malformations	44 (44.4)	55 (49.5)
Hearing Loss	44 (44.4)	39 (35.1)
Thumb Malformations	46 (46.5)	57 (51.4)
Shortened Femoral Necks	13 (13.1)	16 (14.4)
Osteochondromas		
Tibia	38 (38.4)	40 (36.0)
Femur	8 (8.1)	9 (8.1)
Humerus	2 (2.0)	2 (1.8)
Other, Abnormal Gait	1 (1.0)	0
Other, Bone Spurs On Bilateral Feet	1 (1.0)	0
Family history of FOP		
Yes	1 (1.0)	5 (4.5)
No	98 (99.0)	106 (95.5)

Table 9. Study 301. Baseline Flare-up History (Principal Safety Set).

	Study PVO-1A-301 Palovarotene (N = 99)	Study PVO-1A-001 Untreated (N = 111)
Subjects with History of flare-up, n (%)		
Yes	99 (100.0)	108 (97.3)
No	0	3 (2.7)
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[1]		
Mean (SD)	24.5 (36.99)	18.9 (31.11)
Median (min, max)	10.3 (1, 199)	6.3 (0, 181)
Location of last flare-up, n (%)		
Cervical Spine	4 (4.0)	8 (7.2)
Distal Lower Extremities	4 (4.0)	4 (3.6)
Distal Upper Extremities	1 (1.0)	2 (1.8)
Elbow	3 (3.0)	11 (9.9)
Head/Neck	14 (14.1)	9 (8.1)
Hip	13 (13.1)	13 (11.7)
Jaw	8 (8.1)	9 (8.1)
Knee	8 (8.1)	5 (4.5)
Lower Spine/Abdomen	12 (12.1)	8 (7.2)
Missing	5 (5.1)	0
Shoulder	11 (11.1)	12 (10.8)
Upper Back	14 (14.1)	18 (16.2)
Upper Spine/Chest	2 (2.0)	9 (8.1)
Symptoms of last flare-up, n (%)[2]		
Pain	68 (68.7)	88 (79.3)
Swelling	80 (80.8)	89 (80.2)
Stiffness	47 (47.5)	48 (43.2)
Redness	36 (36.4)	35 (31.5)
Warmth	40 (40.4)	50 (45.0)
Fever	5 (5.1)	11 (9.9)
Loss of Appetite	6 (6.1)	17 (15.3)
Decreased Range of Motion	50 (50.5)	49 (44.1)
Change in Mood or Behavior	12 (12.1)	39 (35.1)
Lethargy	8 (8.1)	25 (22.5)
Other	4 (4.0)	6 (5.4)
Cause of last flare-up, n (%)		
Biopsy	0	1 (0.9)
Blunt Muscle Trauma	10 (10.1)	16 (14.4)
Dental Work	0	1 (0.9)
Influenza-Like Viral Illness	1 (1.0)	2 (1.8)
Muscle Fatigue	2 (2.0)	7 (6.3)
Surgery	3 (3.0)	1 (0.9)
Unknown	74 (74.7)	53 (47.7)
Other	9 (9.1)	27 (24.3)

Source: Table B5.

1. Time since last flare-up (months)-calculated as [(ICF- Last flare-up start date)/30.4375]+1.
2. Subjects could have had multiple symptoms for their last flare-up.

ICF=informed consent form; max=maximum; min=minimum; SD=standard deviation.

Flare-up data:

- 69/99 patients had at least one flare-up treated with palovarotene; they experienced a median of 3 flare-ups overall (range: 1, 23; mean: 4.0 ± 4.2). Dose reductions occurred during high-dose flare-up treatment in 31 (44.9%) patients compared to 8 (11.6%) patients during low-dose flare-up treatment (Table 10).

- 128 flare-up cycles occurred in patients treated for at least one flare-up with a median of 1.0 (range: 0, 23) flare-up treated per cycle (mean: 2.2 ±3.0). The duration of flare-up treatment cycles lasted a median of 84 days (range: [1, 530]; mean:110 days [79.6]). Most flare-up cycles had 1 flare-up (61.7%) (Table 11).

Table 10. Study 301. Subjects with Flare-up Treatment (Principal Safety Set).

Variable	Flare-up Cycles n (%)
Subjects with ≥1 flare-up treated with palovarotene	69 (69.7%)
Subjects reporting at least 1 flare-up, n (%)	
1	18 (26.1)
2	14 (20.3)
3	12 (17.4)
4	11 (15.9)
≥5	14 (20.3)
Mean (SD)	4.0 (4.2)
Median (Min, Max)	3.0 (1, 23)
Subjects with at least one dose reduction during high-dose flare-up treatment, n (%)	31 (44.9)
Subjects with at least one dose reduction during low-dose flare-up treatment, n (%)	8 (11.6)
Subjects with at least one interrupted study drug during high-dose flare-up treatment, n (%)	8 (11.6)
Subjects with at least one interrupted study drug during low-dose flare-up treatment, n (%)	10 (14.5)
Subjects with at least one discontinued study drug during high-dose flare-up treatment, n (%)	7 (10.1)
Subjects with at least one discontinued study drug during low-dose flare-up treatment, n (%)	5 (7.2)

Source: Table E11B and Table B7C.
Note: Two subjects were treated with a flare-up dose but were not assessed to be in flare-up status and are not included in the table. Drug interruption was defined as interruption of study drug treatment for >14 days.
max=maximum; min=minimum; SD=standard deviation; SS=safety set.

Table 11. Study 301. Number of Flare-up Treatment Cycles (Principal Safety Set).

Variable	Flare-up Cycles
Total number of flare-up cycles, n[1]	128
Category of number of flare-ups treated per cycle, n[1] (%)	
0 flare-ups	2 (1.6)
1 flare-up	79 (61.7)
2 flare-ups	22 (17.2)
3 flare-ups	9 (7.0)
4 flare-ups	5 (3.9)
≥5 flare-ups	11 (8.6)
Mean (SD)	2.2 (3.0)
Median (Min, Max)	1.0 (0, 23)
Flare-up cycles with at least one dose reduction, (n [%])	
During high-dose flare-up treatment	41 (32.0)
During low-dose flare-up treatment	9 (7.0)
Flare-up cycles with interrupted study drug, (n [%])	
During high-dose flare-up treatment	8 (6.3)
During low-dose flare-up treatment	10 (7.8)
Flare-up cycles with discontinued study drug, (n [%])	
During high-dose flare-up treatment	7 (5.5)
During low-dose flare-up treatment	5 (3.9)
Duration of flare-up cycle treatment, days	
High dose (20 mg), n = 128 cycles	
Mean (SD)	52.8 (61.6)
Median (Min, Max)	28.0 (1, 428)
Low dose (10 mg), n = 116 cycles	
Mean (SD)	63.1 (27.3)
Median (Min, Max)	56.0 (1, 155)
Overall flare-up cycle treatment (days), n = 128	
Mean (SD)	110.0 (79.6)
Median (Min, Max)	84 (1, 530)

Source: Table E11A, Table B7B.
[1] A subject could be counted more than once if they were treated for more than one flare-up cycle.
Note: For counts for "Category of number of flare-ups treated per cycle": two subjects were treated with a study dose administered for flare-up treatment but were not assessed as having a flare-up.
max=maximum; min=minimum; SD=standard deviation; SS=safety set.

Initial analysis and post hoc change of methodology

The original protocol primary efficacy analysis intended to compare the annualised change in new HO volume between subjects treated with palovarotene and untreated subjects using a wLME model in the FAS (without transformation or zeroing negative values).

A protocol amendment changed this to a Bayesian compound Poisson model with a square root transformation of HO volume per region and negative new HO values being set to zero (either by body region; or overall). In IA2, that analysis indicated that the futility boundary (<5% posterior probability of ≥30% reduction in annualised new HO volume) had been crossed. Consequently, as pre-specified, dosing was interrupted, and data were unblinded for *post hoc* analyses. These *post hoc* analyses (Bayesian model without square root transformation and a wLME model with

and without square root transformation) revealed a clinically meaningful benefit when used without square root transformation.

Consequently, the applicant believed that the most appropriate analysis is the simpler wLME analysis without square root transformation (as per original protocol). The wLME analysis without transformation accommodates the annualised new HO as reported (including any observed reductions). A subject-level random effect was used to account for the correlation among repeated measures on the same subject. The model was fitted using only a subject's observations associated with the longest follow-up in Studies 301 and 001 with weights used to account for the different lengths of observed follow-up. Baseline HO volume divided by age was the only included covariate, in addition to the factor identifying study of origin. No imputation of missing data was performed.

Additionally, Wilcoxon rank-sum tests were performed (dependent only on the numeric rank order of the observed new HO volumes rather than their magnitudes) which are less influenced by extreme values.

Thus, only the original/latest protocol wLME analysis has been considered in this overview as the primary analysis. The Bayesian model result are shown in the sponsor documentation.

Analysis sets

- Principal FAS (Principal Full Analysis Set): all enrolled subjects in the Principal EP who had a baseline and at least one post-baseline HO volume measurement.
- Principal PPS (Principal Per-Protocol Set): subset of the Principal FAS including subjects with no major protocol deviations that were expected to interfere with assessments of the primary endpoint, and with at least 80% compliance to the study drug regimen over the first 24 months of participation in the study.

ITT Set (Intention-to-Treat Set): all subjects regardless of whether they restarted palovarotene treatment or remained off treatment until study completion due to the partial clinical hold or other reason. This Set was not part of the original application and is less representative of the treatment effect, as it includes off-treatment periods. A Wilcoxon rank-sum analysis is not available for this set.

Magnitude of the treatment effect and its clinical significance

Primary efficacy results

- Total study population: The primary analysis showed a 60.3% reduction in the mean annualised new HO volume of palovarotene-treated (9427.1 mm^3) vs. untreated (23720.2 mm^3) patients. The primary analysis using weighted linear mixed-effects models (wLME) showed a 53.8% reduction in the LSM annualised new HO volume of palovarotene-treated (9366.8 mm^3) vs. untreated (20273.0 mm^3) patients (wLME treatment p=0.0392; Wilcoxon rank-sum p=0.0003) (Principal FAS). The primary analysis using the PPS and ITT showed similar results, noting that the ITT Set included treatment breaks.
- Target population of patients aged ≥8y/10y (female/male) (i.e., the subgroup for which the FOP indication is sought by the sponsor): The primary analysis showed a 55.7% reduction in the mean annualised new HO volume of palovarotene-treated (11418.8 mm^3) vs. untreated (25796.0 mm^3) patients. The primary analysis using wLME, showed a 48.6% reduction in the LSM annualised new HO volume of palovarotene-treated (11033.2 mm^3) vs. untreated (21476.0 mm^3) patients (wLME treatment p=0.1124; Wilcoxon rank-sum p=0.0107) (Principal FAS).

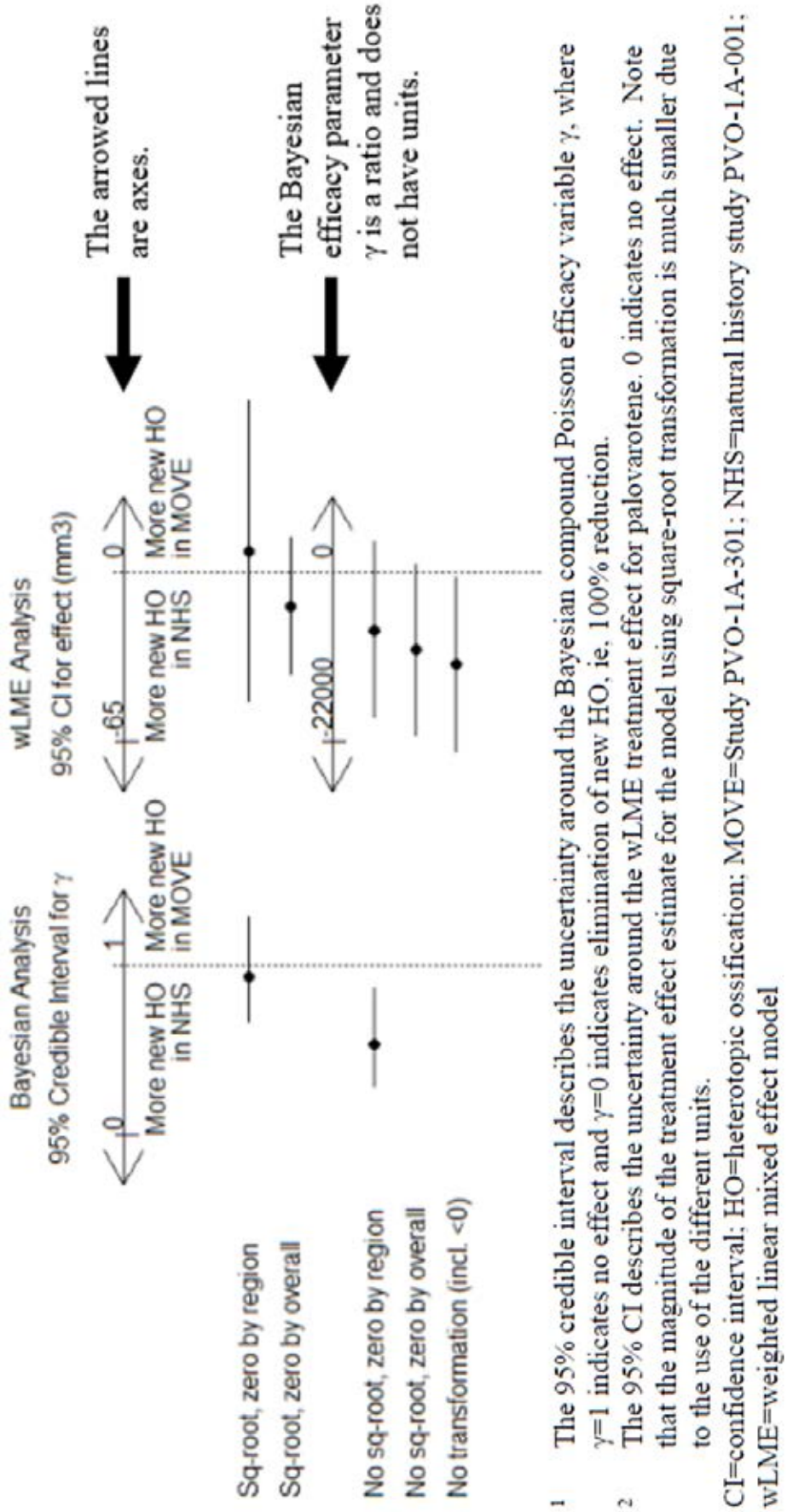
- Other analyses using square root transformation or negative HO volumes set to zero are shown in Table 12.
- A graphical representation of the primary results is shown in Figure 2.

Table 12. Study 301. Summary of main results (primary and other analyses).

Analysis	Method		Mean annualised new HO volume (mm^3)			LSM annualised new HO volume (wLME) (mm^3)			Tests of significance	
	Square root transformation	Negative HO volumes set to zero	Palovarotene (n=97 in Principal FAS; n=86 in PPS)	Untreated (n=101)	Reduction (%)	Palovarotene (n=97 in Principal FAS; n=86 in PPS)	Untreated (n=101)	Reduction (%)	wLME treatment effect p-value	Wilcoxon rank-sum p-value
Primary analysis Principal FAS	N	N	9427.1	23720.2	60.3%	9366.8	20273.0	53.8%	0.0392	0.0003
Primary analysis Principal PPS	N	N	9774.1	23720.2	58.8%	9080.1	20228.7	55.1%	0.0485	0.0005
Primary analysis ITT	N	N	13316.2	23656.4	43.7%	11230.9	20942.7	46.4%	0.0585	N/A
Other analyses Principal FAS	N	By region	14895.8	25468.1	41.5%	15169.7	21937.6	30.9%	0.1996	0.1587
	N	Overall	11539.2	24156.1	52.2%	11545.8	20661.2	44.1%	0.0762	0.0031
	Y	By region	140.2	149.8	6.4%	137.0	129.5	–5.9%	0.7727	0.5165
	Y	Overall	56.2	80.4	30.1%	54.7	66.3	17.5%	0.3313	0.0286

Reductions are shown as positive values. Negative reduction values indicate an increase. HO = heterotopic ossification; LSM = least squares mean; wLME = weighted linear mixed effects; FAS = Full Analysis Set; PPS = Per-protocol Set

Figure 2. Study 301. Graphical representation of primary endpoint results (primary and other analyses) (Principal FAS).



1 The 95% credible interval describes the uncertainty around the Bayesian compound Poisson efficacy variable γ, where γ=1 indicates no effect and γ=0 indicates elimination of new HO, ie. 100% reduction.

2 The 95% CI describes the uncertainty around the wLME treatment effect for palovarotene. 0 indicates no effect. Note that the magnitude of the treatment effect estimate for the model using square-root transformation is much smaller due to the use of the different units.

CI=confidence interval; HO=heterotopic ossification; MOVE=Study PVO-1A-301; NHS=natural history study PVO-1A-001; wLME=weighted linear mixed effect model

Late in the application period (post-Round 2), the sponsor provided additional data on the post-pause treatment period and the off-treatment period:

- Post-pause treatment (i.e., post-restart) period: subjects who restarted palovarotene treatment after a pause, if two 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 subjects that were on active treatment. A comparison with the Principal FAS is shown in Table 13.
- 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 therefore solely represents time off treatment.

Table 13. Study 301. Comparison of the main endpoint results to the post-pause treatment period.

Subgroup	Number of subjects (n)		Mean annualised new HO volume (mm^3)			LSM annualised new HO volume (wLME) (mm^3)			Tests of significance	
	Palovarotene	Untreated	Palovarotene	Untreated	Reduction (%)	Palovarotene	Untreated	Reduction (%)	wLME treatment effect p-value	Wilcoxon rank-sum p-value
Principal FAS	97	101	9427.1	23720.2	60.3%	9366.8	20273.0	53.8%	0.0392	0.0003
Post-pause treatment period	17	101	7728.1	23656.4	67.3%	5980.3	19627.1	69.5%	0.4069	N/A

Reductions are shown as positive values.

HO = heterotopic ossification; LSM = least squares mean; wLME = weighted linear mixed effects

Table 14. Study 301. Annualised New HO Volume (mm^3) results for the post-off-treatment period.

