25 May 2023
EMA/267060/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sohonos

International non-proprietary name: palovarotene

Procedure No. EMEA/H/C/004867/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Expanded form
ACVR1	Activin receptor type IA
ALK2	Activin-receptor like kinase 2
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANCOVA	Analysis of covariance
AUC	Area under the concentration versus time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero to infinity
$AUC_{0-\tau}$	Area under the concentration-time curve during a dosage interval (τ) at steady state
AUC_{0-24}	Area under the concentration-time curve from time zero to hour 24
AE	Adverse event
BCa	Bias-corrected and accelerated bootstrap analysis
BCS	Biopharmaceutics classification system
BCRP	Breast cancer resistance protein
BMD	Bone mineral density
BMP	Bone morphogenetic protein
C_{max}	Peak (maximum) plasma concentration of the drug
$C_{max,ss}$	Peak (maximum) plasma concentration of the drug at steady-state
CAJIS	Cumulative analogue joint involvement scale
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
CMC	Chemistry, manufacturing, and controls
CPP	Critical process parameter
CI	Confidence interval
COX-2	Cyclooxygenase-2
CV%	Percent coefficient of variation
CL/F	Apparent clearance of drug from plasma after extravascular administration
COPD	Chronic obstructive pulmonary disease
C-SSRS	Columbia-suicide severity rating scale
CSR	Clinical study report
CYP	Cytochrome P450 enzymes
DDI	Drug-drug interaction
DMC	Data monitoring committee
DoE	Design of experiments
DS	Design Space
ECG	Electrocardiogram
EU	European union
F	Absolute bioavailability
FAS	Full analysis set
FDA	Food and Drug Administration
FOCBP	Females of childbearing potential
FOP	Fibrodysplasia ossificans progressiva
FOP-PFQ	Fop-physical function questionnaire
FT-IR	Fourrier transform infrared spectroscopy

Abbreviation	Expanded form
GEE	Generalized estimating equation
GC	Gas chromatography
GCP	Good clinical practice
GeoMean	Geometric mean
GMP	Good manufacturing practice
HED	Human equivalent dose
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
HO	Heterotopic ossification
HV	Healthy volunteers
IA2	Second interim analysis
IA3	Third interim analysis
IC50	Concentration of drug producing 50% inhibition
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IF-FAS	Imaged Flare-up FAS
IND	Investigational new drug (application)
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
JP	Japanese pharmacopoeia
LCMS	Liquid chromatography mass spectrometry
LDPE	Low density polyethylene
MAD	Multiple ascending dose
MEDdra	Medical Dictionary for Regulatory Activities
MO	Multiple osteochondromas
MS	Mass spectrometry
NDA	New drug application
NHS	Natural history study
NMP	N-methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
NSAID	Non-steroidal anti-inflammatory drug
λz	Apparent terminal-phase disposition rate constant (first-order)
OAT	Organic anion transporting polypeptide
OCT1	Organic cation transporter
PBO	Placebo
PCS	Potentially clinically significant
PCTFE	Polychlorotrifluoroethylene
PDE	Permitted Daily Exposure
pH	Negative of the logarithm of the hydronium ion activity
Ph. Eur.	European pharmacopoeia
PK	Pharmacokinetic(s)
PPC	Premature physeal closure
PROMIS	Patient reported outcomes measurement information system
PSS	Principal safety set
pVBA	Poly (4-vinylbenzoic acid)
PVO	Palovarotene

Abbreviation	Expanded form
PVC	Polyvinyl chloride
QbD	Quality by design
RAR	Retinoic acid receptor
RARα	Retinoic acid receptor alpha
RARβ	Retinoic acid receptor beta
RARγ	Retinoic acid receptor gamma
RH	Relative humidity
ROM	Range of motion
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLS	Sodium lauryl sulfate
Smad	Phosphorylated signal transduction protein
SMQ	Standardized meddra query(ies)
SmPC	Summary of Product Characteristics
$T_{½}$	Apparent terminal elimination half-life
t_{max}	Time of maximum observed plasma concentration
τ	Dosage interval
TAMC	Total aerobic microbial count
TEA	Triethylamine
TEAE	Treatment-emergent adverse event
TSE	Transmissible spongiform encephalopathy
TTC	Threshold of toxicological concern
TYMC	Total combined yeasts/moulds count
UGT	Uridine 5'-diphosphoglucuronosyltransferases
ULN	Upper limit of normal
US	United states
USP	United states pharmacopoeia
USP/NF	United states pharmacopoeia/national formulary
UV	Ultraviolet
WBCT	Whole body computed tomography
wLME	Weighted linear mixed effects
XR(P)D	X-ray (powder) diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Ipsen Pharma submitted on 15 April 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Sohonos, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 June 2017.

Sohonos was designated as an orphan medicinal product EU/3/14/1368 on 19 November 2014 in the following condition: treatment of fibrodysplasia ossificans progressiva.

The applicant applied for the following indication: Sohonos is indicated for the prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia (myositis) ossificans progressiva (FOP).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0441/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0441/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance palovarotene contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a

medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference
20 July 2017	EMEA/H/SA/3590/1/2017/PA/II

The Protocol assistance pertained to the following clinical aspects:

- Acceptability of the primary endpoint, the external control group, the inclusion criteria, the dosing scheme, the statistical plan,
- Sufficiency of the safety program.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Martina Weise

The application was received by the EMA on	15 April 2021
The procedure started on	20 May 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 August 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	20 August 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	16 September 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	1 June 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	24 August 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	1 September 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	15 September 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 November 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues	30 November 2022

to all CHMP and PRAC members on	
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	13 December 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Sohonos on	26 January 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	26 January 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare, severely disabling disease characterised by painful, recurrent episodes of soft tissue swelling (flare-ups) and abnormal bone formation in muscles, tendons, and ligaments.

The applied indication is for the prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia (myositis) ossificans progressiva (FOP).

2.1.2. Epidemiology

It is estimated that FOP affects about 3,500 people worldwide but there are only approximately 800 confirmed cases of FOP globally. The prevalence is estimated at approximately 1.36 per million individuals, with no geographic, ethnic, racial, or sex preference.

2.1.3. Aetiology and pathogenesis

Fibrodysplasia ossificans progressiva is caused by mutation in the ACVR1/ALK2 gene. This mutation aberrantly activates the BMP-mothers against decapentaplegic homolog (Smad)1/5/8 signalling pathway, diverting normal connective tissue (muscle, tendons, and ligaments) injury repair mechanisms away from tissue regeneration by promoting chondrogenesis and extra-skeletal bone formation, heterotopic ossification (HO). In FOP, HO presents as a catabolic phase of inflammation and tissue destruction followed by an anabolic phase of tissue formation ultimately leading to HO.

2.1.4. Clinical presentation, diagnosis and prognosis

The first appearance of HO has median onset at 6 years of age. A flare-up occurs when the body starts to generate new bone which leads to tissue swelling and discomfort. The result of the recurrent episodes of HO is cumulative immobility, with patients becoming wheelchair-bound or bedridden by the third decade of life. Life-threatening complications include 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. Thoracic insufficiency commonly causes complications such as pneumonia and right-sided heart failure, leading to markedly shortened survival (Kaplan-Meier median survival is 56 years).

2.1.5. Management

Currently, there are no effective medical treatment options to prevent flare-ups, HO, or disease progression in FOP. Surgical resection of heterotopic bone is not recommended as it can exacerbate flare-ups and further HO formation. 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. Long term use of corticosteroids is associated with serious risks and no clear benefit in terms of limiting HO or FOP progression has been established. Chronic pain management in FOP addresses both neuropathic and nociceptive components: Oral or topical acetaminophen, NSAIDs) in combination with a proton pump inhibitor, cyclooxygenase-2 (COX-2) inhibitors, muscle relaxants, opioids, gabapentin, pregabalin, or tricyclic antidepressants.

Presently there are also a number of 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.

In conclusion, standard of care for FOP is restricted to the use of treatments that may provide some symptomatic relief. There is a clear unmet medical need for effective therapies in FOP.

2.2. About the product

Palovarotene is an orally bioavailable retinoic acid receptor gamma (RARγ) agonist. RARγ are 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. Available preclinical evidence indicates that palovarotene reduces mast cell infiltration and fibroproliferative response at the site of muscle injury. Palovarotene also inhibits chondrogenesis by decreasing Smad signaling, diverting mesenchymal progenitor cells to a soft tissue fate, and allowing for normal tissue repair.

The ATC code is M09AX11 (DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM).

The applicant initially applied for the following indications and posology:

Indication:

- Sohonos is indicated for the prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia (myositis) ossificans progressiva (FOP).

Posology (please see SmPC for full text):

- The recommended dosing consists of 5 mg palovarotene once daily (chronic treatment), with an increase in dose at the time of a flare-up to 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks for a total of 12 weeks (20/10 mg flare-up treatment) even if symptoms resolve earlier.

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.

Sohonos dosing is weight-adjusted in patients under 14 years of age.

During the assessment, the applicant amended their indication claim to "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)" and proposed a weight-adjusted based posology in all patients.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as hard capsules containing 1 mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg of palovarotene as active substance.

Other ingredients are:

Capsule content: lactose monohydrate, povidone, croscarmellose sodium, sodium laurilsulfate, microcrystalline cellulose, magnesium stearate;

Capsule shell: gelatin, titanium dioxide (E 171);

Printing ink: shellac (E 904), propylene glycol (E 1520), potassium hydroxide (E 525) and black iron oxide (E 172).

The product is available in perforated unit-dose blister strips composed of PVC/PCTFE (polyvinylchloride/poly-chloro-tri-fluoro-ethylene) backed with push-through aluminium foil containing 28 capsules in a carton providing protection from light as described in section 6.5 of the SmPC.