Parameter	Study PVO-1A-301 (MOVE)
Pre-Pause Treatment	
n	16
Mean (SE)	2346.5 (2463.19)
Post Off-Treatment	
n	16
Mean (SE)	15573.8 (9419.56)

Primary efficacy endpoint subgroup analyses (original application)

Selected subgroup/sensitivity analyses are shown in Table 15 below. Notable examples include:

- Female patients: The primary analysis showed a 25.8% reduction in the mean annualised new HO volume of palovarotene-treated (10617.5 mm^3) vs. untreated (14317.1 mm^3) patients. The primary analysis using wLME, showed a 11.3% increase in the LSM annualised new HO volume of palovarotene-treated (10105.9 mm^3) vs. untreated (9078.0 mm^3) patients (wLME treatment p=0.8740; Wilcoxon rank-sum p=0.0211) (Principal FAS) (Table 15).

- Asian patients: The primary analysis showed a 259.5% increase in the mean annualised new HO volume of palovarotene-treated (5885.1 mm^3) vs. untreated (1636.8 mm^3) patients. The primary analysis using wLME, showed a 280.3% increase in the LSM annualised new HO volume of palovarotene-treated (8960.0 mm^3) vs. untreated (2355.8 mm^3) patients (wLME treatment p=0.6309; Wilcoxon rank-sum p=0.8125) (Principal FAS) (Table 15).
- Flare-up status: In patients without a flare-up, there was a 48.2% reduction in new HO volume (wLME: 44.6%), vs. 69.4% in those with a flare-up (wLME: 71.9%) (Table 15).

Many of the subgroup analyses are underpowered or do not reach statistical significance otherwise and need to be interpreted with caution.

However, it appears that, in Study 301, the treatment effect of palovarotene was mainly driven by the results in males, the age cohort below 18 years, and those with flare-ups. These may be the groups that appear to benefit most from palovarotene treatment based on a HO volume efficacy variable.

Table 15. Study 301. Summary of primary endpoint analyses by subgroup (Principal FAS).

Subgroup	Number of subjects (n)		Mean annualised new HO volume (mm^3)			LSM annualised new HO volume (wLME) (mm^3)			Tests of significance	
	Palovarotene	Untreated	Palovarotene	Untreated	Reduction (%)	Palovarotene	Untreated	Reduction (%)	wLME treatment effect p-value	Wilcoxon rank-sum p-value
All (primary analysis) Principal FAS	97	101	9427.1	23720.2	60.3%	9366.8	20273.0	53.8%	0.0392	0.0003
Female	46	45	10617.5	14317.1	25.8%	10105.9	9078.0	–11.3%	0.8740	0.0211
Male	51	56	8353.4	31276.2	73.3%	10259.1	28726.1	64.3%	0.0108	0.0044
Asian	9	8	5885.1	1636.8	–259.5%	8960.0	2355.8	–280.3%	0.6309	0.8125
Non-Asian	88	93	9789.3	25619.8	61.8%	9232.9	22257.8	58.5%	0.0223	0.0003
Age <8y/10y*	20	22	1759.1	16266.1	89.2%	845.4	15876.1	94.7%	0.0597	0.0034
Age ≥8y/10y*	77	79	11418.8	25796.0	55.7%	11033.2	21476.0	48.6%	0.1124	0.0107
Age <13y/15y*	54	45	8659.0	21588.5	59.9%	8269.4	21590.0	61.7%	0.0231	0.0005
Age ≥13y/15y*	43	56	10391.7	25433.1	59.1%	10925.1	18807.6	41.9%	0.4009	0.0707
Age ≥12y to <17y	28	26	12910.6	50342.5	74.4%	15360.6	35889.0	57.2%	0.2301	0.0721
Age ≥18y	22	40	8649.5	10653.5	18.8%	9315.5	9442.3	1.3%	0.9729	0.2434
NHS participants	39	39	6982.3	15245.5	54.2%	8062.9	16651.8	51.6%	0.0634	0.0077
Follow-up to Month 12	97	92	8776.6	23359.8	62.4%	8187.1	22454.3	63.5%	0.0522	0.0075
Follow-up to Month 24	97	99	9427.1	22997.7	59.0%	9003.5	19288.9	53.3%	0.0620	0.0016
No flare-up by Month 12	33	44	3183.3	6150.0	48.2%	3601.8	6502.7	44.6%	0.2508	0.3491
Flare-up by Month 12	64	46	11660.6	38101.4	69.4%	10485.9	37379.9	71.9%	0.0373	0.0076

Reductions are shown as positive values. Negative reduction values indicate an increase.

HO = heterotopic ossification; LSM = least squares mean; wLME = weighted linear mixed effects

* Female age/male age

Secondary endpoints

- Key secondary endpoint: The proportion of subjects with any new HO (volume >0 mm^3) at Month 12 was similar in palovarotene-treated patients (64.1%) vs. untreated (62.2%). At 18 months, the gap widened to 70.3% vs. 90.9%.
- Other secondary endpoints: The mean number of body regions with new HO at Month 12 was similar between treated and untreated patients. A higher proportion in the palovarotene group reported flare-ups (defined as having at least two symptoms) at month 12: 65% vs. 54%. Overall, the flare-up rates per subject-month of exposure were 0.13 in palovarotene-treated patients vs. 0.07 in untreated patients. Details are shown in Table 16.

Table 16. Study 301. Summary of secondary endpoint results (Principal FAS).

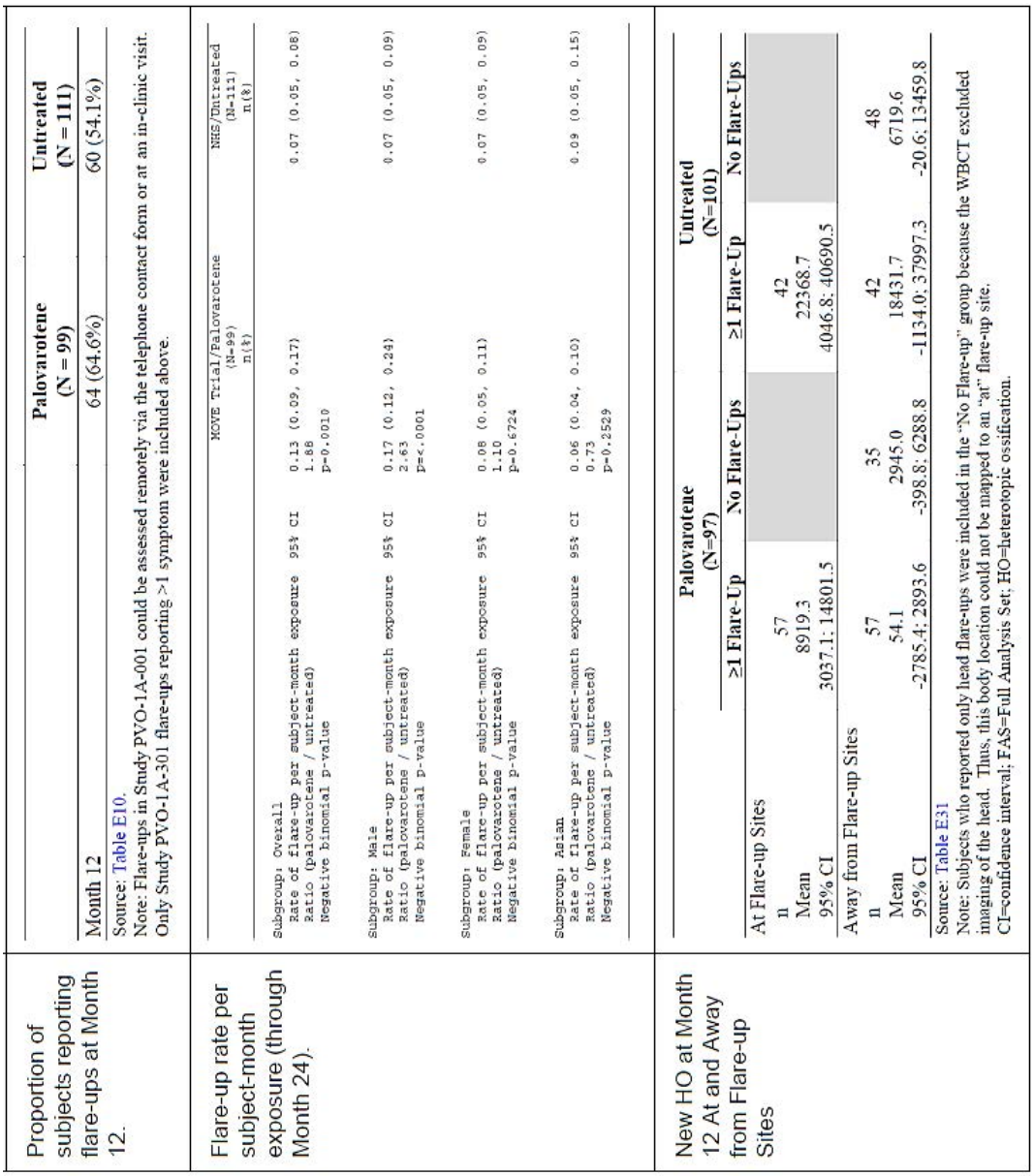
Proportion of subjects with any new HO at Month 12 (key secondary endpoint).

		Statistic	MOVE Trial/ Palovarotene (N=97)	NHS/ Untreated (N=101)
Number of Subjects with any new HO since Baseline	Month 6	n/N (%)	40/94 (42.6%)	2/2 (100.0%)
	Month 12	n/N (%)	59/92 (64.1%)	56/90 (62.2%)
	Month 18	n/N (%)	45/64 (70.3%)	10/11 (90.9%)
	Month 24	n/N (%)	1/1 (100.0%)	42/63 (66.7%)
	Month 30	n/N (%)		7/9 (77.8%)
	Month 36	n/N (%)		27/32 (84.4%)
	Month 42	n/N (%)		4/4 (100.0%)
	Last Timepoint	n/N (%)	68/97 (70.1%)	76/101 (75.2%)
Number of Subjects with any new HO since previous visit	Month 6	n/N (%)	40/94 (42.6%)	2/2 (100.0%)
	Month 12	n/N (%)	56/92 (60.9%)	56/90 (62.2%)
	Month 18	n/N (%)	36/64 (56.3%)	7/11 (63.6%)
	Month 24	n/N (%)	1/1 (100.0%)	36/63 (57.1%)
	Month 30	n/N (%)		4/9 (44.4%)
	Month 36	n/N (%)		24/32 (75.0%)
	Month 42	n/N (%)		4/4 (100.0%)
	Last Timepoint	n/N (%)	59/97 (60.8%)	64/101 (63.4%)

Number of body regions with new HO at Month 12.

	Palovarotene (N = 97)	Untreated (N = 101)
Number (%) of subjects at risk at Month 12	92	90
0 body region with new HO	33 (35.9%)	34 (37.8%)
1 body region with new HO	28 (30.4%)	19 (21.1%)
2 body regions with new HO	16 (17.4%)	20 (22.2%)
3 body regions with new HO	9 (9.8%)	5 (5.6%)
4 body regions with new HO	1 (1.1%)	6 (6.7%)
5 body regions with new HO	5 (5.4%)	3 (3.3%)
6 body regions with new HO		3 (3.3%)
Negative binomial p-value	p=0.3871	

Source: Table E38.1.
P-value is derived from the negative binomial model with dependent variable the number of body regions with new HO and independent variable treatment group.
FAS=full analysis set; HO=heterotopic ossification.



	Palovarotene (N = 99)	Untreated (N = 111)
Month 12	64 (64.6%)	60 (54.1%)

Source: Table E10.
Note: Flare-ups in Study PVO-1A-001 could be assessed remotely via the telephone contact form or at an in-clinic visit. Only Study PVO-1A-301 flare-ups reporting >1 symptom were included above.

	MOVE Trial/Palovarotene (N=99) n(%)		NHS/Untreated (N=111) n(%)
Subgroup: Overall			
Rate of flare-up per subject-month exposure	0.13 (0.09, 0.17)		0.07 (0.05, 0.08)
Ratio (palovarotene / untreated)	1.86		
Negative binomial p-value	p=0.0010		
Subgroup: Male			
Rate of flare-up per subject-month exposure	0.17 (0.12, 0.24)		0.07 (0.05, 0.09)
Ratio (palovarotene / untreated)	2.63		
Negative binomial p-value	p=<.0001		
Subgroup: Female			
Rate of flare-up per subject-month exposure	0.08 (0.05, 0.11)		0.07 (0.05, 0.09)
Ratio (palovarotene / untreated)	1.10		
Negative binomial p-value	p=0.6724		
Subgroup: Asian			
Rate of flare-up per subject-month exposure	0.06 (0.04, 0.10)		0.09 (0.05, 0.15)
Ratio (palovarotene / untreated)	0.73		
Negative binomial p-value	p=0.2529		

	Palovarotene (N=97)		Untreated (N=101)	
	≥1 Flare-Up	No Flare-Ups	≥1 Flare-Up	No Flare-Ups
At Flare-up Sites				
n	57		42	
Mean	8919.3		22368.7	
95% CI	3037.1: 14801.5		4046.8: 40690.5	
Away from Flare-up Sites				
n	57	35	42	48
Mean	54.1	2945.0	18431.7	6719.6
95% CI	-2785.4: 2893.6	-398.8: 6288.8	-1134.0: 37997.3	-20.6: 13459.8

Source: Table E31
Note: Subjects who reported only head flare-ups were included in the "No Flare-up" group because the WBCT excluded imaging of the head. Thus, this body location could not be mapped to an "at" flare-up site.
CI=confidence interval; FAS=Full Analysis Set; HO=heterotopic ossification.

Exploratory results: Exploratory endpoint results are shown in Table 17.

- The proportion of patients with catastrophic new HO was lower in the palovarotene group vs. the control group for all categories of catastrophic new HO (>100,000, >50,000, and >30,000 mm^3) at Month 12 and at the last timepoint assessed.

CAJIS, FOP-PFQ and PROMIS score differences were minimal.

Table 17. Study 301. Exploratory endpoint results (Principal Safety Set).

Endpoint	Summary of results					
			MOVE Trial/Palovarotene (N=99)		NHS/Untreated (N=111)	
	Analysis Visit	Statistics	Value	Change	Value	Change
CAJIS score change from baseline to Month 24 CAJIS = Cumulative analogue joint involvement scale	Baseline	N	99		111	
		Mean (SD)	10.0 (6.1)		11.8 (7.0)	
		Std. Error	0.6		0.7	
		Median	9.0		10.0	
		Q1 ; Q3	6.0 ; 14.0		6.0 ; 17.0	
		Min ; Max	0 ; 26		1 ; 30	
	Month 6	N	88	88		
		Mean (SD)	10.1 (6.0)	0.2 (1.5)		
		Std. Error	0.6	0.2		
		Median	9.0	0.0		
		Q1 ; Q3	6.0 ; 13.0	0.0 ; 1.0		
		Min ; Max	0 ; 25	-3 ; 9		
	Month 12	N	86	86	99	99
		Mean (SD)	10.5 (6.3)	0.5 (2.0)	12.4 (7.3)	0.6 (2.4)
		Std. Error	0.7	0.2	0.7	0.2
		Median	9.0	0.0	11.0	1.0
		Q1 ; Q3	6.0 ; 14.0	-1.0 ; 1.0	6.0 ; 17.0	-1.0 ; 2.0
		Min ; Max	0 ; 26	-3 ; 7	1 ; 30	-7 ; 10
	Month 18	N	63	63		
		Mean (SD)	10.3 (6.3)	0.7 (2.1)		
		Std. Error	0.8	0.3		
		Median	8.0	0.0		
		Q1 ; Q3	5.0 ; 14.0	-1.0 ; 2.0		
		Min ; Max	0 ; 26	-4 ; 8		
	Month 24	N	0	0	70	70
		Mean (SD)			12.3 (7.1)	0.8 (2.5)
		Std. Error			0.9	0.3
		Median			10.5	1.0
		Q1 ; Q3			7.0 ; 17.0	-1.0 ; 2.0
		Min ; Max			1 ; 29	-5 ; 9
	Early EOT	N	9	9		
		Mean (SD)	9.8 (5.0)	0.0 (0.0)		
		Std. Error	1.7	0.0		
		Median	10.0	0.0		
		Q1 ; Q3	6.0 ; 10.0	0.0 ; 0.0		
		Min ; Max	4 ; 21	0 ; 0		
	End of Study	N	14	14		
		Mean (SD)	12.3 (6.8)	2.3 (3.9)		
		Std. Error	1.8	1.0		
		Median	11.0	0.0		
		Q1 ; Q3	8.0 ; 15.0	-1.0 ; 4.0		
		Min ; Max	4 ; 26	-1 ; 8		

FOP-PFQ score change from baseline to Month 24

PFQ = Physical Function Questionnaire

		MOVE Trial/Palovarotene (N=99)		NHS/Untreated (N=111)	
Visit	Statistics	Value	Change	Value	Change
Baseline	N	98		100	
	Mean (SD)	44.28 (26.86)		46.97 (28.06)	
	Std. Error	2.71		2.81	
	Median	42.79		45.84	
	Q1 ; Q3	22.12 ; 61.61		26.44 ; 63.46	
	Min ; Max	0.0 ; 98.2		0.0 ; 100.0	
Month 6	N	82	82	76	76
	Mean (SD)	46.29 (28.38)	2.53 (9.62)	47.71 (28.89)	3.18 (9.34)
	Std. Error	3.13	1.06	3.31	1.07
	Median	45.09	0.96	49.55	1.79
	Q1 ; Q3	21.43 ; 69.23	-1.92 ; 6.73	22.60 ; 65.76	-0.96 ; 6.94
	Min ; Max	1.0 ; 97.3	-17.3 ; 52.9	0.0 ; 100.0	-18.8 ; 47.3
Month 12	N	71	71	82	82
	Mean (SD)	48.76 (28.43)	2.76 (7.77)	51.45 (29.40)	4.50 (8.88)
	Std. Error	3.37	0.92	3.25	0.98
	Median	47.12	1.92	53.37	3.71
	Q1 ; Q3	25.89 ; 69.64	-1.79 ; 6.73	28.85 ; 74.11	0.00 ; 10.58
	Min ; Max	0.0 ; 98.2	-17.3 ; 27.9	0.0 ; 100.0	-23.1 ; 27.7
Month 18	N	51	51	56	56
	Mean (SD)	48.12 (29.15)	4.12 (12.98)	50.33 (30.67)	4.11 (10.08)
	Std. Error	4.08	1.82	4.10	1.35
	Median	48.08	1.79	52.88	1.34
	Q1 ; Q3	25.89 ; 73.21	-1.92 ; 8.04	27.82 ; 75.41	-1.79 ; 9.75
	Min ; Max	0.0 ; 98.2	-47.3 ; 37.5	0.0 ; 100.0	-13.5 ; 29.8

PROMIS score change from baseline to Month 24 (physical function in subjects ≥15 years old)

		MOVE Trial/Palovarotene (N=37)		NHS/Untreated (N=58)	
Analysis Visit	Statistics	Value	Change	Value	Change
Baseline	N	36		57	
	Mean (SD)	43.15 (7.93)		43.35 (8.66)	
	Std. Error	1.32		1.15	
	Median	41.05		42.30	
	Q1 ; Q3	37.40 ; 47.70		37.40 ; 50.80	
	Min ; Max	23.5 ; 61.9		23.5 ; 67.7	
Month 6	N	33	33	43	43
	Mean (SD)	43.87 (8.63)	-0.15 (3.92)	44.12 (8.80)	-0.37 (6.79)
	Std. Error	1.50	0.68	1.34	1.04
	Median	42.30	0.00	44.90	0.00
	Q1 ; Q3	39.80 ; 50.80	-2.60 ; 2.50	37.40 ; 47.70	-4.90 ; 3.60
	Min ; Max	29.6 ; 61.9	-12.8 ; 6.4	23.5 ; 67.7	-15.9 ; 16.9
Month 12	N	33	33	49	49
	Mean (SD)	44.22 (8.44)	0.20 (5.16)	42.45 (9.58)	-1.19 (6.62)
	Std. Error	1.47	0.90	1.37	0.95
	Median	42.30	0.00	42.30	-2.40
	Q1 ; Q3	37.40 ; 47.70	-2.50 ; 2.60	34.90 ; 47.70	-6.40 ; 3.30
	Min ; Max	34.9 ; 67.7	-10.0 ; 13.6	23.5 ; 67.7	-15.9 ; 13.9
Month 16	N	27	27	35	35
	Mean (SD)	42.80 (8.61)	-1.91 (6.28)	43.54 (9.74)	-0.66 (5.57)
	Std. Error	1.66	1.21	1.65	0.94
	Median	42.30	0.00	44.90	0.00
	Q1 ; Q3	37.40 ; 50.80	-6.40 ; 3.10	34.90 ; 50.80	-3.30 ; 3.10
	Min ; Max	19.9 ; 57.7	-15.0 ; 5.9	26.7 ; 61.9	-18.4 ; 10.3
Month 24	N	0	0	38	38
	Mean (SD)			43.32 (8.93)	-1.13 (6.09)
	Std. Error			1.45	0.99
	Median			44.90	0.00
	Q1 ; Q3			34.90 ; 50.80	-5.80 ; 4.90
	Min ; Max			26.7 ; 61.9	-13.4 ; 10.3
Early EOT	N	1	1		
	Mean (SD)	39.80 (NA)	4.90 (NA)		
	Std. Error	NA	NA		
	Median	39.80	4.90		
	Q1 ; Q3	39.80 ; 39.80	4.90 ; 4.90		
	Min ; Max	39.8 ; 39.8	4.9 ; 4.9		
End of Study	N	4	4		
	Mean (SD)	43.68 (3.40)	3.13 (5.35)		
	Std. Error	1.70	2.68		
	Median	43.60	3.70		
	Q1 ; Q3	41.05 ; 46.30	-1.40 ; 7.65		
	Min ; Max	39.8 ; 47.7	-2.8 ; 7.9		

Month 24	N	0	0	61	61
	Mean (SD)			50.58 (29.83)	4.46 (9.10)
	Std. Error			3.82	1.16
	Median			51.79	3.57
	Q1 ; Q3			27.78 ; 74.07	0.00 ; 8.93
	Min ; Max			0.0 ; 100.0	-17.9 ; 25.0
Early EOT	N	9	9		
	Mean (SD)	53.07 (13.82)	0.52 (12.18)		
	Std. Error	4.61	4.06		
	Median	55.77	0.00		
	Q1 ; Q3	48.08 ; 61.54	-4.81 ; 1.92		
	Min ; Max	30.2 ; 70.5	-14.6 ; 25.0		
End of Study	N	12	12		
	Mean (SD)	61.84 (22.56)	11.81 (18.75)		
	Std. Error	6.51	5.41		
	Median	59.62	7.21		
	Q1 ; Q3	48.56 ; 78.61	1.34 ; 13.39		
	Min ; Max	24.1 ; 99.1	-1.0 ; 68.3		

PROMIS score change from baseline to Month 24 (mental function in subjects ≥15 years old)

		MOVE Trial/Palovarotene (N=37)		NHS/Untreated (N=58)	
Analysis Visit	Statistics	Value	Change	Value	Change
Baseline	N	36		57	
	Mean (SD)	52.17 (7.94)		52.70 (9.40)	
	Std. Error	1.32		1.24	
	Median	53.30		53.30	
	Q1 ; Q3	47.05 ; 57.50		45.80 ; 59.00	
	Min ; Max	33.8 ; 67.6		28.4 ; 67.6	
Month 6	N	33	33	45	45
	Mean (SD)	50.71 (8.06)	-2.10 (4.10)	51.75 (8.53)	-1.57 (5.61)
	Std. Error	1.40	0.71	1.27	0.84
	Median	50.80	-2.30	50.80	-2.40
	Q1 ; Q3	45.80 ; 53.30	-5.00 ; 0.00	45.80 ; 59.00	-5.10 ; 0.00
	Min ; Max	33.8 ; 67.6	-12.0 ; 4.7	36.3 ; 67.6	-12.5 ; 17.4
Month 12	N	33	33	49	49
	Mean (SD)	52.02 (8.63)	-0.79 (5.57)	50.86 (9.61)	-1.95 (6.99)
	Std. Error	1.50	0.97	1.37	1.00
	Median	50.80	0.00	50.80	-2.40
	Q1 ; Q3	45.80 ; 56.00	-4.80 ; 2.70	41.10 ; 59.00	-6.50 ; 3.00
	Min ; Max	38.8 ; 67.6	-12.2 ; 11.6	28.4 ; 67.6	-19.9 ; 14.3
Month 18	N	27	27	35	35
	Mean (SD)	50.45 (7.88)	-2.89 (7.19)	50.77 (9.99)	-2.72 (7.20)
	Std. Error	1.52	1.38	1.69	1.22
	Median	50.80	-2.50	50.80	-2.50
	Q1 ; Q3	45.80 ; 56.00	-3.00 ; 0.00	41.10 ; 59.00	-7.20 ; 0.00
	Min ; Max	36.3 ; 67.6	-23.7 ; 7.7	25.1 ; 67.6	-20.7 ; 14.5
Month 24	N	0	0	38	38
	Mean (SD)			52.60 (10.03)	-1.22 (6.91)
	Std. Error			1.63	1.12
	Median			50.80	-2.45
	Q1 ; Q3			45.80 ; 62.50	-5.10 ; 2.50
	Min ; Max			33.8 ; 67.6	-21.8 ; 14.3
Early EOT	N	1	1		
	Mean (SD)	56.00 (NA)	2.70 (NA)		
	Std. Error	NA	NA		
	Median	56.00	2.70		
	Q1 ; Q3	56.00 ; 56.00	2.70 ; 2.70		
	Min ; Max	56.0 ; 56.0	2.7 ; 2.7		
End of Study	N	4	4		
	Mean (SD)	55.63 (8.32)	-2.28 (8.31)		
	Std. Error	4.16	4.15		
	Median	53.30	0.00		
	Q1 ; Q3	50.80 ; 60.45	-7.10 ; 2.55		
	Min ; Max	48.3 ; 67.6	-14.2 ; 5.1		

PROMIS score change from baseline to Month 24 (physical function in subjects <15 years old)

		MOVE Trial/Palovarotene (N=99)		NHS/Untreated (N=111)	
Visit	Statistics	Value	Change	Value	Change
Baseline	N	36		57	
	Mean (SD)	43.15 (7.93)		43.35 (8.66)	
	Std. Error	1.32		1.15	
	Median	41.05		42.30	
	Q1 ; Q3	37.40 ; 47.70		37.40 ; 50.80	
	Min ; Max	23.5 ; 61.9		23.5 ; 67.7	
Month 6	N	33	33	43	43
	Mean (SD)	43.87 (8.63)	-0.15 (3.92)	44.12 (8.80)	-0.37 (6.79)
	Std. Error	1.50	0.68	1.34	1.04
	Median	42.30	0.00	44.90	0.00
	Q1 ; Q3	39.80 ; 50.80	-2.60 ; 2.50	37.40 ; 47.70	-4.90 ; 3.60
	Min ; Max	29.6 ; 61.9	-12.8 ; 6.4	23.5 ; 67.7	-15.9 ; 16.9
Month 12	N	33	33	49	49
	Mean (SD)	44.22 (8.44)	0.20 (5.16)	42.45 (9.58)	-1.19 (6.62)
	Std. Error	1.47	0.90	1.37	0.95
	Median	42.30	0.00	42.30	-2.40
	Q1 ; Q3	37.40 ; 47.70	-2.50 ; 2.60	34.90 ; 47.70	-6.40 ; 3.30
	Min ; Max	34.9 ; 67.7	-10.0 ; 13.6	23.5 ; 67.7	-15.9 ; 13.9
Month 18	N	27	27	35	35
	Mean (SD)	42.80 (8.61)	-1.91 (6.28)	43.54 (9.74)	-0.66 (5.57)
	Std. Error	1.66	1.21	1.65	0.94
	Median	42.30	0.00	44.90	0.00
	Q1 ; Q3	37.40 ; 50.80	-6.40 ; 3.10	34.90 ; 50.80	-3.30 ; 3.10
	Min ; Max	19.9 ; 57.7	-15.0 ; 5.9	26.7 ; 61.9	-18.4 ; 10.3

	Month 24	N	0	0	38	38
		Mean (SD)			43.32 (8.93)	-1.13 (6.09)
		Std. Error			1.45	0.99
		Median			44.90	0.00
		Q1 ; Q3			34.90 ; 50.80	-5.80 ; 4.90
		Min ; Max			26.7 ; 61.9	-13.4 ; 10.3
	Early EOT	N	1	1		
		Mean (SD)	39.80 (NA)	4.90 (NA)		
		Std. Error	NA	NA		
		Median	39.80	4.90		
		Q1 ; Q3	39.80 ; 39.80	4.90 ; 4.90		
		Min ; Max	39.8 ; 39.8	4.9 ; 4.9		
	End of Study	N	4	4		
		Mean (SD)	43.68 (3.40)	3.13 (5.35)		
		Std. Error	1.70	2.68		
		Median	43.60	3.70		
		Q1 ; Q3	41.05 ; 46.30	-1.40 ; 7.65		
		Min ; Max	39.8 ; 47.7	-2.8 ; 7.9		

PROMIS score change from baseline to Month 24 (mental function in subjects <15 years old)

		MOVE Trial/Palovarotene (N=99)		NHS/Untreated (N=111)	
Visit	Statistics	Value	Change	Value	Change
Baseline	N	36		57	
	Mean (SD)	52.17 (7.94)		52.70 (9.40)	
	Std. Error	1.32		1.24	
	Median	53.30		53.30	
	Q1 ; Q3	47.05 ; 57.50		45.80 ; 59.00	
	Min ; Max	33.8 ; 67.6		28.4 ; 67.6	
Month 6	N	33	33	45	45
	Mean (SD)	50.71 (8.06)	-2.10 (4.10)	51.75 (8.53)	-1.57 (5.61)
	Std. Error	1.40	0.71	1.27	0.84
	Median	50.60	-2.30	50.80	-2.40
	Q1 ; Q3	45.80 ; 53.30	-5.00 ; 0.00	45.80 ; 59.00	-5.10 ; 0.00
	Min ; Max	33.8 ; 67.6	-12.0 ; 4.7	36.3 ; 67.6	-12.5 ; 17.4
Month 12	N	33	33	49	49
	Mean (SD)	52.02 (8.63)	-0.79 (5.57)	50.86 (9.61)	-1.95 (6.99)
	Std. Error	1.50	0.97	1.37	1.00
	Median	50.80	0.00	50.80	-2.40
	Q1 ; Q3	45.80 ; 56.00	-4.80 ; 2.70	41.10 ; 59.00	-6.50 ; 3.00
	Min ; Max	30.8 ; 67.6	-12.2 ; 11.6	28.4 ; 67.6	-19.9 ; 14.3
Month 18	N	27	27	35	35
	Mean (SD)	50.45 (7.88)	-2.69 (7.19)	50.77 (9.99)	-2.72 (7.20)
	Std. Error	1.52	1.38	1.69	1.22
	Median	50.80	-2.50	50.80	-2.50
	Q1 ; Q3	45.80 ; 56.00	-3.00 ; 0.00	41.10 ; 59.00	-7.20 ; 0.00
	Min ; Max	30.3 ; 67.6	-23.7 ; 7.7	25.1 ; 67.6	-20.7 ; 14.5
Month 24	N	0	0	38	38
	Mean (SD)			52.60 (10.03)	-1.22 (6.91)
	Std. Error			1.63	1.12
	Median			50.80	-2.45
	Q1 ; Q3			45.80 ; 62.50	-5.10 ; 2.50
	Min ; Max			33.8 ; 67.6	-21.8 ; 14.3
Early EOT	N	1	1		
	Mean (SD)	56.00 (NA)	2.70 (NA)		
	Std. Error	NA	NA		
	Median	56.00	2.70		
	Q1 ; Q3	56.00 ; 56.00	2.70 ; 2.70		
	Min ; Max	56.0 ; 56.0	2.7 ; 2.7		
End of Study	N	4	4		
	Mean (SD)	55.63 (8.32)	-2.28 (8.31)		
	Std. Error	4.16	4.15		
	Median	53.30	0.00		
	Q1 ; Q3	50.80 ; 60.45	-7.10 ; 2.55		
	Min ; Max	48.3 ; 67.6	-14.7 ; 5.1		

Incidence and volume of catastrophic HO per year

Catastrophic HO = new HO >50,000 mm^3 (>30,000 mm^3 at Months 12 and 24)

	Palovarotene		Untreated	
	n/N (%)	Mean (mm^3)	n/N (%)	Mean (mm^3)
Month 12				
Subjects with new HO >100,000 mm^3	1/97 (1.0)	155600.0	4/92 (4.3)	271235.0
Subjects with new HO >50,000 mm^3	8/97 (8.2)	81475.6	12/92 (13.0)	138381.3
Subjects with new HO >30,000 mm^3	10/97 (10.3)	73824.5	15/92 (16.3)	119305.0
Last timepoint				
Subjects with new HO >100,000 mm^3	1/97 (1.0)	236803.8	5/92 (5.4)	191419.9
Subjects with new HO >50,000 mm^3	6/97 (6.2)	95973.7	14/92 (15.2)	118882.7
Subjects with new HO >30,000 mm^3	14/97 (14.4)	62881.2	22/92 (23.9)	89992.8

Study 201 (PVO-1A-201) (supportive phase 2 study)

Design

Phase 2, multicentre, randomised, double-blind (investigator and subject), sponsor-unblinded, placebo-controlled 12-week study (with open-label extension) in 40 female or male patients aged ≥6 years with FOP and an active flare-up.

The study was conducted between 14 July 2014 and 23 May 2016. It had three periods: a screening period within 7 days of a distinct (acute) flare-up (2 symptoms needed), a 6-week double-blind treatment period, and 6-week follow-up period.

Cohort 1: Patients were randomised 3:1 to either PVO 10/5 mg (10 mg for 2 weeks, then 5 mg for 4 weeks), or placebo daily for 6 weeks, after which unblinding occurred and dosing for Cohort 2 was determined.

Cohort 2: Additional patients were randomised 3:3:2 to PVO 10/5 mg (10 mg for 2 weeks, then 5 mg for 4 weeks) and PVO 5/2.5 mg (5 mg for 2 weeks, then 2.5 mg for 4 weeks), or placebo daily for 6 weeks. Weight-adjusted equivalent doses were given.

The primary objective was to evaluate the ability of different doses of PVO to prevent HO at the flare-up site as assessed by plain radiographs in subjects with FOP.

Magnitude of the treatment effect and its clinical significance

The primary endpoint was the responder proportion (defined as patients with no/minimal new HO at the flare-up site at Week 6): 89% in the placebo group and the PVO 5/2.5 mg group, and 100% in the PVO 10/5 mg group.

At Week 12, the proportion of patients with any new HO was lower in the PVO 10/5 mg group (15%) compared to PVO 5/2.5 mg (44%) or placebo (40%).

The results were not statistically significant for either treatment group, but a favourable trend could be observed.

Study 202 (PVO-1A-202) (supportive phase 2 study)

Design

Phase 2, multicentre, open-label, uncontrolled study in 40 (Part A) or 56 (Parts B) or 48 (Part C) male or female patients with FOP aged ≥6 years to investigate different dosing regimens of palovarotene.

Cohorts: Adult Cohort: all subjects with ≥90% skeletal maturity (regardless of age); Paediatric Cohort: all subjects with <90% skeletal maturity.

Part A: enrolled all 40 patients aged ≥6 years from Study 201 and assessed the original flare-up treated in that study plus up to two, new, distinct flare-ups. The Flare-up Component consisted of three periods: a Screening period within 7 days of a new, distinct flare-up; a 6-week treatment period, and a 6-week follow-up period. Any new flare-ups during the 12-week flare-up assessment period were captured as AEs.

- Flare-up treatment: palovarotene 10 mg daily for 2 weeks followed by 5 mg daily for 4 weeks (or equivalent weight-adjusted doses) (PVO 10/5 mg).
- No chronic treatment.

Part B: enrolled patients who successfully completed Study 201 (including any subject who participated in Part A or in Study 203) and 18 additional Adult Cohort subjects were followed for up to 24 months.

- Flare-up treatment: palovarotene 20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks (or equivalent weight-adjusted doses) (PVO 20/10 mg), and could be extended in 4-week intervals.
- Chronic treatment:
  - Adult Cohort: 5 mg palovarotene daily for up to 24 months (including after resolved flare-ups).
  - Paediatric Cohort: no chronic treatment.

Part C: an additional 36 months for Part B patients (no new patients); only one symptom was needed to define a flare-up, and an intercurrent flare-up would restart the PVO 20/10 mg regimen. The dosing regimen was aligned with Study 301.

Magnitude of the treatment effect and its clinical significance

Analyses were limited to descriptive statistics, and due to the lack a control group, not relevant comparisons can be made.

Part A: There was an increase in mean volume in new HO for flare-ups with new HO, from 5,204 mm^3 (Week 6) to 7,506 mm^3 (Week 12) and likely reflects the end of treatment after 6 weeks.