2.3.2. Active Substance

2.3.2.1. General information

The chemical name of palovarotene is 4-[(*E*)-2(5,5,8,8-Tetramethyl-3-pyrazol-1-ylmethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-vinyl]-benzoic acid corresponding to the molecular formula $C_{27}H_{30}N_2O_2$. It has a relative molecular mass of 414.54 and the following structure:

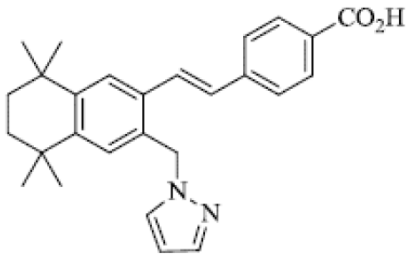


Figure 1: active substance structure

Palovarotene has a non-chiral molecular structure.

The chemical structure of palovarotene has been established using a combination of nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS) and X-ray powder diffraction with

confirmatory data from elemental analysis, Fourier transform infrared (FT-IR) spectroscopy and ultraviolet (UV) spectroscopy. The methods used for elucidation of the structure of the active substance are adequate.

The solid-state form of palovarotene was established as an anhydrous crystal form. Only this form has been observed in all active substance clinical batches manufactured to date. Several studies have been performed to evaluate the properties and stability of the polymorphic form, such as recrystallization from different solvents, preparation of suspensions in various vehicles and analyses following micronisation, microfluidization, and exposure to ICH Q1B light stressed conditions. The manufacturing process has consistently produced a single crystal polymorph which has been demonstrated to be stable in formulated product, under processing conditions and under stress conditions.

The active substance is a white to off-white, not hygroscopic crystalline solid. It is practically insoluble or insoluble in water and in aqueous buffers, slightly soluble in ethanol. As described below, the active substance is micronised and the particle size is controlled in the active substance specification.

2.3.2.2. Manufacture, characterisation and process controls

The active substance is synthesised in three stages.

This route of synthesis was employed for all active substance batches used in the clinical trials including the registration batches.

The proposed starting materials are sourced from qualified suppliers either through custom synthesis or from commercial source. Characterisation of the proposed starting materials has been made using relevant spectroscopic methods. Full addresses of the suppliers are presented as well as synthetic schemes, specifications and batch data. In the first round of assessment, a major objection was raised regarding the two proposed starting materials which were not considered acceptable, and their redefinition was requested. The main reason was concerns regarding potential regioisomeric impurities originating from the synthesis of these two compounds. In response, the applicant proposed a two step approach, addressing the concerns with respect to regioisomeric impurities during the evaluation procedure and implementing the redefinition of starting materials via a post-approval variation application. This approach was supported in principle from a quality point of view, however, the acceptability of a post-approval commitment/variation strategy was dependant on the overall benefit/risk of Sohonos. Since the overall benefit/risk is deemed negative the major objection is unresolved (as it is not possible to define a post-approval commitment for a non-approved product).

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
Specifications for solvents and reagents used in the manufacture of palovarotene are considered acceptable. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The process development including critical steps has been described and discussed in sufficient detail and applied process controls are deemed adequate. Elements of enhanced (multi-variate) DoE studies in combination with traditional (single-variate) studies were applied in the Quality risk assessment for several stages of the palovarotene active substance synthesis. However, the manufacturing process development for palovarotene followed a traditional approach, and no design spaces were developed for the active substance manufacturing process, and hence none are applied for or accepted.

In summary, the manufacturing of the active substance is acceptably described with adequate in-process controls of critical steps. The active substance manufacturing process could be considered to be approvable if the starting materials are redefined as outlined above.

The active substance is packaged in double clear low-density polyethylene (LDPE) bags placed inside a high-density polyethylene (HDPE) drum to protect the active substance from light. The components comply with the EU requirements for contact with food, EU Regulation 10/2011. The information regarding the packaging materials for the active substance is acceptable.

2.3.2.3. Specification

The active substance specification includes tests for description, identification (FT-IR, HPLC), assay (HPLC), related substances (HPLC), residual solvents (GC), particle size distribution (laser diffraction), water content (Ph. Eur.), and residual reagent (colorimetric titration).

The control of the active substance is largely found adequate, but some issues remain to be addressed as described below.

Justifications of the proposed specifications and acceptance criteria have been provided. In response to issues raised, the assay limit has been tightened whereas the particle size limit is kept. The applicant is expected to tighten the limits when more experience is gained. The specifications are considered acceptable.

An extensive discussion on impurities has been provided and the information and proposed control strategy are mainly found adequate. A major objection was raised in the initial assessment with respect to genotoxic impurities evaluation. The TTC level originally used by the applicant for evaluation was considered not acceptably justified. In response, the applicant revalidated the analytical method for evaluation of genotoxic impurities at a lover TTC which was considered acceptable. However, the justification of the omission of testing for three impurities (reported as AMES positive/presumed AMES positive and considered in the initial genotoxic impurities´ evaluation) was still not considered sufficient. The reasoning presented by the applicant to address this Major Objection was not comprehensive. For example, reference is made to purging data where spiking has been made at an earlier step than the one where the impurities are actually controlled, and it is not clear how the purge factor used from stage 1 can be used in the calculation for stage 2. This needs to be explained and justified before it can be concluded that each of the impurities can be controlled to below 30% of the TTC-derived limit in the final active substance if they are present at their maximum permitted level in the intermediate. Hence, unless additional justification and clear explanation of the control strategy is provided by the applicant, tests with a justified limit at a suitable stage should be introduced (other concern).

The other impurities´ limits are generally set according to ICH Q3A. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by clinical studies and appropriate specifications have been set.

The limits set for residual solvents, which are based on ICH Q3C acceptable levels applying either Option 1 or 2 are considered acceptable (the use of Option 2 has been acceptably justified).

The omission of testing in the final active substance for elemental impurities (Class 1 and 2A), residue on ignition, solid state form (crystallinity) and microbiological aspects has been acceptably justified.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. The palovarotene reference standard used for qualitative and quantitative determinations is acceptably described. Additional information

regarding the standard used for analysis of one of the impurities was requested and provided by the applicant. The applicant should still provide an additional method to identify that impurity standard, for example by MS spectroscopy or other suitable method.

Batch analysis data on nine commercial scale batches of the active substance are provided. With a few exceptions/deviations the batch results submitted comply with the proposed specifications and are consistent from batch to batch. An unspecified impurity was found in the toxicology study batch above the current limit, but as it was not observed in subsequent batches, it was not considered for support of the proposed criterion for individual impurities. This is considered acceptable. In general, the batch analysis results provided confirm consistency and uniformity of the product.

2.3.2.4. Stability

Stability studies have been carried out and are ongoing according to ICH Q1A guidelines at the long-term condition of 25 °C/60% RH and at the accelerated condition of 40°C/75% RH. Data from one pilot and four commercial scale batches of palovarotene active substance representative of the manufacturing process and packaged in the intended container closure system has been provided. The ongoing stability studies will be continued for up to 36 months according to the stability protocol.

The stability samples were evaluated for description, assay, related substances, water content, polymorph and particle size distribution. With the exception of the laser diffraction method used for determination of the particle size for the pilot scale batch, the analytical methods used are the same as proposed for release.

Results from storage during 6 months at accelerated conditions and from long-term storage for 24 months (3 batches) and 36 months (2 batches) indicate adequate stability of palovarotene. Additional stability study data has also been provided for three validation batches now included in the stability program and for two of these up to 6 months data has been submitted.

All tested parameters were within the specifications. Only the selected crystalline ~~form~~ has been observed in the active substance which is confirmed by stability data to date.

In addition to the long term and accelerated stability program, the active substance was subjected to stress conditions (thermal, acid, base, oxidation and light) to confirm the suitability of the assay and purity methods to separate and quantify palovarotene and potential degradation products and to confirm that the methods are stability indicating. Data determining the susceptibility of palovarotene across a wide range of pH was also presented. Solutions with pH varying from 2 to 9 were analysed by HPLC after exposure to 60°C and 80°C for up to 7 months. The results showed that palovarotene is stable.

Forced degradation studies were performed exposing active substance in its solid form or in solutions or suspensions to stress conditions. There was no significant change in assay and related substances when exposed to thermal conditions. Neither did the assay change under basic treatment. A decrease in assay was observed under acid and oxidative stress.

Photostability studies following the ICH guideline Q1B were conducted in the solid state and in solution. Significant degradation was observed for all samples.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months for active substance stored in clear double low-density polyethylene bags and a drum providing light protection without any special temperature storage conditions.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The finished product is presented as opaque size 0 white hard capsules in five dosage strengths: 1mg, 1.5 mg, 2.5 mg, 5 mg and 10 mg. To differentiate the strengths, the capsule body is imprinted with black ink with the abbreviated name of the active ingredient (PVO) followed by the capsule dosage strength (e.g. "PVO 1" to identify the 1 mg capsule strength, "PVO 1.5" to identify the 1.5 mg capsule strength, etc.).

The capsules are packaged into a white blister backed with push-through aluminium foil. The blister is then packaged inside a carton. The secondary packaging is required for light protection.

No overage is applied.

The hard gelatin capsule is composed of the following excipients: titanium dioxide, USP/Ph.Eur./JP and gelatin, USP/Ph.Eur./JP. Titanium dioxide is used as an opacifier, and the gelatin is the structure forming component.

The imprinting ink is composed of shellac, NF/Ph.Eur, dehydrated alcohol, USP/Ph.Eur, isopropyl alcohol, USP/Ph.Eur., butyl alcohol, NF, propylene glycol, USP/Ph.Eur., purified water, USP/Ph.Eur., strong ammonia solution, NF/Ph.Eur., potassium hydroxide, NF/Ph.Eur. and black iron oxide, NF/JP.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, except iron oxide used in the ink for the printing of gelatin capsules, which complies with EU Regulation 231/2012/EC.