Part B: Proportions of flare-ups with no new HO: PVO 10/5 mg: 35.7%; PVO 20/10 mg: 41.2%; Chronic/PVO 20/10 mg: 20.6%; Combined PVO 20/10 mg: 27.5% (Table 18).

Part B/C: The mean volume of new HO (for flare-ups with new HO) was 9,134 mm^3 (PVO 20/10 mg), 30,934 mm^3 (chronic/PVO 20/10 mg), and 21,025 mm^3 (combined PVO 20/10 mg) at Week 12 (Table 19).

Pooled phase 2 data: Additionally, the sponsor has combined the phase 2 data (Studies 201 and 202) to compare efficacy in relation to flare-ups in the target population (patients aged ≥8y/10y (female/male)) The placebo data were derived from the placebo group in Study 201 and untreated patients in Study 101 (Table 20).

Noting the small sample size and methodological limitations, the flare-up new volumes were lower in each treatment group compared to: 11,712 mm^3 (placebo/untreated); 1,524 mm^3 (PVO 5/2.5); 2,807 mm^3 (PVO 10/5) and 3,262 mm^3 (PVO 20/10).

Table 18. Study 202. Primary efficacy analysis: Incidence of New HO (Part A Efficacy Population, Part B Flare-up Population – Imaged Flare-ups).

CT scan[1]	Part A PVO 10/5 mg[2] m (%)	Part B PVO 20/10 mg[2,3] m (%)	Part B Chronic/ PVO 20/10 mg[2,3,4] m (%)	Part B Combined PVO 20/10 mg[2,3,4] m (%)
Screen/Base	M=28	M=18	M=33	M=51
No baseline HO	10 (35.7)	4 (22.2)	6 (18.2)	10 (19.6)
Baseline HO	18 (64.3)	14 (77.8)	27 (81.8)	41 (80.4)
Not evaluable[5]	0	0	1	1
Week 6[6]	M=28			
No new HO	21 (75.0)			
New HO	7 (25.0)			
Not evaluable[5]	0			
Week 12	M=28	M=17	M=34	M=51
No new HO	18 (64.3)	10 (58.8)	27 (79.4)	37 (72.5)
New HO	10 (35.7)	7 (41.2)	7 (20.6)	14 (27.5)
Not evaluable[5]	0	1	0	1
End of Treatment[7]		M=0	M=6	M=6
No new HO		0	2 (33.3)	2 (33.3)
New HO		0	4 (66.7)	4 (66.7)
Not evaluable[5]		0	0	0

Source: Tables 14.2.2.1 and 14B.2.2.1

1 Plain radiograph was performed for those unable to undergo CT scan.

2 M is the total number of flare-ups; m is the number of flare-ups per category with non-missing data.

3 Subjects may contribute more than one flare-up within a treatment group and across treatment groups, and therefore may be included in both the PVO 20/10 mg column and the chronic/ PVO 20/10 mg column depending on when chronic dosing began. The combined PVO 20/10 mg group includes any flare-up that was treated with PVO 20/10 mg, regardless of whether the subject received chronic treatment.

4 Subjects in the Adult Cohort were treated with 5 mg palovarotene daily during chronic treatment. These subjects are included in the chronic/ PVO 20/10 mg and combined/ PVO 20/10 mg.

5 Not evaluable defined as the image did not sufficiently include appropriate field of view, thus new HO may not have been determined.

6 Part A only.

7 Part B only, and presents imaging results obtained at the end of the treatment extension period relative to baseline. The End-of-Treatment visit includes only those subjects that had extended treatment beyond Week 12 (treatment may have been extended [in 4-week intervals] if the flare-up was ongoing and continued until the flare-up resolved).

CT = computed tomography, HO = heterotopic ossification, PVO = palovarotene

Table 19. Study 202. Volume of new HO for flare-ups with new HO (Part A Efficacy Population, Part B Flare-up Population).

Flare-ups with New HO	Part A PVO 10/5 mg[1] (M=28)	Part B PVO 20/10 mg[1,2] (M=18)	Part B Chronic/ PVO 20/10 mg[1,2,3] (M=34)	Part B Combined PVO 20/10 mg[1,2,3] (M=52)
Volume of new HO at Week 6 (mm^3)[4]	m=9			
Mean (SD)	5204 (5712)			
Median	1712			
Min, Max	0, 11979			
Volume of new HO at Week 12 (mm^3)	m=8	m=5	m=6	m=11
Mean (SD)	7506 (5970)	9134 (5878)	30934 (42343)	21025 (32247)
Median	6643	8921	7189	7917
Min, Max	1172, 15121	1179, 17351	-7.0, 92042	-7.0, 92042
Volume of new HO at end of treatment (mm^3)[5]		m=0	m=4	m=4
Mean (SD)			34823 (63089)	34823 (63089)
Median			4628	4628
Min, Max			729, 129306	729, 129306

Source: Module 5.3.5.1 Report PVO-1A-202 Table 14.2.4.1b, 14B.2.3.1.

1 M is the total number of flare-ups; m is the number of flare-ups with non-missing data.

2 Subjects may contribute more than one flare-up within a treatment group and across treatment groups, and therefore may be included in both the PVO 20/10 mg column and the chronic/ PVO 20/10 mg column depending on when chronic dosing began. Note that some flare-ups were not evaluable.

3 Subjects in the Adult Cohort were treated with 5 mg palovarotene daily during chronic treatment. These subjects are included in the chronic/ PVO 20/10 mg and combined/ PVO 20/10 mg.

4 Part A only.

Table 20. Pooled phase 2 data (Study 201 and 202). Flare-up new HO volume at Week 12 for the placebo/untreated and palovarotene-treated flare-ups (IF-FAS).

	PBO/ Untreated (M=46)	PVO 5/2.5 mg (M=7)	PVO 10/5 mg (M=46)	PVO 20/10 mg (M=17)	Chronic/ Flare-up 20/10 mg (M=34)	Combined 20/10 mg (M=51)
New HO Status, M	46	7	46	16	34	50
Yes, m (%)	14 (30.4)	2 (28.6)	13 (28.3)	7 (43.8)	7 (20.6)	14 (28.0)
New HO (including 0 mm^3)[1]						
m	43	7	44	14	33	47
Mean	11712	1524	2807	3262	5624	4921
(SD)	(34581)	(3599)	(8254)	(5591)	(20663)	(17522)
SE	5274	1360	1244	1494	3597	2556
Median	0	0	0	0	0	0
(min, max)	(0, 137009)	(0, 9638)	(0, 48422)	(0, 17351)	(-7, 92042)	(-7, 92042)

Note: This is a flare-up-based summary. Percentages are based on number of flare-ups M in corresponding column, where M is number of flare-ups with/without characteristics stated in the row.

1 When a flare-up has no baseline HO, 0 is assigned for analysis.

HO=heterotopic ossification; IF-FAS=Imaged Flare-up Full Analysis Set; NE=not evaluable; PBO=placebo; PVO=palovarotene; SD=standard deviation; SE=standard error.

Study 001 (PVO-1A-001) (observational Natural History Study (NHS))

Design

3-year natural history, non-interventional (observational), longitudinal, multicentre (7 sites in 6 countries), two-part study in 114 male or female subjects with FOP caused by the R206H mutation of the ACVR1 gene:

- Part A: subjects aged ≥18 years were enrolled and completed baseline imaging using low-dose WBCT scans (excluding head) and DEXA scans, to determine the optimal imaging modality for HO assessment. WBCT was chosen.
- Part B: additional subjects aged ≤65 years of age were enrolled; baseline WBCT imaging was performed; Subjects were followed for up to 36 months with annual clinic visits and by telephone every 6 months, except when annual clinic visits were scheduled to evaluate disease progression, impact on physical function, and clinical features that may be useful to diagnose the disease, monitor subjects' disease progression, and assess potential treatment effects in subsequent interventional studies.

Primary objectives: to characterise demographics and disease characteristics in untreated subjects, identify demographic and disease variables that correlate with progression and severity of the disease in the absence of treatment; identify potential endpoints that may be valuable in assessing clinically meaningful response(s) to treatments; and to assess the optimal imaging modality to define total body burden of HO.

Study results

This study did not provide efficacy results, but information on the natural progression of the disease, and an evaluation of imaging and other assessments (e.g., CAJIS, FOP-PFQ, PROMIS, FPS-R, and biomarkers). Summary of the results:

- Heterotopic ossification (HO) was identified a clinically meaningful endpoint with low-dose WBCT scans (excluding head) as the preferred imaging modality (over DEXA scans).
- HO volume increases correlated with worse CAJIS total scores (a 100,000 mm^3 HO volume increase corresponded to a 1.1-point CAJIS total score increase; $r=0.39$, $p<0.0001$).
- HO volume increases correlated with worse FOP-PFQ scores ($r=0.28$, $p<0.0001$).
- Patient age correlated with worsening CAJIS total scores ($r=0.44$, $p<0.0001$) and FOP-PFQ percent of worst total scores ($r=0.19$, $p<0.0001$). However, the functional scores may be too insensitive and too variable to detect changes over 1-2 years (i.e., a typical clinical trial time period).
- Flare-up characteristics are summarised in Table 21.

Table 21. Study 101. Flare-up characteristics (Imaged Flare-up Analysis Set).

Category	M=10	M=17	M=15	M=10	M=52
Location of flare-up[1], m (%)					
Upper back	4 (40.0)	5 (29.4)	0	0	9 (17.3)
Knee	1 (10.0)	2 (11.8)	3 (20.0)	2 (20.0)	8 (15.4)
Hip	0	2 (11.8)	3 (20.0)	1 (10.0)	6 (11.5)
Shoulder	0	0	3 (20.0)	3 (30.0)	6 (11.5)
Lower spine/abdomen	2 (20.0)	2 (11.8)	0	1 (10.0)	5 (9.6)
Head/neck	1 (10.0)	0	2 (13.3)	1 (10.0)	4 (7.7)
Distal upper extremities	1 (10.0)	0	1 (6.7)	1 (10.0)	3 (5.8)
Jaw	1 (10.0)	1 (5.9)	1 (6.7)	0	3 (5.8)
Cervical spine	0	2 (11.8)	0	0	2 (3.8)
Distal lower extremities	0	2 (11.8)	0	0	2 (3.8)
Elbow	0	0	1 (6.7)	1 (10.0)	2 (3.8)
Upper spine/chest	0	1 (5.9)	1 (6.7)	0	2 (3.8)
Symptoms[2], m (%)					
Pain	5 (50.0)	17 (100)	15 (100)	8 (80.0)	45 (86.5)
Soft tissue swelling	10 (100)	14 (82.4)	10 (66.7)	7 (70.0)	41 (78.8)
Decreased range of motion	4 (40.0)	6 (35.3)	6 (40.0)	5 (50.0)	21 (40.4)
Warmth	4 (40.0)	9 (52.9)	3 (20.0)	4 (40.0)	20 (38.5)
Stiffness	4 (40.0)	5 (29.4)	7 (46.7)	3 (30.0)	19 (36.5)
Redness	3 (30.0)	7 (41.2)	3 (20.0)	3 (30.0)	16 (30.8)
Lethargy	2 (20.0)	7 (41.2)	2 (13.3)	2 (20.0)	13 (25.0)
Changes in mood and behavior	2 (20.0)	2 (11.8)	2 (13.3)	3 (30.0)	9 (17.3)
Loss of appetite	2 (20.0)	4 (23.5)	0	1 (10.0)	7 (13.5)
Fever	2 (20.0)	1 (5.9)	0	1 (10.0)	4 (7.7)
Other	1 (10.0)	5 (29.4)	0	3 (30.0)	9 (17.3)
Number of flare-up symptoms[2], m	10	17	15	10	52
Mean (SD)	3.9 (2.1)	4.5 (1.8)	3.2 (1.5)	4.0 (2.1)	3.9 (1.9)
Median (min, max)	3.0 (1, 8)	5.0 (2, 7)	3.0 (1, 6)	4.0 (1, 8)	3.5 (1, 8)
1 symptom, m (%)	1 (10.0)	0	1 (6.7)	1 (10.0)	3 (5.8)
2 symptoms, m (%)	0	3 (17.6)	5 (33.3)	2 (20.0)	10 (19.2)
3 symptoms, m (%)	5 (50.0)	3 (17.6)	4 (26.7)	1 (10.0)	13 (25.0)
≥4 symptoms, m (%)	4 (40.0)	11 (64.7)	5 (33.3)	6 (60.0)	26 (50.0)

[1] As reported by the investigator
[2] As reported by the subject
m=number of flare-ups per category with non-missing data; M=total number of flare-ups; max=maximum; min=minimum; SD=standard deviation.

Participant data from Study 101 were used as historical control data in Study 301. 60 participants in Study 101 transferred to other studies: 8 to Study 201, 13 to Study 202, and 39 to Study 301.

Safety

The main safety population is the FOP Full Analysis Set (FOP-FAS), i.e., all subjects enrolled or dosed in FOP clinical studies, including the natural history study. Most relevant to this application is the age group of ≥8 years for females and ≥10 years for males (FOP-FAS ≥8/10y).

Exposure

FOP-FAS (≥8/10y) (Table 21):

- The mean duration of treatment overall (mean total doses) was: 94.1 weeks (4348.0 mg).
- The mean duration of chronic dosing treatment (mean total doses) was: 72.6 weeks (2370.6 mg).
- The mean duration of flare-up treatment (mean total doses during flare-up treatment) was:
  - 5.9 weeks for 5/2.5 mg (122.9 mg).
  - 11.0 weeks for 10/5 mg (482.3 mg).

– 33.2 weeks for the 20/10 mg (2832.8 mg).

Table 22 Overview of palovarotene exposure (FOP-FAS)

	Age at First Study Entry (y)	Parameter	Placebo	Untreated	PVO Treatment Period				PVO Total
					Chronic 5 mg	Flare-up 5/2.5 mg	Flare-up 10/5 mg	Flare-up 20/10 mg	
Duration of dosing, weeks[1]	≥8/10	N	10	–	130	7	25	100	139
		Mean (SD)	6.0 (0.1)	–	72.6 (39.9)	5.9 (0.16)	11.0 (5.14)	33.2 (23.9)	94.1 (46.1)
		Median	6.0	–	68.6	6.0	12.0	27.4	82.4
		Min, max	6, 6	–	1, 174	6, 6	5, 24	0, 134	4, 199
	≥18	N	4	–	56	5	18	43	62
		Mean (SD)	6.1 (0.1)	–	78.7 (42.4)	5.9 (0.2)	11.6 (5.7)	35.2 (28.3)	99.3 (55.5)
		Median	6.0	–	74.6	6.0	12.0	28.9	93.1
		Min, max	6, 6	–	1, 163	6, 6	5, 24	0, 134	4, 199
	≥8/10 to <18	N	6	–	74	2	7	57	77
		Mean (SD)	6.0 (0.1)	–	68.1 (37.3)	6.0 (0.0)	9.3 (3.3)	31.6 (20.2)	89.9 (36.7)
		Median	6.0	–	66.4	6.0	11.7	26.6	81.6
		Min, max	6, 6	–	3, 174	6, 6	6, 12	2, 82	5, 189
	<8/10	N	–	–	25	2	2	19	25
		Mean (SD)	–	–	33.9 (25.8)	6.0 (0.0)	9.0 (4.2)	38.8 (29.9)	64.6 (34.7)
		Median	–	–	27.9	6.0	9.0	33.7	69.9
		Min, max	–	–	1, 79	6, 6	6, 12	5, 109	8, 145

	Age at First Study Entry (y)	Parameter	Placebo	Untreated	PVO Treatment Period: Chronic 5 mg	PVO Treatment Period: Flare-up 5/2.5 mg	PVO Treatment Period: Flare-up 10/5 mg	PVO Treatment Period: Flare-up 20/10 mg	PVO Total
Total exposure, weeks in study[2]	≥8/10	N	10	91	130	7	25	100	139
		Mean (SD)	11.9 (0.2)	113.0 (53.7)	111.9 (42.7)	12.1 (0.2)	50.8 (30.3)	108.5 (40.3)	192.4 (101.5)
		Median	12.0	130.1	96.5	12.1	50.4	94.2	175.4
		Min, max	11, 12	0, 192	7, 194	12, 12	12, 103	34, 194	7, 457
	≥18	N	4	48	56	5	18	43	62
		Mean (SD)	12.0 (0.0)	108.3 (57.9)	120.0 (50.3)	12.1 (0.3)	46.9 (26.4)	115.9 (45.9)	203.3 (118.8)
		Median	12.0	103.9	104.5	12.1	44.6	98.7	184.6
		Min, max	12, 12	0, 192	7, 194	12, 12	12, 87	35, 194	7, 457
	≥8/10 to <18	N	6	43	74	2	7	57	77
		Mean (SD)	11.9 (0.3)	118.4 (48.7)	105.8 (34.9)	12.1 (0.1)	60.8 (39.3)	102.9 (34.9)	183.7 (84.9)
		Median	12.0	138.6	93.7	12.1	54.6	90.7	174.3
		Min, max	11, 12	8, 181	34, 191	12, 12	12, 103	34, 193	55, 428
	<8/10	N	–	23	25	2	2	19	25
		Mean (SD)	–	131.3 (37.8)	81.7 (21.9)	12.5 (0.3)	23.5 (16.1)	100.8 (50.2)	61.2 (81.6)
		Median	–	136.4	92.6	12.5	23.5	92.6	69.1
		Min, max	–	15, 190	32, 111	12, 13	12, 35	32, 194	51, 334