There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Palovarotene active substance is BCS class 2 drug with low solubility and high permeability and a surfactant is used in the finished product to improve wettability and thus the dissolution of palovarotene in aqueous media.

Palovarotene active substance has been shown to be compatible with the finished product excipients, through accelerated stability studies on binary mixtures with each excipient and on the finished product itself. The stability studies showed that there was no degradation of the palovarotene active ingredient for up to six months of storage at 40°C/75% RH

There are no reconstitution diluent(s) or dosage devices that are used for the palovarotene finished product; however, administration of palovarotene allows capsules to be opened and the contents sprinkled on soft food for patients that have a difficult time swallowing the capsule as a whole unit. As such, the compatibility/stability of the contents of the palovarotene capsules was assessed using various food matrices, namely applesauce, low-fat yogurt, low-fat chocolate pudding, warm oatmeal, warm rice cereal, chocolate milk, warm baby formula, and Boost Nutrition Chocolate Supplement. Samples were stored at room temperature (20-25°C) and under ambient light conditions for 1, 2, and 4 hours after which samples (3 for each food matrix) were removed and extracted for analysis. The results support the possibility to open the capsules for administration and empty the contents onto a teaspoon of soft food and taken within 1 hour of opening provided it was maintained at room temperature and not exposed to direct sunlight proposed in the SmPC.

Apart from food compatibility data on the capsule fill, no discussion and justification in relation to the paediatric use of the product was provided in the initial dossier. Acceptable information on the suitability of the dosage form, feasibility of opening the capsule and removal of the contents from the

capsule, handling instructions, and the possibility of administration through a feeding tube was requested and was provided in the applicant's response. The applicant confirmed there was no acceptability or taste-related issues with Sohonos noted in subject diaries for the completed study PV-1A-201 and ongoing PVO-1A-202, including the paediatric subjects enrolled. As the palovarotene concentration within capsules is very low, the dominant taste profile is that of lactose, the main component, which is very slightly sweet (i.e. nearly tasteless). The applicant committed to continue to monitor the acceptability and palatability of the dosage formulation throughout its clinical development program via subject dosing diaries.

Given the rarity of the use of feeding tubes in FOP patients, it is agreed that the SmPC and PIL do not require instructions of administration through such means.

The development of the proposed dissolution method for the control of the finished product is, as such, in general well described. The discriminatory properties of the dissolution method have been demonstrated by slightly altering the composition or manufacturing process of the capsules.

Dissolution data of nine batches used in the pivotal studies were provided following a Major Objection raised by the CHMP. The batches were tested using the previous dissolution method which was in place at the time of release. The available stability data for the pivotal batches, using the current method, are from different stability time points varying from 6 months to 60 months on. This made the like-for-like comparison between these batches difficult due to the difference in the age of the capsules. Therefore, similarity based on the dissolution profiles could only partly been confirmed. Nevertheless, it is considered sufficiently addressed by the applicant and is not further pursued.

Based on the additional data presented the applicant was requested to revise the acceptance criterion for the dissolution test (Major Objection).

A downward trend of dissolution had been noted at accelerated storage conditions. The root cause of this trend had been found to be cross-linking of the gelatin in the capsules. No impact on the *in vivo* performance of the product is postulated by the applicant.

Given the dissolution results under accelerated conditions (i.e. 40°C/ 75 %RH), the special storage condition "Do not store above 30°C" should be added to the product information (see stability section).

There have been no changes in the formulation of the capsule finished products during clinical development.

The batches used in the clinical studies comply with specifications applied at the time of testing.

Roche Pharmaceuticals was responsible for the initial development of palovarotene as a potential treatment for symptomatic emphysema and chronic obstructive pulmonary disease referred to in this submission primarily to support the safety, tolerability, and pharmacokinetics of palovarotene.

Roche used four palovarotene formulations during clinical development consisting of a hard gelatin capsule, a soft gelatin capsule, and a 1 mg film coated tablet. In addition to the proposed commercial hard capsule strengths also 2 mg, 3 mg and 4 mg hard capsules were used in the clinical program. A bioequivalence study comparing the 1 mg tablets and 0.5 mg soft capsules was conducted. Dissolution data in line with the requirements in the Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 has not been provided for 1 mg tablet and the 0.5 mg soft capsule obtained by Roche. As this concern early supporting batches from Roche this is acceptable.

No Quality by design (QbD) elements were applied during the development.

Palovarotene capsules were initially manufactured for use in Phase 2 clinical studies. The manufacturing process was subsequently transferred. The same formulation used for manufacture of the initial clinical batches for Phase 2 was transferred for the manufacture of the subsequent Phase 2

and Phase 3 clinical batches. A description is provided on the batch sizes and major process parameters and blender volumes. Differences in the manufacture of the clinical batches and the proposed commercial method are not considered critical.The risks identified in the initial risk assessment were investigated and critical process parameters and relevant in-process control strategy were established and implemented in the manufacture in relation to the outcome of these studies.

The primary packaging is perforated unit-dose blister strips composed of PVC/PCTFE (polyvinylchloride/poly-chloro-tri-fluoro-ethylene) backed with push-through aluminium foil placed in secondary carton providing additional light protection. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.3.3.2. Manufacture of the product and process controls

The manufacturing process is a granulation process. The granules are then mixed with excipients to obtain the final blend. Specified amounts of blends are used for manufacturing of the capsule strengths. The capsule dosage unit is then achieved by filling the blend into the size 0 elongated hard gelatine capsules. The manufacturing is a non-standard process due to the low concentration of palovarotene active substance.

Relevant process parameters are laid down in the process description including set points and ranges justified by pharmaceutical development. Relevant in-process controls are presented. The proposed sub-lots and batch ranges are justified in the pharmaceutical development section.

The bulk capsules are packaged at a different site from where the manufacture of the capsule is performed, bulk stability data of 6 months is provided. Intermediate holding times, packaging and transport arrangements are described. The bulk blend holding time of 4 months before encapsulation is acceptable. It has been confirmed that the start of shelf-life of the finished dosage form is set in line with requirements of Note for guidance CPMP/QWP/072/96.

The control of critical process steps and in-process controls are presented:

The overall control strategy, including process parameters and in-process controls are adequately set to control the process leading to consistent quality and are in line with the pharmaceutical development.

No Design Space (DS) is claimed.

Process validation / verification

Production scale process validation data has been provided for the original 8 strengths (1.0 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg and 10 mg). For the most critical blend, process validation data on 3 commercial blend batches have been presented. For the less critical blends, blend data on only 2 commercial blend batches have been presented. A total of 12 blend batches, and 25 capsule batches representative of the manufacturing process were evaluated. A risk-based approach has driven the choice of the number of commercial batches presented in relation to the different blends.

Generally, suitable data has been provided, though a few issues were raised on the rejection rate for one batch of more than 20% and individual capsule weights lower than the lower limit for the target weight for one batch. No verifiable root cause for the high rate of reject seen at the particular batch 3 mg was identified. Since data from three other 3 mg batches presented in section 3.2.P.3.5 showed acceptable results the question was not pursued further.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

2.3.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC-UV, in-house), assay (HPLC-UV, in-house), degradation products (HPLC-UV, in-house), content uniformity (HPLC-UV, in-house), dissolution (Ph. Eur.), water content (Ph. Eur.), microbial limits (TAYMC, TYMC, *E. coli*) (Ph. Eur.).

Relevant control parameters in relation to the dosage form are included in the specification.

The assay shelf-life limit was tightened as requested by the CHMP. This is in line with the limit for total degradation products in the finished product specification that has been tightened in a previous assessment round.

The limits for the identified impurity and for any unspecified impurity are in line with ICH Q3B (R2) and are thus qualified.

As discussed above the acceptance criterion proposed for the dissolution limit was revised as requested by CHMP.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The elemental impurities considered in the assessment included the Class 1 and 2A. Class 2B was also included in the evaluation as it is used in the production of the palovarotene active substance.

The components of the finished product evaluated included the active substance, the excipients, the capsule shells, and primary packaging components. Based on information from the individual component manufacturers regarding potential presence of elemental impurities, and the maximum daily intake of the finished product, the maximum intake of each element considered in the assessment was determined. The exposure to elemental impurities was determined to be below the threshold corresponding to 30% of the permissible daily exposure (PDE) for each element (the limit is based on maximum daily dose of 2.3 grams of finished product (4 x 5 mg capsules)).

The finished product manufacturing and packaging processes as it relates to potential contamination from equipment contact surfaces were evaluated.

It was concluded that elemental impurities contamination from all the components of the dosage form and the manufacturing and packaging processes is low to moderate. Confirmatory testing was conducted on three capsules strengths (2.5 mg, 5 mg and 10 mg) representing all blend strengths.

The results demonstrated that each elemental impurity is below the threshold corresponding to 30% of the permissible daily exposure (PDE). Based on these results no additional controls for elemental impurities is required for the finished product. The information on the control of elemental impurities is satisfactory.

To address a Major Objection from the CHMP, an updated risk assessment for the presence or formation of nitrosamines in the finished product was provided by the applicant. Risk evaluation considering the active substance and bulk capsule manufacturing and packaging processes; raw materials, excipients, process conditions, equipment, packaging components and equipment cleaning methods has been performed. The overall risk of nitrosamines was initially deemed to be "likely" for the finished product packaged in blisters due to nitrites in an excipient and amines in the formulation.