					PVO Treatment Period				
	Age at First Study Entry (y)	Parameter	Placebo	Untreated	Chronic 5 mg	Flare-up 5/2.5 mg	Flare-up 10/5 mg	Flare-up 20/10 mg	PVO Total
Distribution of months in study, n (%)	≥8/10	>0 to 3 months	10 (100)	7 (7.7)	7 (7.7)	7 (100)	6 (24.0)	0	5 (3.6)
		>3 to 6 months	0	4 (4.4)	4 (4.4)	0	2 (8.0)	0	1 (0.7)
		>6 to 9 months	0	2 (2.2)	2 (2.2)	0	2 (8.0)	2 (2.0)	0
		>9 to 12 months	0	1 (1.1)	1 (1.1)	0	3 (12.0)	1 (1.0)	1 (0.7)
		>12 to 18 months	0	6 (6.6)	6 (6.6)	0	7 (28.0)	9 (9.0)	7 (5.0)
		>18 to 24 months	0	18 (19.8)	18 (19.8)	0	5 (20.0)	55 (55.0)	19 (13.7)
		>24 to 30 months	0	8 (8.8)	8 (8.8)	0	0	12 (12.0)	2 (1.4)
		>30 months	0	45 (49.5)	45 (49.5)	0	0	21 (21.0)	104 (74.8)
	≥18	>0 to 12 months	4 (100)	8 (16.7)	8 (16.7)	5 (100)	10 (55.6)	2 (4.7)	7 (11.3)
		>12 to 18 months	0	3 (6.3)	3 (6.3)	0	6 (33.3)	5 (11.6)	2 (3.2)
		>18 to 24 months	0	13 (27.1)	13 (27.1)	0	2 (11.1)	17 (39.5)	6 (9.7)
		>24 to 30 months	0	3 (6.3)	3 (6.3)	0	0	7 (16.3)	0
		>30 months	0	21 (43.8)	21 (43.8)	0	0	12 (27.9)	47 (75.8)
	≥8/10 to <18	>0 to 12 months	6 (100)	6 (14.0)	6 (14.0)	2 (100)	3 (42.9)	1 (1.8)	0
		>12 to 18 months	0	3 (7.0)	3 (7.0)	0	1 (14.3)	4 (7.0)	5 (6.5)
		>18 to 24 months	0	5 (11.6)	5 (11.6)	0	3 (42.9)	38 (66.7)	13 (16.9)
		>24 to 30 months	0	5 (11.6)	5 (11.6)	0	0	5 (8.8)	2 (2.6)
		>30 months	0	24 (55.8)	24 (55.8)	0	0	9 (15.8)	57 (74.0)
	<8/10	>0 to 12 months	–	1 (4.3)	1 (4.3)	2 (100)	2 (100)	2 (10.5)	1 (4.0)
		>12 to 18 months	–	0	0	0	0	3 (15.8)	3 (12.0)
		>18 to 24 months	–	5 (21.7)	5 (21.7)	0	0	10 (52.6)	4 (16.0)
		>24 to 30 months	–	3 (13.0)	3 (13.0)	0	0	0	2 (8.0)
		>30 months	–	14 (60.9)	14 (60.9)	0	0	4 (21.1)	15 (60.0)

	Age at First Study Entry (y)	Parameter	Placebo	Untreated	PVO Treatment Period: Chronic 5 mg	PVO Treatment Period: Flare-up 5/2.5 mg	PVO Treatment Period: Flare-up 10/5 mg	PVO Treatment Period: Flare-up 20/10 mg	PVO Total
PVO total dose, mg	≥8/10	N	10	–	130	7	25	100	139
		Mean (SD)	0	–	2370.6 (1458.2)	122.9 (21.3)	482.3 (237.8)	2832.8 (2201.1)	4348.0 (2652.3)
		Median	0	–	2040.0	132.5	448.0	2182.5	4010.0
		Min, max	0	–	30, 6090	84, 140	168, 1120	40, 11530	133, 13645
	≥18	N	4	–	56	5	18	43	62
		Mean (SD)	0	–	2714.9 (1497.5)	132.9 (12.1)	523.0 (258.0)	3135.9 (2531.3)	4789.6 (3119.5)
		Median	0	–	2427.5	140.0	560.0	2677.5	4686.5
		Min, max	0	–	30, 5720	112, 140	224, 1120	40, 11530	133, 13645
	≥8/10 to <18	N	6	–	74	2	7	57	77
		Mean (SD)	0	–	2110.1 (1381.4)	98.0 (19.8)	377.7 (140.7)	2604.1 (1906.7)	3992.4 (2162.4)
		Median	0	–	1901.0	98.0	448.0	2035.0	3565.0
		Min, max	0	–	90, 6090	84, 112	168, 560	275, 9215	165, 10870
	<8/10	N	–	–	25	2	2	19	25
		Mean (SD)	–	–	662.0 (505.1)	84.0 (0.0)	252.0 (118.8)	2393.2 (1948.9)	2507.7 (1933.7)
		Median	–	–	490.0	84.0	252.0	1672.5	1638.0
		Min, max	–	–	27, 1638	84, 84	168, 336	320, 7226	133, 7675

[1] Duration of dosing (weeks) = (last dose date – first dose date + 1)/7 – days without dosing.
[2] Total exposure (weeks) = (last date on study – first dose date + 1)/7.
The age at first entry of 8/10 years indicates 8 years of age for female subjects and 10 years of age for male subjects.
Subjects may appear multiple times within and across dose group(s), as they may have participated in multiple studies/ periods. As such, the PVO Total column reflects the cumulative exposure across all columns.
FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; max=maximum; min=minimum; PVO=palovarotene; y=years.

Adverse event overview

FOP-FAS (≥8/10y): An overview of AEs is in Table 23. Most TEAEs were mild (25%) or moderate (54%). Severe TEAEs occurred in 22%. 7% discontinued study drug due to a TEAE, mostly due to mucocutaneous TEAEs.

Table 23 Overview of TEAEs and Post-Treatment AEs (FOP-FAS ≥8/10y).

		PVO Treatment Period				
Characteristics	Placebo/ Untreated (N=20)	Chronic 5 mg (N=130)	Flare-up 5/2.5 mg (N=7)	Flare-up 10/5 mg (N=25)	Flare-up 20/10 mg (N=100)	PVO Total (N=139)
Any TEAE[1]	19 (95.0)	126 (96.9)	7 (100)	25 (100)	95 (95.0)	139 (100)
Treatment-related TEAEs[2]	10 (50.0)	121 (93.1)	7 (100)	24 (96.0)	93 (93.0)	137 (98.6)
Severity of TEAEs						
Mild	10 (50.0)	53 (40.8)	5 (71.4)	14 (56.0)	29 (29.0)	34 (24.5)
Moderate	7 (35.0)	53 (40.8)	2 (28.6)	11 (44.0)	48 (48.0)	75 (54.0)
Severe	2 (10.0)	20 (15.4)	0	0	18 (18.0)	30 (21.6)
Treatment-emergent SAEs	5 (25.0)	21 (16.2)	0	2 (8.0)	20 (20.0)	37 (26.6)
Treatment-related SAEs[2]	0	8 (6.2)	0	1 (4.0)	11 (11.0)	19 (13.7)
TEAEs leading to dose modification	0	10 (7.7)	0	0	41 (41.0)	46 (33.1)
TEAEs leading to dose interruption	1 (5.0)	18 (13.8)	0	1 (4.0)	19 (19.0)	33 (23.7)
TEAEs leading to study drug discontinuation	0	5 (3.8)	0	0	5 (5.0)	10 (7.2)
TEAEs leading to study discontinuation	0	3 (2.3)	0	0	1 (1.0)	4 (2.9)
Deaths	0	0	0	0	0	0
Any post-treatment AE[3]	8 (40.0)	14 (10.8)	6 (85.7)	19 (76.0)	10 (10.0)	44 (31.7)
Treatment-related AEs[2]	2 (10.0)	3 (2.3)	3 (42.9)	7 (28.0)	5 (5.0)	17 (12.2)
Severe post-treatment AEs	1 (5.0)	1 (0.8)	0	1 (4.0)	2 (2.0)	4 (2.9)
Post-treatment SAEs	1 (5.0)	1 (0.8)	1 (14.3)	2 (8.0)	3 (3.0)	7 (5.0)
Treatment-related SAEs[2]	0	1 (0.8)	0	1 (4.0)	1 (1.0)	3 (2.2)
Post-treatment deaths	0	0	0	0	0	0

1 TEAEs are AEs with onset dates on or after the first dose date of study drug and on or before the last dose date of study drug + 7 days.
2 Treatment related includes possibly, probably, or definitely related to palovarotene based on Investigator-reported causality.
3 Post-treatment AEs have a start date after last dose date + 7 days.
Adverse events in untreated subjects in Study PVO-1A-202/Part A were also classified as treatment emergent.
Subjects may appear multiple times within and across dose group column(s), as they may have participated in multiple studies/periods.
The placebo/untreated group includes subjects from Studies PVO-1A-201 and PVO-1A-202/Part A.
AE=adverse event; FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; TEAE=treatment-emergent adverse event; PVO=palovarotene; SAE=serious adverse event.

The most common TEAEs (≥10% of subjects) are shown in Table 24, and included mucocutaneous AEs (e.g., dry skin, dry lips, alopecia, pruritis, and erythema), or musculoskeletal AEs (e.g., arthralgia and extremity pain).

Table 24. TEAEs in ≥10% of subjects (FOP-FAS (≥8/10y)).

System Organ Class Preferred Term	Placebo/ Untreated (N=20)	PVO Treatment Period Chronic 5 mg (N=130)	Flare-up 5/2.5 mg (N=7)	Flare-up 10/5 mg (N=25)	Flare-up 20/10 mg (N=100)	PVO Total (N=139)
Any TEAE	19 (95.0)	126 (96.9)	7 (100)	25 (100)	95 (95.0)	139 (100)
Skin and subcutaneous tissue disorders	9 (45.0)	114 (87.7)	6 (85.7)	24 (96.0)	91 (91.0)	136 (97.8)
Dry skin	3 (15.0)	75 (57.7)	5 (71.4)	22 (88.0)	58 (58.0)	109 (78.4)
Alopecia	0	31 (23.8)	0	1 (4.0)	30 (30.0)	58 (41.7)
Pruritus	1 (5.0)	28 (21.5)	0	8 (32.0)	31 (31.0)	56 (40.3)
Erythema	0	22 (16.9)	2 (28.6)	5 (20.0)	29 (29.0)	47 (33.8)
Rash	0	26 (20.0)	1 (14.3)	2 (8.0)	25 (25.0)	44 (31.7)
Pruritus generalised	0	21 (16.2)	1 (14.3)	9 (36.0)	25 (25.0)	43 (30.9)
Skin exfoliation	0	20 (15.4)	0	2 (8.0)	29 (29.0)	43 (30.9)
Drug eruption	0	12 (9.2)	0	0	15 (15.0)	23 (16.5)
Eczema	0	13 (10.0)	1 (14.3)	5 (20.0)	8 (8.0)	21 (15.1)
Skin irritation	0	8 (6.2)	0	1 (4.0)	8 (8.0)	16 (11.5)
Gastrointestinal disorders	9 (45.0)	93 (71.5)	5 (71.4)	20 (80.0)	56 (56.0)	115 (82.7)
Lip dry	1 (5.0)	48 (36.9)	4 (57.1)	14 (56.0)	29 (29.0)	78 (56.1)
Nausea	3 (15.0)	19 (14.6)	0	6 (24.0)	14 (14.0)	33 (23.7)
Vomiting	4 (20.0)	19 (14.6)	0	3 (12.0)	13 (13.0)	32 (23.0)
Chapped lips	2 (10.0)	10 (7.7)	0	6 (24.0)	12 (12.0)	24 (17.3)
Abdominal pain	2 (10.0)	12 (9.2)	0	4 (16.0)	7 (7.0)	22 (15.8)
Diarrhoea	1 (5.0)	17 (13.1)	0	3 (12.0)	7 (7.0)	20 (14.4)
Dry mouth	0	9 (6.9)	1 (14.3)	4 (16.0)	6 (6.0)	18 (12.9)
Cheilitis	0	5 (3.8)	0	0	11 (11.0)	15 (10.8)
Infections and infestations	8 (40.0)	82 (63.1)	3 (42.9)	11 (44.0)	56 (56.0)	109 (78.4)
Upper respiratory tract infection	1 (5.0)	25 (19.2)	2 (28.6)	5 (20.0)	8 (8.0)	33 (23.7)
Nasopharyngitis	0	23 (17.7)	1 (14.3)	0	12 (12.0)	31 (22.3)
Paronychia	0	13 (10.0)	0	0	11 (11.0)	22 (15.8)
Ear infection	0	10 (7.7)	0	0	6 (6.0)	14 (10.1)
Musculoskeletal and connective tissue disorders	12 (60.0)	79 (60.8)	4 (57.1)	16 (64.0)	58 (58.0)	102 (73.4)
Arthralgia	10 (50.0)	40 (30.8)	1 (14.3)	11 (44.0)	30 (30.0)	61 (43.9)
Pain in extremity	5 (25.0)	34 (26.2)	2 (28.6)	6 (24.0)	24 (24.0)	52 (37.4)
Back pain	0	15 (11.5)	0	1 (4.0)	11 (11.0)	25 (18.0)
Musculoskeletal pain	2 (10.0)	13 (10.0)	0	2 (8.0)	14 (14.0)	24 (17.3)
Joint swelling	0	9 (6.9)	1 (14.3)	2 (8.0)	14 (14.0)	23 (16.5)
Neck pain	0	11 (8.5)	1 (14.3)	1 (4.0)	7 (7.0)	17 (12.2)
Musculoskeletal chest pain	0	9 (6.9)	0	2 (8.0)	7 (7.0)	14 (10.1)
Injury, poisoning and procedural complications	5 (25.0)	66 (50.8)	0	7 (28.0)	41 (41.0)	89 (64.0)
Skin abrasion	0	13 (10.0)	0	2 (8.0)	22 (22.0)	32 (23.0)
Contusion	1 (5.0)	15 (11.5)	0	1 (4.0)	5 (5.0)	19 (13.7)
Fall	2 (10.0)	10 (7.7)	0	2 (8.0)	8 (8.0)	17 (12.2)

System Organ Class Preferred Term	Placebo/ Untreated (N=20)	PVO Treatment Period Chronic 5 mg (N=130)	Flare-up 5/2.5 mg (N=7)	Flare-up 10/5 mg (N=25)	Flare-up 20/10 mg (N=100)	PVO Total (N=139)
General disorders and administration site conditions	10 (50.0)	39 (30.0)	3 (42.9)	14 (56.0)	41 (41.0)	65 (46.8)
Condition aggravated	8 (40.0)	15 (11.5)	1 (14.3)	10 (40.0)	18 (18.0)	31 (22.3)
Pyrexia	3 (15.0)	11 (8.5)	2 (28.6)	2 (8.0)	12 (12.0)	21 (15.1)
Peripheral swelling	1 (5.0)	6 (4.6)	0	2 (8.0)	12 (12.0)	19 (13.7)
Fatigue	0	5 (3.8)	1 (14.3)	0	10 (10.0)	15 (10.8)
Respiratory, thoracic and mediastinal disorders	6 (30.0)	45 (34.6)	1 (14.3)	6 (24.0)	27 (27.0)	62 (44.6)
Cough	2 (10.0)	13 (10.0)	0	2 (8.0)	11 (11.0)	23 (16.5)
Epistaxis	0	13 (10.0)	1 (14.3)	1 (4.0)	10 (10.0)	20 (14.4)
Oropharyngeal pain	0	9 (6.9)	0	0	9 (9.0)	16 (11.5)
Nervous system disorders	8 (40.0)	38 (29.2)	2 (28.6)	10 (40.0)	32 (32.0)	60 (43.2)
Headache	4 (20.0)	18 (13.8)	0	7 (28.0)	17 (17.0)	36 (25.9)
Dizziness	0	5 (3.8)	1 (14.3)	1 (4.0)	10 (10.0)	14 (10.1)
Eye disorders	2 (10.0)	24 (18.5)	1 (14.3)	6 (24.0)	32 (32.0)	49 (35.3)
Dry eye	0	13 (10.0)	1 (14.3)	5 (20.0)	21 (21.0)	36 (25.9)
Metabolism and nutrition disorders	2 (10.0)	19 (14.6)	1 (14.3)	9 (36.0)	17 (17.0)	37 (26.6)
Decreased appetite	0	6 (4.6)	0	2 (8.0)	9 (9.0)	16 (11.5)

TEAEs have onset dates on or after the first dose date of study drug and on or before the last dose date of study drug + 7 days. Adverse events in untreated subjects in Study PVO-1A-202/Part A were also classified as treatment emergent.
The age at first entry of 8/10 years indicates 8 years of age for female subjects and 10 years of age for male subjects.
The placebo/untreated group includes subjects from Studies PVO-1A-201 and PVO-1A-202/Part A.
FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; TEAE=treatment-emergent adverse event; PVO=palovarotene.

Chronic vs flare-up treatment: some mucocutaneous AEs (e.g., alopecia, skin exfoliation, and pruritis) were more frequent during the 20/10 mg flare-up treatment (41% vs 8% for chronic dosing) and may be dose-dependent.

Biological sex: Some Skin and Subcutaneous Tissue Disorders and Musculoskeletal and Connective Tissue Disorders TEAEs occurred more frequently in females, e.g., alopecia (females, 58.0%; males, 25.7%), rash (37.7% vs. 25.7%), skin exfoliation (39.1% vs. 22.9%), arthralgia (50.7% vs. 37.1%), and pain in extremity (43.5% vs. 31.4%).

Ethnicity: no significant differences.

Most common TEAEs by FOP-FAS age subgroup

- Adults (≥18 years) (n=62): dry skin (87.1%), alopecia (48.4%), dry lips (54.8%), arthralgia (51.5%), pain in extremity (46.8%), erythema (43.5%), headache (43.5%), rash (41.9%), pruritus (40.3%)/generalized pruritus (40.3%), skin exfoliation (38.7%), dry eye (37.1%), skin abrasion (37.1%), nausea (35.5%), vomiting (33.9%) and condition aggravated (33.9%).
- ≥8/10 years to <18 years (n=77): dry skin (71.4%), dry lip (57.1%), pruritus (40.3%), arthralgia (37.7%), and alopecia (36.4%).
- <8/10 years subgroup (n=25): similar to those in the ≥8/10 to <18 years population except for PPC and childhood infections (e.g., impetigo). The most common TEAEs included dry skin, dry lips, PPC, rash, arthralgia, erythema, alopecia, drug eruption, pruritis, and URTI.

There were some notable differences between age groups (≥18 year group vs. ≥8/10 to <18 year group vs. <8/10 year group):

- Tachycardia: 11.3% vs. 3.9% vs. 0%
- Nausea: 35.5% vs. 14.3% vs. 0%
- Drug eruption: 9.7% vs. 21.1% vs. 24.0%
- PPC: 0% vs. 13.0% vs. 56.0%.

Treatment related adverse event (adverse drug reaction) overview

The most common treatment-related TEAEs (≥10% of subjects in the palovarotene group) in the FOP-FAS ≥8/10 years population are presented in Table 25 and were mainly mucocutaneous events.

Table 25. Treatment-related TEAEs in ≥10% of subjects (FOP-FAS ≥8/10y).