Hence, testing for potential nitrosamines was performed on finished product packaged in blisters using a validated analytical method (LC-MS/MS). No individual nitrosamine impurities were found above the limit of quantitation. Therefore, the applicant's conclusion that controls of nitrosamines or nitrosating agents is thus not required for the finished product or at any steps during manufacture of the active substance and capsules is justified.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Adequate information regarding the palovarotene reference standard has been provided. No other standards are applied in the control of the finished product.

Batch data has been provided for all batches used in the stability (12 batches) and pivotal clinical studies (19 batches) generated by Ipsen. Data provided comply with the specifications in force at release and confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.3.3.4. Stability of the product

Stability data from 12 batches of pilot and production scales batches of finished product made from all three bulk blends stored for up to 36 months under long term (25°C / 60% RH) and intermediate (30°C/75%RH) conditions and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of Sohonos are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance (including ease of opening and emptying the capsule and appearance of capsule fill), assay, degradation products, dissolution, water content and microbial limits testing (reduced frequency) and were analysed using the analytical methods described in section 3.2.P.5.2, except for dissolution method at early time points since there was a change in the dissolution method (see above). The analytical procedures used are stability indicating.

Additionally, certain capsule lots were assessed for ease of capsule opening and the emptying of the capsule contents as the product label allows patients who have difficulty swallowing to open the capsule and sprinkle the contents on various food matrices. The results showed that at all timepoints capsules were opened without difficulty and the contents easily removed.

None of the registration stability batches have shown any sign of degradation or other signs of instability at long term condition 25°C/ 60 % RH for up to 36 months. While an increase in water content was observed, it had no effect on any of the other stability test parameters.

At 30°C/75 % RH, a decrease of dissolution results over time was observed. An investigation was conducted showing this is due to cross-linking of the gelatin. Dissolution results were compliant up to the 36 months timepoint at 30°C/ 75 % for 5 out of the 12 stability batches, but all capsules strength and all batches were compliant for at least 12 months at 30°C/ 75 % RH. 30°C/75 % RH can be considered a worse case of the intermediate condition 30°C/ 65 % RH as per ICH guideline Q1A. Consequently, the dissolution fulfilled the acceptance criteria up to 12 months in the intermediate condition. No impact on the *in vivo* performance of the product is postulated by the applicant. This is supported by the enzyme pre-treatment dissolution test.

Decrease of dissolution results over time due to cross-linking was also observed at the accelerated conditions 40°C/ 75 % RH resulting in non-compliance observed at 6 months at 40°C/ 75 % RH.

As the newly proposed acceptance criterion is not met for all batches at the 6-month timepoint under accelerated conditions (i.e. 40°C/ 75 %RH), the applicant was requested to add the special storage condition "Do not store above 30°C" to the product information (other concern).

In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

An initial ICH Q1B photostability (Option 2) study on 10 mg capsules was conducted on bulk capsules, capsules packed in the commercial blister package and capsules wrapped in aluminium foil. Exposure to light of the bulk capsules showed an expected significant increase in degradation products, assay and dissolution. Exposure to light in the blister strip samples showed a relatively small increase and out of specification for individual degradation product. Total degradation products were also out of specification. Assay and dissolution were within specification.

A second photostability study was conducted with 10 mg capsules (using the commercial blister strips contained in the secondary packaging described in section 3.2.P.7 and blister strips in the secondary packaging wrapped in aluminium foil. The results with the blister strips placed inside the secondary packaging showed an acceptable result for appearance, assay, degradation products, dissolution, and water content with no light degradation product detected. Based on these results the secondary packaging is required to protect the capsules from light. The storage statement: 'keep blister strip in the outer carton in order to protect from light' is required in the product information.

A thermal cycling study on 10 mg capsules was conducted with three cycles with storage of 2 days each at -20°C and 25°C/60% RH. No effect was seen on the results.

A freeze/thaw study on one batch of palovarotene 1 mg capsules and one registration batch of 10 mg capsules packaged in the commercial blister material stored for 4, 8, and 12 weeks at -20°C was also conducted. At each time point samples were removed from storage, thawed, and tested. The results showed that storage at -20°C for up to 12 weeks did not affect any of the capsule stability parameters evaluated.

For the bulk capsule stability palovarotene 1 mg, 3 mg, and 10 mg capsules were packaged in a down-sized volume of the proposed bulk pack material of double PE bags in HDPE black drum and lid at 15.6-28.9°C, 45 ± 15% RH up to 6 months. The results showed no change in any stability test parameter through 6 months of storage.

A forced degradation study was performed in relation to the method validation with palovarotene 1 mg capsules or the blend which was obtained by emptying the contents of the 1 mg capsules. The 1 mg capsules used for this study are the same as the commercial finished product. Samples were exposed to heat/humidity, light, acid, base and oxidation . Light was the primary cause of degradation. Samples showed degradation upon exposure to light. Due to the sensitivity of the product to light, the specific storage statement proposed "Keep blister strip in the outer carton in order to protect from light." is acceptable.

Based on available stability data, the proposed shelf-life of 36 months with the proposed storage condition: 'keep the blister in the outer carton in order to protect from light', and the additional storage condition to be added to the product information requested by the CHMP "Do not store above 30°C" could be acceptable.

2.3.3.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the

1 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatin obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatin used in the manufacture is provided.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

The information regarding the palovarotene active substance and its development, manufacture, control and stability is generally adequate. The active substance is a crystalline solid with very low solubility and which is micronised in the last stage of manufacturing.

The manufacturing of the active substance is acceptably described with adequate in-process controls of critical steps, however several issues raised on quality aspects have not been resolved.

In the initial assessment, a major objection was raised regarding two of the proposed starting materials which were not considered acceptable. The main reason was a concern regarding potential regioisomeric impurities. In response to the major issue, the applicant suggested a two-step approach: 1. to address the concerns with respect to regioisomeric impurities during the ongoing procedure whereas 2. the redefinition of starting materials would be implemented via a post-approval variation application. While the concerns regarding regioisomeric impurities were mainly addressed, the major objection on redefinition of starting materials remains unresolved. The active substance manufacturing process could be considered to be approvable if the starting materials redefined in a future application.

An extensive discussion on impurities was provided and the information and proposed control strategy are mainly considered to be adequate. However, the justification of the omission of testing for three impurities is not comprehensive and tests with a justified limit at a suitable stage should be introduced, unless an additional justification and clear explanation of the control strategy is provided by the applicant.

The control of the active substance is adequate, with the exception of the impurities issue described directly above and another issue related to the need to include an additional method to identify one of the impurity standards for example by MS spectroscopy or other suitable method which also remains unresolved.

Stability studies have been carried out and are ongoing with a total of five palovarotene batches. Results provided indicate adequate stability of the substance. A retest period of 36 months for the active substance stored in clear double low-density polyethylene bags and a drum affording light protection without any special temperature storage conditions has been accepted.

The finished product is presented as hard gelatin capsules. In the early development multiple formulations were used; the Phase 3 clinical program was performed with the same formulation except for minor adjustments. Sufficient bridging data between the clinical and commercial formulation is presented.

The finished product contains an active substance with very low solubility and the dissolution is a critical quality attribute. Efforts have been made to present a discriminating analytical method for control of dissolution and the limit for the control has been acceptably justified.

The manufacturing is a non-standard process given the low active substance content. It involves wet granulation and capsule filling.

The control of the finished product is in general sufficient to guarantee consistent/ satisfactory quality/performance of the product. All specified degradation products are qualified.

The finished product is stable, but sensitive to light. Based on the stability data submitted the proposed shelf life of 3 years is acceptable, with the special storage conditions "Keep blister strip in the outer carton in order to protect from light", and "Do not store above 30°C". The latter is still not included by the applicant at the time of opinion.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality part of the application is not approvable due to an outstanding major objection requesting the redefinition of two of the proposed starting materials in the active substance synthesis.

If this major objection is addressed in a future procedure, the quality of this product could be considered to be acceptable when used in accordance with the conditions defined in the product information, with the inclusion of the statement "Do not store above 30°C".

Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way, notwithstanding the remaining major objection and other concerns described above. Information has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendations for future quality development

n/a

2.4. Non-clinical aspects

2.4.1. Introduction

Palovarotene is an orally bioavailable retinoic acid receptor gamma (RARγ) agonist. RARγ are 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.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

The applicant has conducted four primary pharmacodynamics studies: i) binding and transactivation were analysed in *in vitro* assays, ii) palovarotene inhibition of Smad phosphorylation was studied in Human FOP Fibroblast Cell Line Carrying the R206H ALK2 Mutation and finally, iii) palovarotene's effect on HO was investigated in two *in vivo* studies using a mouse model for the disease.

Report No. AT 7801: Binding and Transactivation Assays Specific for Retinoic Acid Receptors RARα, RARβ, and RARγ *In Vitro* Assessment of RO3300074 and Metabolites

The receptor binding assay showed that binding of palovarotene to the RARγ receptor was approximately 10 fold greater than to RARα or 6.5 fold greater than to RARβ based upon IC50 values (α: 4700nM, β: 2900nM and γ: 450nM). Only the metabolites M4b and M4a had measurable binding to RARγ, but with lower affinity relative to palovarotene. In the cellular transactivation assays, activation

of RARγ receptors was 10-fold greater than for RARα receptors and ≥2.5 fold over RARβ receptors, based upon the EC50 values (first set of assays: α: 94.2 nM, β: 25.0 nM and γ: 8.1 nM; or second set of assays: α: 192 nM, β: 47 nM and γ: 18 nM). A similar pattern was observed in metabolites M2, M3, M4a and M4. Transactivation activities of M1a and M1b approached the lower limit of detection and were not receptor selective.

According to IUPHAR/BPS Guide to Pharmacology[2], there are two human splice variants of RARγ (1 and 2). However, the activity (binding and transactivation) of palovarotene on the 2 splice variants of RARγ were not investigated.

Report No. CLM001-PD-001: Palovarotene Inhibition of Smad Phosphorylation in Human FOP Fibroblast Cell Line Carrying the R206H ALK2 Mutation

BMP4-mediated induction of pSmad1/5 protein levels was prevented at 1.0 μM palovarotene treatment in a human FOP fibroblast cell line carrying the overactive ALK2 R206H mutation. No palovarotene inhibitory effect was observed on pSmad1/5 basal (without BMP4 induction) protein levels. It was noted that treatment with 0.1 μM palovarotene did not produce any effect but a higher dose of 1.0 μM did.

Report No. 001: Palovarotene Inhibition of Heterotopic Ossification in the ALK2 (Q207D) Mouse Model

When administered prior to injury, palovarotene at 5 mg HED reduced HO formation and nearly eliminated HO formation at 10 mg HED and was associated with maintenance of mobility.

Report No. CLM001-PD-002: Evaluation of palovarotene inhibition of heterotopic ossification in Q207D mice

The study consisted of four parts: window of intervention, dose-response relationship, effect of corticosteroid and effects of various dosing regimens on heterotopic bone formation.

- When the 2-week palovarotene treatment was delayed by 3 days post injury, the heterotopic bone volume (BV) was decreased to 6.5% relative to vehicle control (93.5% inhibition). However, if the 2-week treatment initiation was delayed by 7 days post injury, the heterotopic BV was only decreased to 29% relative to vehicle control (71% inhibition).

- MicroCT results from three independent studies demonstrated a dose-response relationship in which higher doses of palovarotene resulted in less HO in this injury-based Q207D mouse model of FOP. However, it was noted that while the effects on HO at 20 mg HED daily and 10 mg HED twice daily were numerically better compared to 10 mg HED once daily, the difference was not statistically significant. Also, the adverse effects on femur length was more pronounced at both 20 mg HED daily and 10 mg HED twice daily compared to 10 mg HED once daily. Findings on bone development and growth were also observed in repeat dose toxicity studies and are further discussed in the Toxicology section.

- Corticosteroid treatment (at maximum daily clinical equivalent dose of prednisone, 4.4mg/kg for 4 days) had no effect on heterotopic BV in Q207D mice. When corticosteroid treatment was extended to 15 days, the estimated duration of the full HO process in Q207D mice, results showed a not statistically significant inhibitory effect on HO in treated Q207D mice: Heterotopic BV was decreased to 38% relative to vehicle control. Palovarotene daily treatment for 15 days at 2.94 mg/kg (10 mg HED) statistically significantly reduced heterotopic BV (to 30% relative to vehicle control) in Q207D mice.

- Except for the 5.88 mg/kg qad regimen, treatments with palovarotene at 2.94 mg/kg QD and BID and 5.88 mg/kg QD statistically significantly reduced heterotopic BV at all dosing regimens from 4.1 to 19% of the vehicle control (>80% inhibition) in Q207D treated mice. Statistically significant reduced

[2] IUPHAR/BPS Guide to Pharmacology - http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=592

femur length (81 to 91% of vehicle control [up to 19% reduction]) was observed across all palovarotene dosing regimens. Statistically significant reduced body weight (79 and 85% of vehicle control [up to 21% reduction]) was also observed in 2.94 mg/kg BID and 5.88 mg/kg (20 mg HED) QD dosing groups, respectively. No effects were observed on crown-rump length.

Published literature

The applicant reports results from a publication by Chakkalakal et al. (2016)[3] using an Acvr1[R206H]FlEx/+:Prrx1-Cre (termed Prrx1-R206H) mouse model in which the expression of the mutant allele (ACVR1/ALK2 R206H) in the developing embryo is limited to a population of skeletal progenitor cells (Prrx1+) leading to HO in the absence of injury. In the cited reference, lactating dams were treated with 50 µg palovarotene/mouse (described by the applicant as 2 mg/kg) in order to expose the pups during lactation. However, no information on concentrations of palovarotene or its metabolites in milk of mice are available.

It is reported that Palovarotene-treated Prrx1-R206H mice (Chakkalakal et al., 20160 showed improved mobility with markedly (by about 80%) reduced HO.

Citing the publication by Lees-Shepard et al. (2018)[4] the applicant states that an effect on skeletal growth was observed in a juvenile mouse model of FOP (Pdgfrα-R206H) with daily intraperitoneal (IP) injection of palovarotene at 0.7 or 1.5 mg/kg for 4 weeks (i.e., from 2 to 6 weeks of age) and postulates these adverse skeletal effects are due to higher palovarotene exposure and differences in the growth plate morphology in the Pdgfrα-R206H model compared to the Prrx1-R206H model. In response to a request, the applicant elaborated on the differences between both models and, although no data on exposure to palovarotene are available, the conclusion of the applicant can be followed that dosing regimen and/or study endpoint may explain the disparate study outcomes.

2.4.2.2. Secondary pharmacodynamic studies

The applicant has conducted an *in vitro* secondary pharmacodynamic study to evaluate the affinity of palovarotene at 10 µM (4146 ng/ml) against a panel of receptors (75) and enzymes (24) using radioligand binding assays and enzyme activities. The study shows that palovarotene was inactive against most receptors and enzymes and demonstrated only modest affinity for the adenosine A3 receptor (IC50 = 3940 nM; Ki = 2710 nM); the benzodiazepine BZD peripheral receptor (IC50 = 2120 nM; Ki = 1910 nM); and the δ opioid receptor (IC50 = 1850 nM; Ki =969 nM).

With respect to enzyme inhibition, results (>10% inhibition) were phosphodiesterase I (24%), phosphodiesterase IV (18%), cathepsin G (23%), and human immunodeficiency virus type 1 (HIV-1) protease (31%). Palovarotene also increased the activity of guanylate cyclase by 14%. It is noted that the secondary pharmacodynamics study was conducted at 10 µM (4146 ng/ml) palovarotene which is higher than the population pharmacokinetic analysis which indicates that, at the MRHD of 20 mg once daily, the median C_{max} will range from 138 to 202 ng/mL (333 to 487nM) across weight categories.

The off-target interactions noted in the secondary pharmacodynamics study appear to be unlikely to cause adverse effects in humans.

[3] Chakkalakal SA, Uchibe K, Convente MR, et al. Palovarotene Inhibits Heterotopic Ossification and Maintains Limb Mobility and Growth in Mice With the Human ACVR1(R206H) Fibrodysplasia Ossificans Progressiva (FOP) Mutation. J Bone Miner Res 2016;31(9):1666-75.

[4] Lees-Shepard JB, Nicholas SE, Stoessel SJ, et al. Palovarotene reduces heterotopic ossification in juvenile FOP mice but exhibits pronounced skeletal toxicity. Elife 2018;7:e40814.

2.4.2.3. Safety pharmacology programme

Palovarotene was tested in a battery of safety pharmacology assays including assessment of potential effects on central nervous system (CNS), renal and gastrointestinal (GI) systems in male rats. Effects on the cardiovascular system was evaluated *in vitro* and in conscious telemetered dogs. The metabolites M2, M3, M4a and M4b were tested individually in a hERG assay. In addition, safety pharmacology parameters were included in the dog repeat-dose toxicity studies.

In all rat studies, dose levels of 0.2, 1 and 5 mg/kg were employed but no evaluation of plasma exposure was included. However, dose levels of 1 and 5 mg/kg using identical vehicle were evaluated in a single dose oral PK study in male rats (Report No. 1008700). The C_{max} values following 1 and 5 mg/kg were 65.2 and 310 ng/mL, respectively. T_{max} was observed at 0.25 and 3 hours, respectively. Thus, exposures around or below the clinical exposure (200 ng/mL) have been evaluated in the rat studies.

CNS system

In a rat Irwin test in male rats, palovarotene demonstrated no potential for adversely affecting nervous system function. Findings were limited to mild diarrhea manifested as soft feces observed at 1.5 to 5 hours post dose at ≥1 mg/kg. The C_{max} at 1 mg/kg is estimated to ~65 ng/mL which is below the clinical C_{max} of 200 ng/mL.

There were no findings in repeat-dose toxicity studies up to 26 weeks in rats and 39 weeks in dogs that would suggest an effect on nervous system function. On the contrary, nervous system disorders were very common (headache) or common (seizure) in clinical trials.

Renal system

In a rat renal study, the evaluated parameters were limited to evaluation of total urinary output, and urinary sodium, potassium and chloride concentrations at up 24 hours post dose. Compared with baseline values, lower urine volumes and electrolyte excretion occurred 3 and 6 hours after dosing in the vehicle-control and all palovarotene-treated groups, suggesting an effect of the vehicle on urine output. Twenty-four hours after dosing, decreases in chloride output in rats given ≥1.0 mg/kg and decreases in sodium, potassium, and chloride output in rats given 5.0 mg/kg were noted. Given the low exposure at the NOEL (0.2 mg/kg), there are no margins to decreases in electrolyte excretion.

No effects on electrolyte excretion were noted in repeat-dose toxicology studies. Higher mean serum blood urea nitrogen (BUN), higher mean urine specific gravity, and lower urine output (volume) were seen in adult rats given palovarotene at 5 mg/kg/day for 4 weeks, however, this dose exceeded the MTD, and there were no associated histopathologic findings in the kidneys. Therefore, the findings were likely secondary to dehydration and haemoconcentration and not to a direct effect of palovarotene on renal function. In juvenile rats, lower mean urine output and pH and higher mean urine specific gravity and serum BUN were noted, but there were no associated histopathologic findings in the kidneys. Therefore, these effects were considered to be a consequence of lower food consumption or suspected lower water intake and not a direct effect of palovarotene on renal function. The differences were absent, or had resolved, in part, by the end of the recovery period. In clinical trials, proteinuria was a common adverse reaction.