System Organ Class Preferred Term	Placebo/ Untreated (N=20)	PVO Treatment Period Chronic 5 mg (N=130)	Flare-up 5/2.5 mg (N=7)	Flare-up 10/5 mg (N=25)	Flare-up 20/10 mg (N=100)	PVO Total (N=139)
Any TEAE	10 (50.0)	121 (93.1)	7 (100)	24 (96.0)	93 (93.0)	137 (98.6)
Skin and subcutaneous tissue disorders	4 (20.0)	113 (86.9)	6 (85.7)	23 (92.0)	90 (90.0)	136 (97.8)
Dry skin	3 (15.0)	75 (57.7)	5 (71.4)	22 (88.0)	58 (58.0)	109 (78.4)
Alopecia	0	31 (23.8)	0	1 (4.0)	29 (29.0)	57 (41.0)
Pruritus	0	28 (21.5)	0	8 (32.0)	31 (31.0)	56 (40.3)
Erythema	0	19 (14.6)	1 (14.3)	5 (20.0)	28 (28.0)	44 (31.7)
Pruritus generalised	0	21 (16.2)	1 (14.3)	9 (36.0)	25 (25.0)	43 (30.9)
Skin exfoliation	0	20 (15.4)	0	2 (8.0)	28 (28.0)	43 (30.9)
Rash	0	26 (20.0)	1 (14.3)	1 (4.0)	24 (24.0)	42 (30.2)
Drug eruption	0	12 (9.2)	0	0	15 (15.0)	23 (16.5)
Eczema	0	12 (9.2)	1 (14.3)	5 (20.0)	8 (8.0)	20 (14.4)
Skin irritation	0	8 (6.2)	0	1 (4.0)	8 (8.0)	16 (11.5)
Gastrointestinal disorders	4 (20.0)	71 (54.6)	4 (57.1)	20 (80.0)	52 (52.0)	105 (75.5)
Lip dry	1 (5.0)	48 (36.9)	4 (57.1)	13 (52.0)	29 (29.0)	77 (55.4)
Chapped lips	1 (5.0)	10 (7.7)	0	6 (24.0)	12 (12.0)	24 (17.3)
Dry mouth	0	9 (6.9)	1 (14.3)	4 (16.0)	6 (6.0)	18 (12.9)
Cheilitis	0	5 (3.8)	0	0	11 (11.0)	15 (10.8)
Nausea	2 (10.0)	7 (5.4)	0	4 (16.0)	6 (6.0)	15 (10.8)
Infections and infestations	0	42 (32.3)	1 (14.3)	5 (20.0)	36 (36.0)	68 (48.9)
Paronychia	0	11 (8.5)	0	0	11 (11.0)	20 (14.4)
Musculoskeletal and connective tissue disorders	3 (15.0)	27 (20.8)	2 (28.6)	8 (32.0)	30 (30.0)	49 (35.3)
Pain in extremity	0	8 (6.2)	1 (14.3)	2 (8.0)	14 (14.0)	22 (15.8)
Arthralgia	1 (5.0)	8 (6.2)	1 (14.3)	4 (16.0)	13 (13.0)	19 (13.7)
Eye disorders	2 (10.0)	21 (16.2)	1 (14.3)	6 (24.0)	31 (31.0)	46 (33.1)
Dry eye	0	13 (10.0)	1 (14.3)	5 (20.0)	21 (21.0)	36 (25.9)
Injury, poisoning and procedural complications	0	24 (18.5)	0	4 (16.0)	25 (25.0)	46 (33.1)
Skin abrasion	0	10 (7.7)	0	2 (8.0)	20 (20.0)	29 (20.9)
Respiratory, thoracic and mediastinal disorders	0	23 (17.7)	1 (14.3)	5 (20.0)	14 (14.0)	38 (27.3)
Epistaxis	0	11 (8.5)	1 (14.3)	1 (4.0)	7 (7.0)	17 (12.2)
Nervous system disorders	3 (15.0)	13 (10.0)	2 (28.6)	7 (28.0)	21 (21.0)	32 (23.0)
Headache	2 (10.0)	9 (6.9)	0	7 (28.0)	10 (10.0)	23 (16.5)

Source: Module 5.3.5.3 ISS Table 14.1.8.6.1 FOP.
The FOP-FAS includes all subjects enrolled or dosed in FOP clinical studies.
TEAEs have onset dates on or after the first dose date of study drug and on or before the last dose date of study drug + 7 days. Adverse events in untreated subjects in Study PVO-1A-202/Part A were also classified as treatment emergent.
The age at first entry of 8/10 years indicates 8 years of age for female subjects and 10 years of age for male subjects.
Treatment related includes possibly, probably, or definitely related to palovarotene based on Investigator-reported causality.
The placebo/untreated group includes subjects from Studies PVO-1A-201 and PVO-1A-202/Part A.
FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; TEAE=treatment-emergent adverse event; PVO=palovarotene.

In FOP-FAS ≥8/10 year group, the incidence of treatment-related TEAEs was 98.6% (palovarotene) vs. 50.0% (placebo).

The most common treatment-related TEAEs were in the SOCs of Skin and subcutaneous tissue disorders (97.8%) and Gastrointestinal disorders (75.5%), including dry skin, dry lips, alopecia, and pruritis. In most cases, there was no significant difference between the chronic and flare-up treatment periods, except for erythema, skin exfoliation, cheilitis, pain in the extremity, arthralgia, and skin abrasion (approx. twice as frequent in the 20/10 mg flare-up group vs. untreated).

The common treatment-related TEAEs (≥1% to <10% of subjects in the palovarotene group) in the FAS-FOP ≥8/10 years population are presented in Table 26.

Table 26. Treatment-related TEAEs in ≥1% to <10% of subjects (FOP-FAS ≥8/10 Years).

		PVO Treatment Period				
System Organ Class Preferred Term	Placebo/ Untreated (N=20)	Chronic 5 mg (N=130)	Flare-up 5/2.5 mg (N=7)	Flare-up 10/5 mg (N=25)	Flare-up 20/10 mg (N=100)	PVO Total (N=139)
Any TEAE	10 (50.0)	121 (93.1)	7 (100)	24 (96.0)	93 (93.0)	137 (98.6)
Skin and subcutaneous tissue disorders	4 (20.0)	113 (86.9)	6 (85.7)	23 (92.0)	90 (90.0)	136 (97.8)
Onychoclasis	0	5 (3.8)	0	1 (4.0)	5 (5.0)	11 (7.9)
Skin fissures	0	4 (3.1)	0	0	9 (9.0)	11 (7.9)
Blister	0	4 (3.1)	0	0	5 (5.0)	9 (6.5)
Decubitus ulcer	0	3 (2.3)	0	0	5 (5.0)	8 (5.8)
Dermatitis	0	2 (1.5)	0	0	6 (6.0)	8 (5.8)
Rash generalised	0	5 (3.8)	0	0	4 (4.0)	8 (5.8)
Rash maculo-papular	0	3 (2.3)	0	2 (8.0)	3 (3.0)	8 (5.8)
Skin reaction	0	4 (3.1)	0	0	5 (5.0)	8 (5.8)
Ingrowing nail	0	2 (1.5)	0	0	5 (5.0)	7 (5.0)
Madarosis	0	3 (2.3)	0	0	4 (4.0)	7 (5.0)
Acne	0	3 (2.3)	0	1 (4.0)	3 (3.0)	6 (4.3)
Skin lesion	0	4 (3.1)	0	1 (4.0)	2 (2.0)	6 (4.3)
Dandruff	0	2 (1.5)	1 (14.3)	0	2 (2.0)	5 (3.6)
Dermatitis acneiform	0	1 (0.8)	0	4 (16.0)	0	5 (3.6)
Skin discolouration	0	2 (1.5)	0	0	3 (3.0)	5 (3.6)
Skin ulcer	0	4 (3.1)	0	0	3 (3.0)	5 (3.6)
Hyperhidrosis	0	0	0	1 (4.0)	3 (3.0)	4 (2.9)
Pain of skin	1 (5.0)	0	0	0	4 (4.0)	4 (2.9)
Rash macular	0	3 (2.3)	0	0	1 (1.0)	4 (2.9)
Skin burning sensation	0	0	0	0	4 (4.0)	4 (2.9)

System Organ Class Preferred Term	Placebo/ Untreated (N=20)	PVO Treatment Period Chronic 5 mg (N=130)	Flare-up 5/2.5 mg (N=7)	Flare-up 10/5 mg (N=25)	Flare-up 20/10 mg (N=100)	PVO Total (N=139)
Musculoskeletal and connective tissue disorders	3 (15.0)	27 (20.8)	2 (28.6)	8 (32.0)	30 (30.0)	49 (35.3)
Back Pain	0	3 (2.3)	0	1 (4.0)	4 (4.0)	8 (5.8)
Epiphysis premature fusion	0	5 (3.8)	0	0	2 (2.0)	7 (5.0)
Joint swelling	0	2 (1.5)	1 (14.3)	0	5 (5.0)	7 (5.0)
Musculoskeletal chest pain	0	1 (0.8)	0	1 (4.0)	2 (2.0)	4 (2.9)
Musculoskeletal stiffness	0	2 (1.5)	0	1 (4.0)	1 (1.0)	4 (2.9)
Myalgia	1 (5.0)	2 (1.5)	0	1 (4.0)	1 (1.0)	4 (2.9)
Groin pain	0	1 (0.8)	1 (14.3)	0	1 (1.0)	3 (2.2)
Joint range of motion decreased	0	2 (1.5)	0	0	1 (1.0)	3 (2.2)
Muscle spasms	1 (5.0)	1 (0.8)	0	0	2 (2.0)	3 (2.2)
Muscle tightness	0	1 (0.8)	0	0	2 (2.0)	3 (2.2)
Musculoskeletal pain	1 (5.0)	0	0	0	3 (3.0)	3 (2.2)
Bone pain	0	0	0	0	2 (2.0)	2 (1.4)
Joint noise	0	2 (1.5)	0	0	0	2 (1.4)
Joint stiffness	0	0	0	1 (4.0)	1 (1.0)	2 (1.4)
Mobility decreased	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Musculoskeletal discomfort	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Neck pain	0	0	0	0	2 (2.0)	2 (1.4)
Pain in jaw	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Eye disorders	2 (10.0)	21 (16.2)	1 (14.3)	6 (24.0)	31 (31.0)	46 (33.1)
Ocular hyperaemia	0	1 (0.8)	0	1 (4.0)	7 (7.0)	9 (6.5)
Eye irritation	0	0	0	0	4 (4.0)	4 (2.9)
Eyelid skin dryness	0	2 (1.5)	0	0	2 (2.0)	4 (2.9)
Eye pruritus	1 (5.0)	0	0	0	3 (3.0)	3 (2.2)
Eye swelling	0	0	0	1 (4.0)	2 (2.0)	3 (2.2)
Vision blurred	1 (5.0)	0	0	0	3 (3.0)	3 (2.2)
Blepharitis	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Conjunctival hyperaemia	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Eyelid oedema	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Lacrimation increased	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Visual impairment	0	0	0	0	2 (2.0)	2 (1.4)
General disorders and administrative site conditions	1 (5.0)	12 (9.2)	3 (42.9)	6 (24.0)	22 (22.0)	33 (23.7)
Peripheral swelling	0	2 (1.5)	0	1 (4.0)	7 (7.0)	10 (7.2)
Condition aggravated	0	1 (0.8)	1 (14.3)	4 (16.0)	5 (5.0)	9 (6.5)
Fatigue	0	0	1 (14.3)	0	4 (4.0)	5 (3.6)
Feeling cold	0	1 (0.8)	1 (14.3)	0	2 (2.0)	4 (2.9)
Oedema peripheral	0	1 (0.8)	0	0	2 (2.0)	3 (2.2)
Pyrexia	1 (1.5)	0	2 (28.6)	1 (4.0)	1 (1.0)	3 (2.2)
Gait disturbance	0	2 (1.5)	0	0	0	2 (1.4)
Malaise	0	0	0	0	2 (2.0)	2 (1.4)
Swelling	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Thirst	0	1 (0.8)	0	1 (4.0)	0	2 (1.4)

System Organ Class Preferred Term	Placebo/ Untreated (N=20)	PVO Treatment Period Chronic 5 mg (N=130)	Flare-up 5/2.5 mg (N=7)	Flare-up 10/5 mg (N=25)	Flare-up 20/10 mg (N=100)	PVO Total (N=139)
Injury, poisoning and procedural complications	0	24 (18.5)	0	4 (16.0)	25 (25.0)	46 (33.1)
Sunburn	0	4 (3.1)	0	1 (4.0)	3 (3.0)	8 (5.8)
Laceration	0	2 (1.5)	0	0	2 (2.0)	3 (2.2)
Scratch	0	3 (2.3)	0	0	0	3 (2.2)
Ankle fracture	0	0	0	1 (4.0)	1 (1.0)	2 (1.4)
Contusion	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Fall	0	0	0	1 (4.0)	1 (1.0)	2 (1.4)
Investigations	4 (20.0)	14 (10.8)	1 (14.3)	8 (32.0)	19 (19.0)	37 (26.6)
Lipase increased	1 (5.0)	4 (3.1)	0	4 (16.0)	4 (4.0)	10 (7.2)
ALT increased	0	1 (0.8)	0	0	5 (5.0)	6 (4.3)
Amylase increased	1 (5.0)	2 (1.5)	0	0	4 (4.0)	6 (4.3)
GGT increased	0	1 (0.8)	1 (14.3)	0	4 (4.0)	5 (3.6)
AST increased	0	0	0	0	3 (3.0)	3 (2.2)
TSH increased	0	1 (0.8)	0	2 (8.0)	0	3 (2.2)
Bacterial test	0	0	0	0	2 (2.0)	2 (1.4)
ALP increased	1 (5.0)	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Bilirubin increased	1 (5.0)	0	0	2 (8.0)	0	2 (1.4)
TSH decreased	0	0	1 (14.3)	1 (4.0)	0	2 (1.4)
Haemoglobin decreased	0	0	0	2 (8.0)	0	2 (1.4)
Protein urine present	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Urobilinogen urine increased	0	0	0	1 (4.0)	1 (1.0)	2 (1.4)
Weight increased	0	0	0	0	2 (2.0)	2 (1.4)
Respiratory, thoracic and mediastinal disorders	0	23 (17.7)	1 (14.3)	5 (20.0)	14 (14.0)	38 (27.3)
Nasal dryness	0	5 (3.8)	0	0	2 (2.0)	6 (4.3)
Oropharyngeal pain	0	2 (1.5)	0	0	3 (3.0)	5 (3.6)
Dyspnoea	0	1 (0.8)	0	1 (4.0)	2 (2.0)	4 (2.9)
Cough	0	1 (0.8)	0	1 (4.0)	1 (1.0)	3 (2.2)
Dry throat	0	0	0	1 (4.0)	1 (1.0)	2 (1.4)
Nervous system disorders	3 (15.0)	13 (10.0)	2 (28.6)	7 (28.0)	21 (21.0)	32 (23.0)
Dizziness	0	2 (1.5)	1 (14.3)	0	4 (4.0)	6 (4.3)
Burning sensation	0	0	0	0	4 (4.0)	4 (2.9)
Migraine	0	1 (0.8)	1 (14.3)	1 (4.0)	1 (1.0)	4 (2.9)
Hyperaesthesia	0	1 (0.8)	0	0	3 (3.0)	3 (2.2)
Hypoaesthesia	0	0	0	0	3 (3.0)	3 (2.2)
Epilepsy	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Paraesthesia	1 (1.5)	0	1 (14.3)	0	1 (1.0)	2 (1.4)
Seizure	0	0	0	0	2 (2.0)	2 (1.4)
Syncope	0	2 (1.5)	0	0	0	2 (1.4)
Psychiatric disorders	0	15 (11.5)	0	6 (24.0)	16 (30.2)	31 (22.3)
Irritability	0	3 (2.3)	0	3 (12.0)	2 (2.0)	8 (5.8)
Depressed mood	0	4 (3.1)	0	0	3 (3.0)	7 (5.0)
Anxiety	0	3 (2.3)	0	0	3 (3.0)	6 (4.3)
Insomnia	0	2 (1.5)	0	0	2 (2.0)	4 (2.9)
Depression	0	0	0	0	3 (3.0)	3 (2.2)
Suicidal ideation	0	2 (1.5)	0	1 (4.0)	1 (1.0)	3 (2.2)
Mood altered	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Mood swings	0	0	0	1 (4.0)	1 (1.0)	2 (1.4)
Sleep disorder	0	0	0	0	2 (2.0)	2 (1.4)

System Organ Class Preferred Term	Placebo/ Untreated (N=20)	PVO Treatment Period Chronic 5 mg (N=130)	Flare-up 5/2.5 mg (N=7)	Flare-up 10/5 mg (N=25)	Flare-up 20/10 mg (N=100)	PVO Total (N=139)
Metabolism and nutrition disorders	0	8 (6.2)	1 (14.3)	8 (32.0)	13 (13.0)	25 (18.0)
Decreased appetite	0	3 (2.3)	0	2 (8.0)	7 (7.0)	11 (7.9)
Increased appetite	0	1 (0.8)	1 (14.3)	2 (8.0)	0	4 (2.9)
Hypertriglyceridemia	0	2 (1.5)	0	2 (8.0)	3 (3.0)	3 (2.2)
Abnormal loss of weight	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Hypercholesteremia	0	0	1 (14.3)	1 (4.0)	0	2 (1.4)
Polydipsia	0	0	0	1 (4.0)	1 (1.0)	2 (1.4)
Ear and labyrinth disorders	0	6 (4.6)	0	0	15 (15.0)	20 (14.4)
Ear pain	0	0	0	0	4 (4.0)	4 (2.9)
Hypoacusis	0	2 (1.5)	0	0	2 (2.0)	4 (2.9)
Conductive deafness	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Ear pruritis	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Tympanic membrane perforation	0	0	0	0	2 (2.0)	2 (1.4)
Renal and urinary disorders	1 (5.0)	3 (2.3)	4 (57.1)	6 (24.0)	5 (5.0)	14 (10.1)
Proteinuria	0	0	0	5 (20.0)	0	5 (3.6)
Pollakiuria	0	1 (0.8)	2 (28.6)	2 (8.0)	0	4 (2.9)
Hematuria	0	0	1 (14.3)	1 (4.0)	2 (2.0)	3 (2.2)
Urogenital haemorrhage	0	1 (0.8)	0	0	1 (1.0)	2 (1.4)
Vascular disorders	0	2 (1.5)	0	0	8 (8.0)	9 (6.5)
Flushing	0	1 (0.8)	0	0	6 (6.0)	7 (5.0)
Peripheral coldness	0	0	0	0	2 (2.0)	2 (1.4)
Cardiac disorders	0	2 (1.5)	0	0	3 (3.0)	5 (3.6)
Tachycardia	0	2 (1.5)	0	0	1 (1.0)	3 (2.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (0.8)	0	0	3 (3.0)	4 (2.9)
Pyogenic granuloma	0	1 (0.8)	0	0	2 (2.0)	3 (2.2)
Blood and lymphatic system disorders	1 (5.0)	0	0	0	2 (2.0)	2 (1.4)
Anaemia	0	0	0	0	2. (2.0)	2 (1.4)

Source: Module 5.3.5.3 ISS Table 14.1.8.6.2 FOP
The FOP-FAS includes all subjects enrolled or dosed in FOP clinical studies.
TEAEs have onset dates on or after the first dose date of study drug and on or before the last dose date of study drug +7 days. Adverse events in untreated subjects in Study PVO-1A-202/Part A were also classified as treatment emergent.
The age at first entry of 8/10 years indicates 8 years of age for female subjects and 10 years of age for male subjects.
Treatment related includes possibly, probably, or definitely related to palovarotene based on Investigator-reported causality.
The placebo/untreated group includes subjects from Studies PVO-1A-201 and PVO-1A-202/Part A.
ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; FOP= fibrodysplasia ossificans progressive; FAS=full analysis set; GGT=gamma-glutamyltransferase; PVO=palovarotene; TEAE=treatment-emergent adverse event; TSH=thyroid stimulating hormone.