Gastrointestinal system

In a rat gastrointestinal function study, palovarotene caused a slight slowing of gastric emptying as noted by higher stomach weights at all dose levels (0.2, 1 and 5 mg/kg) with no clear impact on intestinal motility. This mild effect was noted at exposures below the clinical exposure.

Following administration of high repeated doses to rats and rabbits, decreased and/or absent feces were noted that were considered a consequence of decreased food consumption or secondary to poor clinical condition; such effects were not noted in dogs. In clinical trials, GI disorders were very common (lip dry, chapped lips, dry mouth, cheilitis, nausea) or common (vomiting, diarrhoea, abdominal pain, gastroesophageal reflux disease). Decreased appetite is also a common adverse reaction.

Respiratory system

No dedicated studies on the respiratory system have been submitted. As the respiratory system is considered a vital organ system, ICH S7A recommends an evaluation prior to first administration in humans. At this stage, the absence of a dedicated study can be replaced by information from toxicology studies and information from clinical studies. However, according to ICHS7A, clinical observation of animals is generally not adequate to assess respiratory function, and thus these parameters should be quantified by using appropriate methodologies. The Applicant states regarding repeated dose toxicity studies that there were no clinical signs (e.g., altered respiratory rate or breathing pattern) that suggested any effect on respiratory function. In response to a request the applicant summarised clinical study data investigating palovarotene in healthy subjects and patients with chronic obstructive pulmonary disease (COPD), fibrodysplasia ossificans progressiva (FOP) and multiple osteochondromas (MO) which did not raise concerns regarding respiratory safety. Taken together, the data available to date indicate that palovarotene is unlikely to affect respiratory system function in humans and the absence of a dedicated study on the respiratory system is considered acceptable.

In clinical trials, with exception of epistaxis (vey common), no adverse reactions related to the respiratory system were observed.

Cardiovascular system

Cardiovascular effects of palovarotene and metabolites were evaluated *in vitro* and *in vivo*. *In vitro* non-GLP data in CHO cells indicate that palovarotene inhibited hERG ionic conductance with an IC50 of ~7.2 µM (~2985 ng/mL). Given the palovarotene clinical free Cmax of ~4 ng/mL, the margin to hERG IC50 is about 400-fold. In a second non-GLP study in HEK293 cells, palovarotene and metabolites M2, M3, M4a and M4b were tested at higher concentrations. All compounds tested were fairly weak blockers of hERG current amplitude failing to reach a 50% inhibition level at the highest concentration tested of 30 µM. Palovarotene inhibited potassium current by 5%, 10%, 15%, 18%, and 33% at tested concentrations of 0.3, 1, 3, 10, and 30 µM, respectively. The highest tested concentration of palovarotene, 12437 ng/mL, corresponds to about 3000-fold the estimated clinical free C_{max} of 4 ng/mL.

In an *in vitro* GLP study in canine Purkinje fibers, palovarotene at up to 10 µM had no effect on resting membrane potential, depolarization rate, upstroke amplitude, or action potential duration. The highest tested concentration of palovarotene, 4146 ng/mL, corresponds to about 1000-fold the estimated clinical free Cmax (4 ng/mL).

In vivo, the effect of palovarotene on cardiovascular function was evaluated in two GLP telemetry studies in conscious dogs. Oral administration of palovarotene at up to 10 mg/kg did not have any effects on arterial blood pressure (systolic, diastolic, and mean) or the lead II ECG variables (RR PR, QT, QTcF and QTcQ interval and QRS duration) at selected time points over 8 hours post-dose. At the highest tested dose of palovarotene, 10 mg/kg, the Cmax, 2175 ng/mL, corresponds to about 10-fold the clinical Cmax (200 ng/mL). It is also noted that administration of palovarotene at 10 mg/kg resulted in skin lesions, ranging from mild to marked, necessitating in euthanasia in 2 animals indicating that the highest tested dose was above MTD.

Additionally, no evidence of electrocardiographic abnormalities was seen in repeat-dose toxicity studies up to 39 weeks long in dogs.

Taken together, based on the available data palovarotene and metabolites have a low potential for adverse effects on cardiovascular function at the intended therapeutic exposure.

2.4.2.4. Pharmacodynamic drug interactions

No studies were performed to investigate potential pharmacodynamic drug interactions. Palovarotene intended pharmacodynamic activity is to inhibit chondrogenesis and thereby heterotopic bone formation. There are no available therapies demonstrated to prevent heterotopic bone formation therefore, potential pharmacodynamic interactions with palovarotene is unlikely.

2.4.3. Pharmacokinetics

Palovarotene is an orally bioavailable drug with moderately rapid absorption. Palovarotene is highly distributed in tissue, metabolised by both phase I cytochrome P450 (CYP) enzymes and phase II conjugating enzymes, and cleared from the body primarily via biliary excretion with limited renal elimination. *In vitro* assessments of the interaction of palovarotene with CYP enzymes and transporters indicate that palovarotene is not expected to have significant substrate or inhibitor interactions with these systems with the exception of CYP3A4, which was identified as the major metabolising enzyme. Coadministration with strong inhibitors or inducers of CYP3A4 are, therefore, expected to affect the metabolism of palovarotene.

The intravenous and oral single-dose plasma PK parameters of palovarotene were determined in male mice, male and female rats, male and female dogs, and male monkeys. Adequate analytical methods were developed and validated to support the GLP-compliant pivotal nonclinical studies.

After a single intravenous administration at 1 mg/kg, palovarotene exhibited low systemic clearance in dog and moderate clearance in mouse, rat and monkey. Palovarotene had a low apparent volume of distribution in dog and higher in mouse, rat and monkey. After a single oral administration, palovarotene was rapidly absorbed in mouse and rat and slower in dog and monkey. In non-fasted animals at 1 mg/kg, apparent oral bioavailability was high in dog (70%), medium in mouse and rat (28 to 44%) and low in Monkey (13%). In all species, the C_{max} and $AUC_{0\text{-last}}$ were approximately proportional to dose, except for monkeys whose values were less than proportional to dose, most likely due to limited absorption. In general, the effect of food on palovarotene pharmacokinetics was not significant in the animal species evaluated.

The multiple-dose oral plasma PK parameters of palovarotene were determined in adult and juvenile rats, adult rabbits, and adult dogs of both sexes in conjunction with repeat-dose toxicity studies.

After repeated administration in TK studies, C_{max} and $AUC_{0\text{-}24}$ of palovarotene and its metabolites increased with increasing dose and were generally proportional to dose for rats, dogs, and rabbits within the dose range tested. Exposures were higher in female than in male rats, while there was no significant sex difference in dogs and rabbits (palovarotene); exposure to metabolites were lower in male than female rabbits. In 26- and 39-week toxicity studies in rats and dogs, respectively, the exposures after multiple doses were mostly similar to those after the initial dose, suggesting no accumulation of palovarotene and no enzyme induction after repeated administration. In the 6-week juvenile toxicity study in 3- to 9-week-old rats, systemic exposure increased with increasing dose and were mostly dose proportional on Day 1 of dosing but less than dose proportional on Day 42 of dosing. Following repeated administration in juvenile rats, systemic exposure decreased at all dose levels with accumulation ratios ranging from 0.329 to 0.674 on Day 42 of dosing relative to Day 1. It is unknown

whether the decreased exposure over time was a consequence of enzyme induction following chronic exposure to palovarotene, metabolic enzyme maturation of the juvenile rats, or both. Despite the reduced exposure over time after repeated administration in juvenile rats, the overall exposure adjusted for doses (0.1, 0.5 and 1.2 mg/kg/day) on Day 42 of dosing was similar or slightly higher than that reported in adult rats following chronic administration up to 177 days at doses of 0.3, 0.6 and 1 mg/kg/day.

The *in vitro* metabolism of palovarotene was studied in hepatic microsomes prepared from mice, rats, dogs, monkeys, and human volunteers, and in cryopreserved hepatocytes prepared from rats, dogs, monkeys, and humans. The *in vitro* metabolic profiles in hepatic microsomes were qualitatively similar but quantitatively different across species. The major metabolites were M2 (6-hydroxy), M3 (7 hydroxy), M4a (6-oxo), and M4b (7-oxo). M5, the carboxyl β-glucuronide of the parent compound, was also detected after incubation with cryopreserved hepatocytes. In addition, the *in vivo* metabolic profiles were similar in rats, dogs and rabbits. The exposure to each of the metabolites, M2, M3, M4a, and M4b, was much lower than exposure to parent drug (metabolite-to-parent drug ratios ranged from 1 to 27%) in adult rats and dogs but was higher in rabbits (metabolite-to-parent drug ratios was <29% for M2 and M4a with highest ratio observed for M3 [90 to 187%] and M4b [98 to 649%]). In general, there were dose-proportional increases in exposure for M2, M3, M4a and, M4b following repeated administration of palovarotene to adult rats, dogs and rabbits with no significant accumulation in rats and dogs but accumulation of the four metabolites was observed in rabbits, predominantly M3 and M4b.

Following 13-week repeated administration of a mixture of M2 and M3 (which are further metabolized to M4a and M4b, respectively) to adult rats and dogs, exposure of all four metabolites increased with increasing dose, were generally dose proportional in rats and appear to be more than dose proportional in dogs. No significant or consistent accumulation was observed in both rats and dogs.

Palovarotene was extensively bound to proteins in mouse, rat, dog, monkey and human plasma without significant species differences (mean of 97.5% to 99.0% bound in all species, 97.9 to 99.6% in human).