Deaths

FOP-FAS: No deaths were reported during treatment or for 30 days post-treatment. In Study 301, a 13-year-old patient with a history of restrictive lung disease died 2.5 months after discontinuing palovarotene treatment. The cause of death was restrictive lung disease from complications of FOP.

Serious adverse events

FOP-FAS (≥8/10y): Treatment-emergent SAEs occurred in 27% of subjects (25% for placebo in FOP-FAS), and post-treatment SAEs in 5%. The SAE incidence was similar during the chronic

and 20/10 mg flare-up treatment periods (16% and 20%, respectively), and lower in the off-treatment period (11%).

The most common SAEs included PPC (5.0%); condition aggravated (3.6%); pneumonia and arthralgia (each 2.2%); and extremity pain, abdominal pain, impacted teeth, cellulitis, local swelling, syncope, and respiratory distress, each in 1.4% of subjects.

14% had treatment-emergent SAE at least possibly related to palovarotene, including PPC, pain in extremity, condition aggravated, peripheral swelling, and cellulitis.

Adverse events of special interest

Linear growth data: Linear height generally increased over time in most paediatric patients (treated or untreated groups). Height z-scores declined in all groups but were greater in magnitude in the palovarotene group (Table 27), noting the small sample size.

Clinical trial data suggest that in younger children (<8/10 years), palovarotene may affect linear growth independent of PPC. In older children, linear growth effects are mostly evident in those with PPC. Knee height, femur/tibia length measurements were fairly similar between groups.

Growth monitoring is generally limited by spinal abnormalities (e.g., scoliosis or kyphosis). These should be considered during monitoring.

Table 27. Studies 301 and 101 (NHS). Summary of linear height z-scores and growth velocity at Month 12 in patients with age <18 years at first entry (FOP-FAS).

		Untreated (NHS) Age at First Entry, y			PVO Total (PVO-1A-301) Age at First Entry, y		
Measure	Statistic	<8/10 (N=23)	≥8/10 to <14 (N=21)	≥14 to <18 (N=22)	<8/10 (N=21)	≥8/10 to <14 (N=36)	≥14 to <18 (N=23)
Baseline, z-score	n	23	21	20	21	36	19
	Mean (SD)	0.44 (1.46)	0.09 (1.12)	0.18 (1.24)	0.34 (1.73)	-0.35 (1.60)	-0.50 (1.69)
	Median	0.76	0.21	0.20	0.65	-0.39	-0.03
	Min, Max	-4.0, 2.4	-1.9, 2.1	-2.95, 2.55	-3.53, 3.73	-4.38, 1.88	-4.64, 1.55
CFB at Month 12	n	22	17	18	15	31	13
	Mean (SD)	-0.18 (0.49)	-0.30 (0.34)	-0.55 (1.16)	-0.57 (0.66)	-0.36 (0.43)	-0.02 (1.54)
	Median	-0.05	-0.20	-0.21	-0.52	-0.24	-0.39
	Min, Max	-1.5, 0.6	-1.2, 0.1	-4.9, 0.5	-2.0, 1.0	-1.2, 0.5	-1.1, 4.9
GV at Month 12, cm/y	n	22	17	18	15	31	13
	Mean (SD)	5.2 (2.6)	4.2 (3.2)	-1.5 (7.8)	3.4 (3.4)	3.0 (3.2)	2.6 (13.1)
	Median	5.8	4.5	0.3	3.3	3.6	0.0
	Min, max	-1.9, 9.5	-4.9, 8.6	-30.0, 4.6	-2.6, 9.9	-4.0, 8.2	-6.2, 45.5
GV at Month 12, n (%)	<4 cm/y	6 (27.3)	7 (41.2)	16 (88.9)	8 (53.3)	19 (61.3)	12 (92.3)
	≥4 to 5 cm/y	1 (4.5)	4 (23.5)	2 (11.1)	1 (6.7)	2 (6.5)	0
	>5 cm/y	15 (68.2)	6 (35.3)	0	6 (40.0)	10 (32.3)	1 (7.7)
	Missing	1	4	4	6	5	10

Source: Module 5.3.5.3 ISS Tables 14.2.16.1.2.1 FOP, 14.2.16.1.2.2 FOP, 14.2.16.1.2.3 FOP, 14.2.16.1.3.1 FOP, 14.2.16.1.3.2 FOP, 14.2.16.1.3.3 FOP, 14.2.16.2.4 FOP.
The FOP-FAS includes all subjects enrolled or dosed in FOP clinical studies.
The 8/10 years age limit indicates 8 years of age for female subjects and 10 years of age for male subjects.
CFB=change from baseline; FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; GV=growth velocity; max=maximum; min=minimum; NHS=natural history study; PVO=palovarotene; y=years.

Avascular Necrosis/Osteonecrosis: No cases identified.

Premature physeal closure (PPC): All PPC events (MedDRA PT: epiphyses premature fusion) were categorised as SAEs (in both treatment-emergent and post-treatment periods). PPC occurred in 23.5% (24/102) of subjects aged <18 years and was more common in younger patients:

- Age <8/10 years: 56.0% (14/25)
- Age ≥8/10 to <14 years: 25.6% (10/39)
- Age ≥8/10 to <18 years: 13.0% (10/77).

Consistent with other retinoids, PPC typically affected the lower extremities first and was symmetric.

PPC primarily occurred during exposure to both the chronic and flare-up treatment regimens, but also in 5 patients on chronic dosing only. There appeared to be a slight trend for longer duration and greater total palovarotene flare-up exposure in the <8/10 year population with PPC (vs. without PPC), but no exposure threshold could be established.

Bone mineral density: A retrospective analysis of WBCT scans in Study 301 and the NHS showed greater decreases in vertebral bone strength, bone mineral content (BMC), bone mineral density (BMD) and an increased risk of vertebral fractures in palovarotene-treated subjects compared with untreated subjects.

Fractures: At 12 months, 11.76% of untreated subjects had a new-onset vertebral fracture compared with 24.24% of palovarotene-treated subjects. In the FOP-FAS (≥8/10y), the risk of vertebral fractures was 2.98 times higher in palovarotene-treated subjects (vs. untreated) suggesting a causal association, even though not statistically significant for moderate/severe vertebral fractures. The consistent effect was still present when adjusted for potential confounders (e.g., age, glucocorticoid use).

Mental health: There appeared to be no treatment-related increase in suicide ideation/suicidal behaviour (based on a C-SSRS assessment) in the FOP-FAS.

Hepatic: In the FOP-FAS, no subjects met PCS criteria for Hy's Law.

Teratogenicity: Teratogenicity is an important identified risk and a class effect of systemic retinoids. Pregnant and breastfeeding females were excluded from all palovarotene clinical studies. No pregnancies occurred. Appropriate risk minimisation activities need to be present (including appropriate labelling and a potential prescriber restriction).

Breastfeeding: Breastfeeding females were excluded from all palovarotene clinical studies. There are no data on the presence of palovarotene or its main metabolites in human breast milk. At this stage, breastfeeding is contraindicated while on palovarotene and for at least 1 month following drug cessation.

Risk management plan

The summary of safety concerns and their associated risk monitoring and mitigation strategies are presented in Table 28. The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 28: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Teratogenicity	P	P	P	P
	Premature Physeal Closure including inhibition of long bone growth (in growing children)	P	P	P	P
	Radiological observed vertebral fractures	P	P	P	P
	Mucocutaneous effects	P	P	P	P
Important potential risks	Fractures and impaired fracture healing	P	P	P	-
Missing information	Long term safety	P	P		-

The RMP evaluation recommended conditions of registration relating to the versions of the risk management plan, requirement for periodic safety update reports, and inclusion of the medicine in the Black Triangle Scheme.

The summary of safety concerns is acceptable from an RMP perspective. The sponsor has stated in its Milestone 5 response that at a maximal frequency of 4 X-rays per year the radiation exposure is equivalent to about 4 days of normal environmental background radiation exposure (or ~0.004 mSv), or approximately 7 times less than an airplane ride. Therefore, "increased risk of cancer from more frequent imaging" will not be included in the summary of safety concerns. However, the sponsor will monitor reports of neoplasms as part of routine pharmacovigilance and signal detection activities. This is satisfactory.

Pharmacovigilance plan

Routine and additional pharmacovigilance activities have been proposed. Additional pharmacovigilance activities include a Voluntary Registry Study, which will include Australian patients. The sponsor also proposes to conduct KAB (Knowledge, Attitude and Behaviour) surveys to test the awareness of the additional risk minimisation activities. This is acceptable, however, the KAB survey test is considered to be additional pharmacovigilance and the sponsor has agreed to include this in the ASA.

Risk minimisation plan

Routine and additional risk minimisation activities have been proposed. Additional risk minimisation activities include educational materials for HCPs and patients. The patient additional risk minimisation material includes specific information regarding the prevention of pregnancy and premature physeal closure. The educational material also provides advice on expected side effects. The risk minimisation plan is acceptable.

Recommended conditions of registration

The suggested wording is:

> *The Sohonos EU-Risk Management Plan (RMP) (version 5.0, dated 7 April 2023, data lock point 27 April 2022), with Australian Specific Annex (version 3.0 dated 25 July 2023), included with submission PM-2022-03518-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

The following wording is recommended for the PSUR requirement:

> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*
>
> *Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.*
>
> *If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.*

The following wording is recommended for the Black Triangle Scheme condition of registration:

> *Sohonos (palovarotene) is to be included in the Black Triangle Scheme. The PI and CMI for Sohonos must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.*

The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit analysis

Delegate's considerations

Clinical trial program

Clinical trial overview and study contributions

There are approximately 800 confirmed cases of FOP worldwide. The clinical trial program included 219 patients. 164 of those patients received at least one dose of study drug. The

reliance on a single phase 3 trial was not ideal, but given the extreme rarity of the disease, this considered acceptable.

Study 301 was the single, pivotal, open-label phase 3 trial and used historical controls (discussed below). It contributed the most clinical data for this application, in particular for a combined chronic and flare-up regimen.

Studies 201 and 202 (incorporating Study 204) were rather small studies with incompletely refined endpoints that make interpreting the data difficult. They act as supportive studies.

Study 001 was a prospective, non-interventional natural history study. It characterised demographics and disease characteristics in untreated subjects (including information on flare-ups) and identified heterotopic ossification (HO) as a clinically meaningful endpoint with low-dose WBCT scans (excluding head) as the preferred imaging modality (over DEXA scans). Furthermore, it correlated HO with other CAJIS and FOP-PFQ.

Endpoints and clinical relevance

No definite regulatory guidance is available for FOP. As a consequence, no guidance with regard to endpoints is available. In such a case, endpoints and endpoint variables are typically derived from the scientific medical literature considering clinical factors.

Potential FOP study endpoints/variables include heterotopic ossification (HO), assessments of physical function (e.g., CAJIS score), and patient-reported outcomes of functional impairment and flare-up symptoms (e.g., FOP-PFQ).

To assess the *chronic/flare-up regimen* (Study 301, and Study 202 Part B and C), the main endpoint was the annualised change in new HO volume as assessed by low-dose WBCT (excluding head) imaging compared with similar data from untreated patients.

To assess the *flare-up only regimen* (Study 201, and Study 202 Part A), the main endpoint was the formation of HO following a flare-up (assessed by low-dose CT of the flareup site).

HO volume was chosen as the main endpoint variable due to the following: (1) HO formation is the pathognomonic feature of FOP and an objective measure (noting limitations with regard to inter-rater- or intra-rater-reliability, and variations due to bone remodelling); (2) measurable changes in whole body HO in untreated subjects are demonstrated over a clinical trial timeframe (more than one year); (3) changes in functional and patient-reported outcomes may not demonstrate sufficient disease progression over this timeframe; and (4) correlations between whole body HO and functional and patient-reported outcomes (e.g., CAJIS or FOP-PFQ scores).

Use of an external control group in Study 301

The use of a historical control group is adequately justified and support the validity of Study 301. For rare diseases, it may not be feasible to have access to a sufficiently large control group, including for ethical reasons. Biases may be introduced through this but can be sufficiently minimised.

The natural history of the disease was adequately investigated in Study 101. With regard to baseline characteristics, the two groups were reasonably balanced, and both studies had similar inclusion/exclusion criteria. The small differences in baseline characteristics seen in Study 301 are not dissimilar to minor differences experienced by trials with a contemporaneous control group. With regard to standard of care treatment received additionally to Sohonos, it can be reasonably assumed that this would have been reasonably consistent in Studies 301 and 101.

39 patients in Study 301 had participated in Study 101 previously, and essentially were their own control, but in a different age range. With regard to endpoints/endpoint variables, Studies

301 and 101 had been sufficiently similar. The reading method of the WBCT scans was sufficiently robust with blinded readings, and acceptable inter-rater and intra-rater-reliability.

However, in Study 301, WBCT scan were conducted at Months 6, 12, 18, and 24 while in Study 001 at Months 12, 24, and 36 (or study termination). To investigate this, the sponsor conducted sensitivity analysis to assess a potential impact of the differences in length of follow-up (e.g., results at Month 12, additional covariates, and a propensity score derived from a logistic regression model using the additional covariates).

Clinical trial post hoc analyses

The sponsor's favourable primary analysis in Study 301 relies on a *post hoc* wLME analysis rather than a Bayesian compound Poisson model with a square root transformation of HO volume per region and negative new HO values being set to zero (either by body region; or overall). The changes are described in section 2.4.2.1.

Post hoc changes are not ideal, but in this case, the provided *post hoc* analysis is considered acceptable. It was adequately justified by the sponsor. The wLME analysis could be considered as the original prespecified analysis, as it was the analysis in the original protocol. Its simpler approach without transformation and inclusion of negative values was a more appropriate analysis. Additionally, Wilcoxon rank-sum tests were performed (dependent only on the numeric rank order of the observed new HO volumes rather than their magnitudes) which are less influenced by extreme values.

Efficacy

Study 301 (MOVE) was the pivotal phase 3 trial, and instrumental to this application.

Treatment of acute flare-ups

In Study 201, at Week 12, the proportion of patients with any new HO was lower in the PVO 10/5 mg group (15%) compared to PVO 5/2.5 mg (44%) or placebo (40%). The was not statistically significant for either treatment group, but a favourable trend could be observed.

In Study 202 Part A, there was an increase in mean volume in new HO for flare-ups with new HO, from 5,204 mm^3 (Week 6) to 7,506 mm^3 (Week 12) and likely reflects the end of treatment after 6 weeks. This indicated that a higher dose than the used PVO 10/5 mg regimen and for a longer period of time may be more efficacious.

Efficacy of the proposed chronic/flare-up regimen

In Study 202 Part B, the proportions of flare-ups with no new HO were (at Week 12): PVO 10/5 mg: 35.7%; PVO 20/10 mg: 41.2%; Chronic/PVO 20/10 mg: 20.6%; Combined PVO 20/10 mg: 27.5%. This provided some support for an additional chronic dosing regimen. In Part B/C, the mean volume of new HO (for flare-ups with new HO) was 9,134 mm^3 (PVO 20/10 mg), 30,934 mm^3 (chronic/PVO 20/10 mg), and 21,025 mm^3 (combined PVO 20/10 mg) at Week 12. It has been postulated the increased HO volume may be due to oedema associated with flare-ups.

In Study 301, in the total study population, the primary analysis showed a 60.3% reduction in the mean annualised new HO volume of palovarotene-treated (9427.1 mm^3) vs. untreated (23720.2 mm^3) patients. The primary analysis using wLME, showed a 53.8% reduction in the LSM annualised new HO volume of palovarotene-treated (9366.8 mm^3) vs. untreated (20273.0 mm^3) patients (wLME treatment p=0.0392; Wilcoxon rank-sum p=0.0003) (Principal FAS).

In the target population of patients aged ≥8y/10y (female/male) (i.e., the subgroup for which the FOP indication is sought by the sponsor), the primary analysis showed a 55.7% reduction in the mean annualised new HO volume of palovarotene-treated (11418.8 mm^3) vs. untreated

(25796.0 mm^3) patients. The primary analysis using wLME, showed a 48.6% reduction in the LSM annualised new HO volume of palovarotene-treated (11033.2 mm^3) vs. untreated (21476.0 mm^3) patients (wLME treatment p=0.1124; Wilcoxon rank-sum p=0.0107) (Principal FAS).

Overall, these are clinically meaningful reductions of new HO in a relevant population. Study 301 (MOVE) used the same dosing regimen as proposed for this application. Population PK data have supported this dosing, including the weight-based dose adjustment.

There were no statistically significant differences in functional or patient reported outcomes (FOP-PFQ, PROMIS, or CAJIS scores) or range of motion at flare-up locations.

Potential issues with regard to efficacy are outlined below.

Efficacy in certain subgroups

Notable subgroup analyses include the following:

- Female patients: The primary analysis showed a 25.8% reduction in the mean annualised new HO volume of palovarotene-treated (10617.5 mm^3) vs. untreated (14317.1 mm^3) patients. The primary analysis using wLME, showed a 11.3% increase in the LSM annualised new HO volume of palovarotene-treated (10105.9 mm^3) vs. untreated (9078.0 mm^3) patients (wLME treatment p=0.8740; Wilcoxon rank-sum p=0.0211) (Principal FAS).
- Asian patients: The primary analysis showed a 259.5% increase in the mean annualised new HO volume of palovarotene-treated (5885.1 mm^3) vs. untreated (1636.8 mm^3) patients. The primary analysis using wLME, showed a 280.3% increase in the LSM annualised new HO volume of palovarotene-treated (8960.0 mm^3) vs. untreated (2355.8 mm^3) patients (wLME treatment p=0.6309; Wilcoxon rank-sum p=0.8125) (Principal FAS). It is noted that the untreated HO values were significantly lower than for other subgroups and even though a large relative increase is shown, the absolute increase is low.

More information is requested from the sponsor on the potential implications on efficacy in certain subgroups.

Flare up triggers

Comparing Studies 301 and 101, the baseline mean number of flare-ups (in the last 12 months) was 1.4 vs. 2.5. Study 301 collected flare-up data as part of the secondary endpoints. Proportion of subjects reporting flare-ups at Month 12 was 64.4% vs. 54.1%. Flare-up rate per subject-month exposure is shown in Table 29.

Table 29. Study 301. Flare-up rate per subject-month exposure (through Month 24).

		MOVE Trial/Palovarotene (N=99) n(%)	NHS/Untreated (N=111) n(%)
Subgroup: Overall			
Rate of flare-up per subject-month exposure	95% CI	0.13 (0.09, 0.17)	0.07 (0.05, 0.08)
Ratio (palovarotene / untreated)		1.88	
Negative binomial p-value		p=0.0010	
Subgroup: Male			
Rate of flare-up per subject-month exposure	95% CI	0.17 (0.12, 0.24)	0.07 (0.05, 0.09)
Ratio (palovarotene / untreated)		2.63	
Negative binomial p-value		p=<.0001	
Subgroup: Female			
Rate of flare-up per subject-month exposure	95% CI	0.08 (0.05, 0.11)	0.07 (0.05, 0.09)
Ratio (palovarotene / untreated)		1.10	
Negative binomial p-value		p=0.6724	
Subgroup: Asian			
Rate of flare-up per subject-month exposure	95% CI	0.06 (0.04, 0.10)	0.09 (0.05, 0.15)
Ratio (palovarotene / untreated)		0.73	
Negative binomial p-value		p=0.2529	

It appears that the flare-up rate was greater in the treated group compared to the historical control. It is unclear whether this is associated with palovarotene treatment.

69/99 patients had at least one flare-up treated with palovarotene; they experienced a median of 3 flare-ups overall (range: 1, 23; mean: 4.0 ± 4.2). Dose reductions occurred during high-dose flare-up treatment in 31 (44.9%) patients compared to 8 (11.6%) patients during low-dose flare-up treatment.

Safety

The safety profile has been outlined in section 2.4.3. There are known class effects of retinoids, including palovarotene. These include teratogenicity, PPC, reduced bone mineral density, osteoporosis, arthralgia, and myositis.

Initially, in Study 301, patients aged 4 years or older were eligible to participate. However, after the emergence of a high incidence of premature physeal closure (PPC), a partial clinical hold was implemented for patients under the age of 14 years. At the time of this report, the partial clinical hold remained in place for subjects <14 years of age.

Overall, there were no deaths related to treatment. In Study 301, a 13-year-old patient with a history of restrictive lung disease died 2.5 months after discontinuing palovarotene treatment. The cause of death was restrictive lung disease from complications of FOP.

The most common TEAEs (≥10% of subjects) included mucocutaneous AEs (e.g., dry skin, dry lips, alopecia, pruritis, and erythema), or musculoskeletal AEs (e.g., arthralgia and extremity pain). Some mucocutaneous AEs (e.g., alopecia, skin exfoliation, and pruritis) were more frequent during the 20/10 mg flare-up treatment (41% vs 8% for chronic dosing) and may be dose-dependent requiring dose reductions.

Bone safety (including premature physeal closure)

A retrospective analysis of WBCT scans in Study 301 and the NHS showed greater decreases in vertebral bone strength, bone mineral content (BMC), bone mineral density (BMD) and an increased risk of vertebral fractures in palovarotene-treated subjects compared with untreated subjects.

Premature physeal closure (PPC) is a known risk with retinoid treatment in growing patients. All PPC events were categorised as SAEs. PPC occurred in 23.5% (24/102) of subjects aged <18

years and was more common in younger patients: Age <8/10 years: 56.0% (14/25); Age ≥8/10 to <14 years: 25.6% (10/39); Age ≥8/10 to <18 years: 13.0% (10/77). PPC primarily occurred during exposure to both the chronic and flare-up treatment regimens, but also in 5 patients on chronic dosing only.

This is an important identified risk in the RMP. Monitoring with imaging (including a baseline assessment) is required to mitigate the risk. The sponsor is currently proposing additional risk minimisation activities including educational materials for HCPs and patients. The proposed PI contains a boxed warning with regard to PPC and teratogenicity.

At this stage, the proposed PI contains no specified frequency for the imaging to monitor for PPC.

Teratogenicity

The teratogenicity of systemic retinoids is well established. Classic retinoid type malformations (e.g., cleft palate, misshapen skull bones, short long bones) were demonstrated with palovarotene in rats at doses yielding exposure well below that in patients. The findings justify assignment to Pregnancy Category X, and a contraindication in women who are pregnant or may become pregnant.

Appropriate risk minimisation activities are required. At this stage, the sponsor is not proposing a strict pregnancy prevention program, but prescriber and patient education, and enhanced labelling in the PI.

Translation to clinical practice

Based on the clinical data presented, palovarotene appears to be efficacious for chronic use, flare-up use, and also to reduce or prevent catastrophic HO.

The age group 8 years and older for females and 10 years and older for males to 18 years of age appears to benefit most from palovarotene, even though simultaneously is at the greatest risk for PPC.

Some subgroups may benefit to a lesser extent from palovarotene, but it can be a useful tool in the armamentarium against FOP. Monitoring for effectiveness and safety issues is essential.

Based on the evidence available, it would not be unreasonable to register Sohonos for a FOP indication, as long as appropriate conditions are in place to maintain a positive benefit-risk balance. These conditions include: an appropriate indication, appropriate risk minimisation activities, and appropriate reporting of the remaining clinical study data.

Given the complexities, appropriate risk minimisation activities may take the form of specialist use restriction, and prescriber education and training. It is desirable that only clinicians experienced in the treatment of FOP in conjunction with best practice guidelines would use palovarotene for treatment after a careful, individual benefit-risk assessment.

Questions for the sponsor

The sponsor provided the following response to the question from the Delegate.

1. ***Noting that subgroup analyses are typically not sufficiently powered and may not produce meaningful results, the following subgroup analyses in Study 301 (MOVE trial) appear notable:***

   – ***Female patients: The primary analysis showed a 25.8% reduction in the mean annualised new HO volume of palovarotene-treated (10617.5 mm^3) vs. untreated (14317.1 mm^3) patients. The primary analysis using wLME, showed a 11.3% increase in the LSM annualised new HO volume of palovarotene-treated (10105.9***

mm3) vs. untreated (9078.0 mm3) patients (wLME treatment p=0.8740; Wilcoxon rank-sum p=0.0211) (Principal FAS).

- ***Asian patients: The primary analysis showed a 259.5% increase in the mean annualised new HO volume of palovarotene-treated (5885.1 mm3) vs. untreated (1636.8 mm3) patients. The primary analysis using wLME, showed a 280.3% increase in the LSM annualised new HO volume of palovarotene-treated (8960.0 mm3) vs. untreated (2355.8 mm3) patients (wLME treatment p=0.6309; Wilcoxon rank-sum p=0.8125) (Principal FAS).***

The sponsor should comment on these results, in particular with regard to efficacy of palovarotene in those subgroups. Are there other factors (e.g., disease or demographic factors) that may have contributed to these results specifically?

Gender subgroup analysis

To illustrate the difference in HO volume between male and female patients Table 30 summarises the annualised new HO volume by gender in treated and untreated patients.

Table 30: Annualised New HO Volume by gender Study PVO-1A-301 and NHS

	Palovarotene N = 97		Untreated N = 101		
	n	mm^3	n	mm^3	Percent Reduction (palovarotene vs untreated)
Males	51	8,353	56	31,276	73%
Females	46	10,618	45	14,317	26%

The potential reasons for these results include the fact that untreated females formed 54% less new HO compared with untreated male patients. It has been established in the NHS that adolescent patients have the greatest increases in total HO volume, which decreased in adulthood. As such the differences observed could be due to differences in mean age of untreated female patients (18.7 years) compared with untreated male patients (16.5 years). Additionally, treated females were even younger (13.6 years) compared with untreated females (18.7 years) and thus more likely to form HO. There was minimal difference in HO formation between treated male and female patients.

The Wilcoxon rank-sum test, which depends only on the numeric rank order of the observed volumes of new HO and is thus less influenced by extreme values, yields evidence of a difference in annualised new HO volume between palovarotene-treated- female subjects and untreated female subjects (nominal p=0.0211). This is also supported when looking at median annualised new HO where in treated patients it was 66 mm3 and in untreated patients it was 3992 mm3.

Given what is known about FOP, and the mechanism of action of palovarotene in preventing new HO, it is unlikely that these apparent differences in mean new HO reflect a true differential response to palovarotene based on sex.

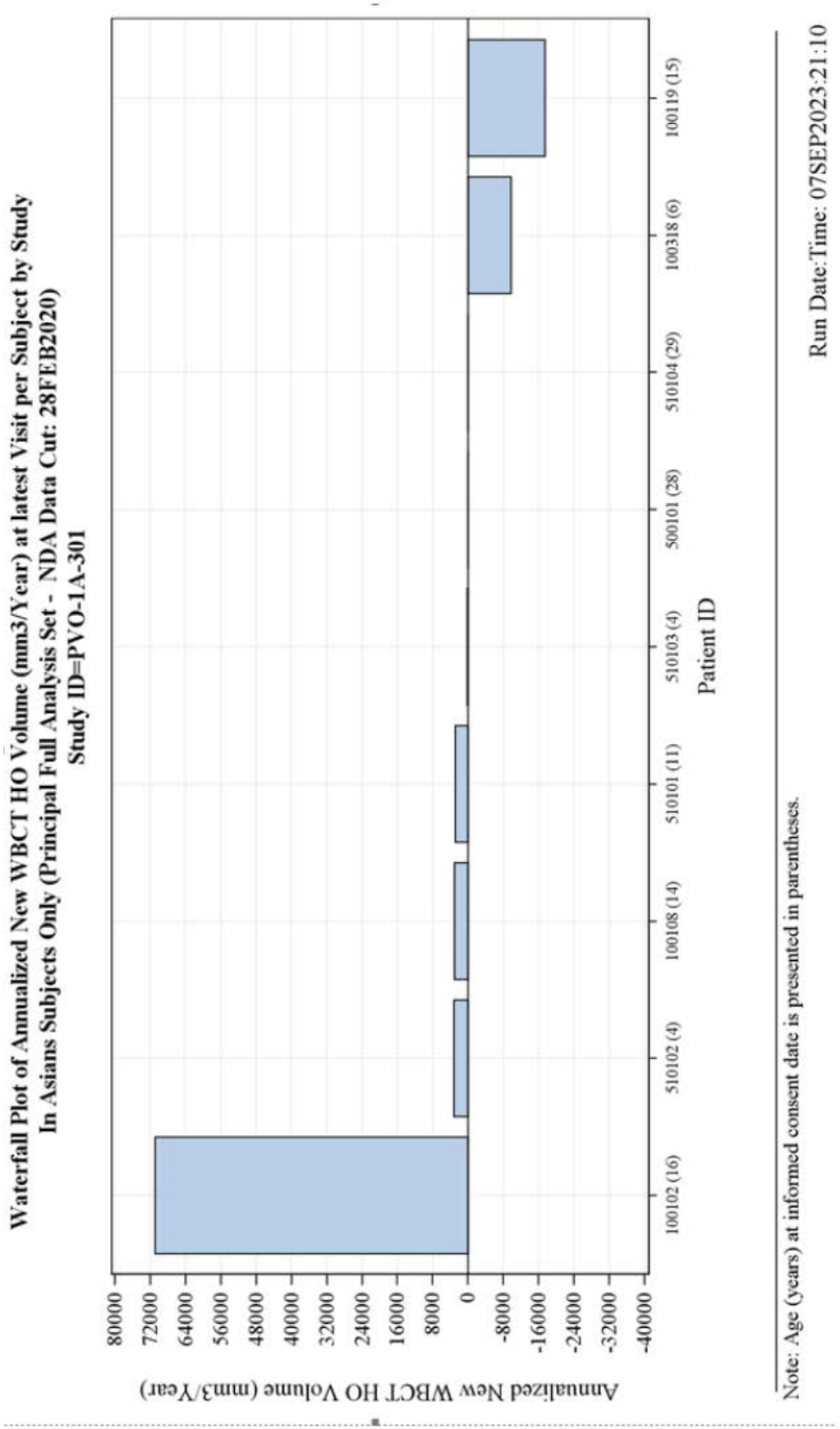
Asian subgroup analysis

There are nine treated patients and eight untreated patients in the Asian subgroup analysis. The mean annualised new HO volume in treated compared with untreated patients was 5885 mm3 and 1637 mm3 respectively while the median was 164 mm3 and 1657 mm3 respectively. Given such a small number of patients, means are highly influenced by outliers. The waterfall plot (Figure 3: Waterfall plot Asian Subjects in PVO-1A301 and NHS) demonstrates that one treated

patient formed a large amount of HO. It is important to note that this patient had experienced a flare-up that was not treated, which may account for this result.

Additionally, this sub-group for both treated and untreated patients formed relatively smaller volumes of HO compared with the total population (9427 mm3 and 23720 mm3 respectively), making it challenging to interpret any differences. In conclusion, given that this is a small subset of the total population with one patient who was undertreated driving the mean, this observation is likely spurious as opposed to a differential effect of palovarotene based on race. Additionally, given the high variability in HO formation in this small subset, median values of HO volume may be better suited for comparison, which were lower in treated compared with untreated patients.

Figure 3: Waterfall plot Asian Subjects in PVO-1A301 and NHS



Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. ***Sufficient data for registration: Can the ACM comment on whether the provided data are sufficient to support registration for the proposed indication?***

The ACM was of the view that the provided data are sufficient to support registration for the proposed indication noting that FOP is a rare life limiting condition.

The ACM agreed the clinical trial program is appropriate to address a rare condition. The ACM noted that the trials included 219 patients, of whom 164 received at least 1 dose of palovarotene. Given that there are appropriately 800 cases of FOP globally, the ACM was of the view there was a sufficient number of patients to assess efficacy and safety in this rare condition. The ACM also noted that the trial program included chronic and flare regimens and included patients across the age spectrum and phases of the condition.

The ACM also commented that the mechanism of action for palovarotene is biologically plausible and the clinical trials sufficiently demonstrated a reduction in new bone growth.

2. ***Monitoring for effectiveness and safety: Assuming Sohonos were registered for the sponsor-proposed or a similar indication, can the ACM comment on the need to monitor for effectiveness (e.g., for disease progression) and safety (e.g., for PPC, or vertebral fractures)?***

The ACM advised that patients with FOP would be treated by specialist physicians familiar with this condition and they would likely have specialist visits appropriately every 3 months.

The ACM discussed the use of radiological evaluation for HO and PPC and was of the view that it would be used when considered appropriate (i.e. symptoms present) rather than routinely, as cumulative WBCT and X-ray exposure risks need to be considered.

The ACM recommended clinical outcome monitoring at least every 12 months including new HO (number and sites), flare-ups, cumulative analogue joint involvement scale (CAJIS) and FOP physical function questionnaire (PFQ) assessments.

From a safety perspective the ACM noted the importance of monitoring and recording growth parameters and assessing for spinal abnormalities until the end of puberty. The ACM also highlighted the importance of (at least) yearly documented discussions about contraception for females of childbearing age.

3. ***Risk minimisation activities: Assuming Sohonos were registered for the sponsor-proposed or a similar indication, can the ACM comment on the need for specific risk minimisation activities (e.g., prescriber restriction and education, or a specific pregnancy prevention program)?***

On balance, the ACM agreed that a prescriber restriction in the PI would be appropriate and suggested the following wording:

> *prescription of Sohonos is restricted to paediatricians, endocrinologists, rheumatologists and other specialist medical practitioners with expertise in managing metabolic bone disease.*

The ACM noted the importance of equitable access, particularly for rural and remote areas however agreed that these patients would be under the care of a specialist who would work in partnership with the GP.

The ACM was also supportive of targeted education to relevant prescribers.

The ACM acknowledged the importance of pregnancy prevention however did not consider a specific pregnancy prevention program was warranted. Rather, the ACM reiterated the importance of regular documented discussions about pregnancy and contraception with relevant patients.

4. ***General: The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.***

The ACM noted that patients with this condition have no effective treatment for this extremely debilitating, life limiting disorder, resulting in a risk benefit profile that supports use, with an appropriate RMP and prescriber and patient education.

The ACM agreed that the age restriction within the indication wording is appropriate (children aged 8 years and above for females and 10 years and above for males), noting that younger children have significantly increased rates of PPC that make the risk benefit of this drug unclear.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Sohonos is indicated to reduce the formation of heterotopic ossification in adults and children aged 8 years and above for females and 10 years and above for males with fibrodysplasia ossificans progressiva (FOP).*

Outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Sohonos (palovarotene) 1 mg, 1.5 mg, 2.5 mg, 5 mg, 10 mg, hard capsule, blister pack, indicated for:

> *Sohonos is indicated to reduce the formation of heterotopic ossification in adults and children aged 8 years and above for females and 10 years and above for males with fibrodysplasia ossificans progressiva (FOP).*

Specific conditions of registration applying to these goods

Sohonos (palovarotene) is to be included in the Black Triangle Scheme. The PI and CMI for Sohonos must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

The Sohonos EU-Risk Management Plan (RMP) (version 5.0, dated 7 April 2023, data lock point 27 April 2022), with Australian Specific Annex (version 3.0 dated 25 July 2023), included with submission PM-2022-03518-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs). Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually

from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Attachment 1. Product Information

The Product Information (PI) approved with the submission for Sohonos which is described in this AusPAR can be found as Attachment 1. It may have been superseded. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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