In humans, the relative plasma exposure of metabolite M3 is approximately 10% of total drug-related radioactivity and 50-60% compared to the parent compound and the Applicant was asked to better characterise this metabolite and also to determine the fraction unbound for metabolite M3 and M4b in humans and animals *in vitro*. The applicant conducted a plasma protein binding study to determine the unbound fractions of palovarotene and M3 and M4b metabolites. The results confirmed that palovarotene, M3 and M4b were extensively bound to proteins in rat, rabbit, dog and human plasma. The exposure margins accounting for the unbound fractions in plasma were calculated and presented as requested.

Results from radiolabelled studies showed that palovarotene is well absorbed and extensively distributed to tissues with the highest exposures seen in the adrenal cortex, adrenal medulla, liver, and the walls of the small intestine and caecum. Palovarotene distributes to fur/skin with no preferential binding to melanin as evidenced by concentrations below quantifiable levels at 96 hours. Palovarotene was not phototoxic in a 3T3-fibroblast assay. Skin and bone were identified as target organs of toxicity (see toxicity section). No data was presented on the distribution over the placenta or excretion into milk. However, palovarotene as a lipophilic compound is expected to be excreted into breast milk.

After a single 2-mg/kg oral dose of [14C]-palovarotene in adult rats and a single 0.2-mg/kg oral dose of [14C]-palovarotene in dogs, elimination of the radioactivity was almost exclusively biliary/fecal, and recovery was complete within 7 days, with most of the administered radioactivity recovered within the first 24 hours. In both species, small fractions of the dose (<1%) were recovered in urine.

Mice, rats, rabbits and dogs were selected as the nonclinical toxicology species based on the similar metabolic profile to that of humans. The choice of dog as the non-rodent toxicology species was further justified because the plasma exposures following oral administration of palovarotene exhibited greater bioavailability and better dose proportionality as compared to monkeys. The metabolites M2 and M3 (further metabolised to M4a and M4b) were administered as a mixture for evaluation in repeat-dose toxicity studies in the rat and the dog. The potential genotoxic hazard posed by the M2, M3, M4a, and M4b metabolites was also evaluated in two *in vitro* non-mammalian cell system studies.

2.4.4. Toxicology

The toxicological profile of palovarotene has been evaluated in non-clinical studies in agreement with relevant guidelines.

The toxicity profile of palovarotene has been characterised via single-dose toxicity (in mouse, rats and dogs), repeat-dose toxicity studies (1 month in rabbit, and up to 6 months in Sprague Dawley rats and 9 months in beagle dogs) *in vitro* and *in vivo* genetic toxicology, fertility/early embryonic and embryo foetal development in rats, *in vitro* phototoxicity and an *in vitro* investigative study. Juvenile toxicity was investigated in a 6-week repeat-dose toxicity study in young rats. In addition, the metabolites to palovarotene (M2, M3, M4a, and M4b metabolites) has been evaluated in repeat toxicity, genetic toxicity and photo toxicity studies.

The oral route of administration was utilised in all pivotal toxicity studies to match the intended clinical administration route.

Relevance of animal models

The rat and dog were the selected as main rodent and non-rodent species, respectively, based on their suitable pharmacokinetic profiles and representation of the major metabolism pathways in humans. Based on demonstration of target-related findings, both species are considered as pharmacologically relevant. The rabbit was chosen as a second non-rodent species to evaluate the effects of palovarotene on chondrocytes since effects were seen in rats but not in dogs.

2.4.4.1. Single dose toxicity

Single-dose toxicity was tested in mice, rat and dog. No lethality occurred and for the intended oral administration the MTD was set to the highest dose which was 12.5 mg/kg in mice, 25 mg/kg in rat and 10 mg/kg in dog.

2.4.4.2. Repeat dose toxicity

In repeat-dose toxicity studies the main organs and tissues affected were primarily skin and male reproduction organs in all species, bone and cartilage in rats and stomach or esophagus in rat and rabbits. No or limited toxicity were seen in other organs or tissues.

Mortality

Treatment related mortality, due to findings such as extreme effects on skin, bone effects, decrease of body weight or various clinical signs, occurred in all tested species.

In the rat 4-week study, one male animal was euthanised *in extremis* during week 4 due to an apparent broken hindlimb at 5.0 mg/kg/day. Histopathology of this animal together with clinical signs and histopathology of the remaining animals in this dose group indicated that the moribund conditions was a result of the test-article. In rabbits, early euthanasia was performed for humane reasons at 2.5

mg/kg/day due to body weight loss, inappetence, and/or generally poor condition. All males were euthanised on Day 12, and one female was euthanised on Day 17. Clinical signs that led to the decision to euthanise these rabbits were cold skin, hypoactivity, increased frequency and duration of alopecia, unkempt coat, decreased body weight, decreased food consumption, and eye, lip, and/or feet encrustation. Foot lesions were characterised microscopically as pododermatitis. In dogs, termination occurred in both the 4 weeks study and 39- weeks study. Two male and 2 female dogs at 0.2 mg/kg/day in the 4-weeks study and 2 males and 5 females at 0.12 mg/kg/day in the 39-weeks study were sacrificed prior to their scheduled necropsy due to test-article related skin effects. It can be concluded that palovarotene related deaths (sacrifice) occurred in rats, rabbits, and dogs at 5.0, 2.5 and 0.12 mg/kg/day with no or similar exposure marginals to the human intended dose.

Skin effects

Skin lesions was found in adult rats, dogs, and rabbits. In rats, skin lesions were limited to dry skin, thin fur cover, and/or scab in juvenile animals. In adults the severity of the lesions became worse in a dose-dependent manner with dose duration. In the 4-week rat study, skin lesions up to mild in severity were seen and most of the animals had hair loss of the fur and reddening/swelling of the facial area at 5.0 mg/kg/day. In the long-term rat study, single animals with moderate skin findings (acanthosis and chronic-active inflammation) were seen at 0.6 mg/kg/day that became more frequent and severe at 1.0 mg/kg/day which corresponds to approximately 0.6X AUC margin to the clinical intended dose. In rabbits, hair loss was seen at 1.0 mg/kg/day in few animals that become more frequent at 2.5 mg/kg/day and included all males that were euthanised at study day 12 and 3 female rabbits. At this dose marked inflammation of the skin of the feet (pododermatitis) were seen in 3 females. After 4-weeks recovery one male with marked pododermatitis remained in the 1.0 mg/kg/day dose group. The were no marginals to the intended clinical dose at the NOAEL for skin lesions in rabbits. In dogs, test-article related skin findings occurred at all dose levels. In the 4-weeks study early termination of 2 males and 2 females at 0.2 mg/kg/day occurred due to skin lesions of head, neck, torso, feet and/or ears. The remaining animals in this dose group, that was terminated after 4-weeks had similar findings. The severity of the histopathology findings was not presented for this study. In the 39-week dog study 2 males and 5 females (dosed at 0.025 mg/kg/day for 13 weeks and then at 0.12 mg/kg/kg for 39 weeks) was sacrificed after 26 weeks due to severe skin effects, occurrences of otitis externa and conjunctivitis, that were manifested systematically with inflammatory response and hypergranulosis. One low dose male (0.012 mg/kg/day) had moderate erosions in skin but other skin effects in this animal as well as animals in the intermediated and high dose groups were graded as minimal or mild lesions.

The proposed NOAELs in the dog repeated-dose studies needed re-evaluation. Regarding the 4-weeks study (study 1009512) the applicant proposed a NOAEL of 0.008 mg/kg bw/day. The applicant stated that skin erythema, epithelial hyperplasia, and secondary inflammation occurred at all dose levels in this study, but that these findings were minimal at 0.008 mg/kg/day. No such findings were reported in vehicle and 0.008 mg/kg/day dose groups after 28 days of treatment, but after further 28 days of recovery both male rats in the 0.008 mg/kg/day dose group showed findings described as minimal or mild. Taking the low grade of these effects in the two affected male recovery animals into account, the fact that no clinical observations corresponded to these findings and the at least partial recovery of the skin effects in general, the low dose can be accepted as the NOAEL of this study.

Further, in the 13-week study (study 1011046) the applicant proposed a NOAEL of 0.15 mg/kg bw/day. In this study not palovarotene itself, but a mixture of the two metabolites M2+M3 was administered. The applicant based the NOAEL of 0.15 mg/kg bw/day on the skin findings accompanied by reductions in mean body weight and increased number of animals with unkempt appearance in the 0.5 mg/kg/day dose group.

In the mid dose group (0.15 mg/kg bw/day) at the end of dosing none of the animals (0/12) showed black aural discharge, whereas in the control group as well as in the low dose group one animal, each, (1/12; 1/12) was found to present with black aural discharge. Therefore, a low background incidence of black aural discharge, unrelated to palovarotene metabolite exposure, may have to be assumed and the NOAEL of 0.15 mg M2+M3/kg bw/day, as proposed by the Applicant, can be accepted. At the end of the recovery period 100% of high dose group animals (4/4) showed black aural discharge and, therefore, no reversibility could be demonstrated for black aural discharge.

Finally, in the 39-weeks study (study 1013980) the applicant proposed a NOAEL of 0.04 mg/kg bw/day. The applicant stated that skin effects seen at ≤0.040 mg/kg/day were not associated with adverse health effects based on in-life and pathological evaluations. At the dose level of 0.04 mg/kg/day 7 of 14 investigated animals were identified with aural discharge and 10 of 14 animals were identified with scabs, while in none of the 13-vehicle treated animal presented with aural discharge and only one out of 11 vehicle treated animals presented a scab. Aural discharge was diagnosed in the study itself as otitis externa and was not shown to be reversible. Taking into account that otitis externa is an inflammation at a critical side with the potential to lead to more serious consequences and that the data did not show reversibility, otitis externa should well be interpreted as an adverse effect. In response to a request the applicant is to accept the dose of 40 µg/kg bw/day as the LOAEL and the low dose of 12 µg/kg bw/day as the NOAEL of this study. In summary, skin effects were observed in all toxicological species evaluated. The NOAEL for skin lesions occurred below or at similar exposures compared to the intended clinical dose. That skin lesions are generally observed at all dose levels, starting below the clinically relevant exposures is stated in SmPC section 5.3. However, as skin lesions can easily monitored and are controllable in the clinic, they are considered not to pose a risk to human safety.

Stomach and esophagus

Effects on stomach and esophagus were observed in adult rats and rabbits. In rats, the findings were seen in the mucosa and included epithelial hyperplasia, hyperkeratosis and acute inflammation. In the 4-week rat study, adverse stomach findings were seen at 5.0 mg/kg/day while in the 26-weeks study milder effects was seen at 1.0 mg/kg/day (the highest dose) with a more or less resolved findings after 13-weeks of recovery. In rabbits, non-adverse findings (hypogranulosis and expansion of granular layer) in the esophagus at ≥0.5 mg/kg/day. According to the applicant these findings did not compromise the integrity of the esophageal mucosa or the health of the animal and were not interpreted to be toxicologically significant, which is agreed.

Testicular effects

Male reproductive organs were affected after administration of palovarotene in all toxicological species. In the 4-week rat study, four males dosed at 5.0 mg/kg/day (found dead or terminated early) had findings in reproduction organs which included luminal debris in epididymis (1M mild, 3M moderate) and degeneration of seminiferous tubules in testes (1M, minimal). In males dosed at 5.0 mg/kg/day (with scheduled termination) the testicular findings included decreased mean epididymis weight, lower motile and normal sperms, lower mean sperm count in left epididymis. The histopathology evaluation revealed degeneration of testes and cellular debris in one male dosed at 5.0 mg/kg/day. The findings were only partially resolve after the recovery period with lower mean epididymis and testes weight, abnormal sperm, lower mean sperm count in epididymis remaining. The applicant claimed that these findings were attributed to the test-article but as the test-article produced systematic toxicity at 5.0 mg/kg/day these testes findings were secondary effects to ill produced by the test-article. Findings on male reproductive organs were seen in more studies and species that were considered by the applicant as related background findings. In the 2-week rat non-GLP study, males dosed at 5.0 mg/kg/day showed testes toxicity. In the 26-weeks rat study two males (one terminated early; day 148 and the

other with scheduled termination) had findings in testis that included moderate atrophy/degeneration and minimal lymphohistiocytic infiltrate and one male at 1.0 mg/kg/day had testicular degeneration/atrophy and hypospermia in the epididymides. In rabbits treated for 4 weeks, two males dosed at 2.5 mg/kg/day (terminated early; day 12) had testicular degeneration/atrophy and hypospermia in the epididymides. In the 39-weeks dog study, multifocal testicular atrophy/degeneration was found in one male terminated early (week 33) and dosed at 0.12 mg/kg/day and after 13-weeks recovery these findings remained in two (out of three) males dosed at 0.012 mg/kg/day. Furthermore, in dogs treatment with the two hydroxy metabolites (M2 and M3) of palovarotene for 13-weeks generated testicular degeneration in one male dosed at 0.5 mg/kg/day and after 4 weeks of recovery in in one (out two) males dosed at 0.15 mg/kg/day. In the same study, increased incidence of multinucleated giant cells in testes were observed. This finding was observed in 4 (out of 6) males dosed at 0.5 mg/kg/day although the same finding was seen in 2 (out of 6) males in vehicle group. The NOAEL for testicular findings in rats and rabbits were 1.0 mg/kg/day and in dogs 0.12 mg/kg/day which corresponds to no margin to the intended clinical dose. Since it has been shown that vitamin A generates testicular toxicity and that these findings were seen across the toxicological species evaluated one can suspect that these findings are test-article related. Testicular findings were also observed in the 6-week toxicity study in juvenile rats [670013]. These included mild to moderate decreased secretory content in the seminal vesicles at 1.2 mg/kg/day in 2 animals after the treatment and 1 animal after the recovery period and marked degeneration of testes in one male animal at 1.2 mg/kg/day after the 6-week recovery period. In summary, the testicular findings occurred in all toxicological species but were found in animals with poor clinical condition or control animals, and were either mild, sporadic, or dissimilar.

Skeletal effects

Effects of bones and cartilage were seen in rats only. In juvenile rats, adverse findings were observed at 0.5 mg/kg/day. At this dose, findings seen were, among others, moderate abnormal shape, up to moderate bone enlargement, bone loss, and enlargement of vertebral/intersternal space (detected by radiology) and up to moderate and severe thinning/closure physis of femur and ulna, and severe decreased bone in vertebrae. The severity of cartilage lesions (chondrodysplasia and thinning/closure) at this dose were graded as minimal or mild. In the high dose group (1.2 mg/kg/day) severe decrease in bone length/width (femur and tibia) and femur area was recorded, and the lesions in the bones and the cartilage get worsened and included marked/severe lesions in the humerus, radius, ulna, femur, tibia, hindpaw, vertebrae and sternum of many animals. After 6-weeks recovery many of the lesions sustained with moderate/severe findings in bones and cartilage in animals, dose at 0.5 and 1.2 mg/kg/day. The NOAEL was set to 0.1 mg/kg/day due to limited severity and infrequency of lesions. In adult rats, bone lesions seemed milder while severe cartilage lesions sustained. In the 4-weeks rat study, no effects of bone size were recorded while up to moderate and severe chondrodystrophy in femur knee joint was recorded at 1.0 and 5.0 mg/kg/day, respectively. This lesion remained after recovery. Up to moderate and marked chondrodystrophy of the growth plate in the stifle joint at 1.0 mg/kg/day. After 13-weeks of recovery these lesions sustained, with possible tendency of recovery, with up to moderate chondrodystrophy 4 females. As said, skeleton effects was not observed in rabbits and dogs. The applicant claimed that this reflects the fact that the growth plate remains open in rats well into adulthood, unlike in rabbits, dogs or humans. Further, the incidence and frequency of chondrodystrophy in adult rats tended to increase with dose level but not with duration which is similar to what has been seen with other RAR agonist in this species. Therefore, it seems likely that the chondrodystrophy seen in adult rat pose no risk for adult patients.

2.4.4.3. Genotoxicity

The genotoxicity potential was evaluated in a standard battery of *in vitro* and *in vivo* tests.

Palovarotene was not mutagenic in the Ames test. A standard plate incorporation and a preincubation modification assay were performed in absence and in presence of an exogenous metabolic activation system (S9). Five Salmonella typhimurium tester strains (TA1535, TA97, TA98, TAl00, and TA102) were employed. Borderline clastogenic activity was noted for palovarotene in an *in vitro* chromosomal aberration assay with human peripheral blood lymphocytes, but only at cytotoxic concentrations that reduced the mitotic index by more than 50%. Therefore, the overall conclusion from that study is that palovarotene is not clastogenic. This was further corroborated in micronucleus assay in mouse bone marrow. Palovarotene was administered orally at daily doses of 5, 12.5 or 25 mg/kg on two consecutive days and bone marrow preparations were made on the following day. The administration scheme was identical for the satellite animals for toxicokinetics monitoring and blood sampling took place 0.25, 1, 7 and 24 hours after the second administration. No inhibition of cellular proliferation as measured by reductions of the ratio of polychromatic to normochromatic erythrocytes was noted in the bone marrow. Toxicokinetics data indicate that at a dose of 25 mg/kg the mean C_{max} and AUC_{0-24} across males and females were 412 ng/mL and 4545 ng·h/mL, respectively. Exposure to palovarotene did not increase the frequency of micronucleated polychromatic erythrocytes. Therefore, it is concluded that palovarotene does not show genotoxic activity in mouse bone marrow cells.

In addition, the four human metabolites (M2, M3, M4a, M4b) of palovarotene were not mutagenic in the Ames test and was not clastogenic *in vitro* in human peripheral lymphocytes.

2.4.4.4. Carcinogenicity

No studies have been done to evaluate the carcinogenic hazard posed by palovarotene. The applicant has provided a weight-of-evidence analysis indicating that a 2-year rat carcinogenicity study with palovarotene is not likely to add value to the human carcinogenicity risk assessment. This is in line with the draft Addendum to the ICH guideline S1B on testing for carcinogenicity of pharmaceuticals (EMA/CHMP/ICH/272147/2021). A review of the carcinogenic potential of marketed retinoids evaluated in rodents suggests that the carcinogenicity risk due to the pharmacological mechanism is minimal. It has also been demonstrated that palovarotene and its metabolites lack genotoxic potential, did not show any evidence of preneoplastic lesions, evidence of hormonal disturbance, nor immunosuppression in chronic toxicity studies. The epithelial hyperplasia identified in chronic toxicity is a well-known class effect of marketed retinoids. In conclusion, a 2-year rat carcinogenicity study with palovarotene is not likely to add value to the benefit-risk evaluation, also taking into account that the MTD to be used in a 2-year rat carcinogenicity study likely would result in an exposure margin below 1.

2.4.4.5. Reproductive and developmental toxicity

The reproductive and developmental program included studies on fertility and embryonic development in rats. No peri-post natal study was conducted while a 6-weeks repeat-dose toxicity study in young rats, aged 3-weeks at the study initiation, was conducted with the intention to cover juvenile toxicity. In early fertility and embryonic studies, males did not tolerate daily dosing of 3 mg/kg/day palovarotene and was sacrificed on study day 39 due to adverse clinical signs. Males in the remaining groups (dosed at 0.3 and 1.0 mg/kg/day) had milder clinical signs but showed no testicular toxicity or effects on the fertility performance. In females, body weight loss, reduced food consumption and slight reduction in the number of corpora lutea, and consequently, the number of implantation sites and live embryos were observed at 3 mg/kg/day. The NOAEL for male and female fertility is 1 mg/kg/day under the conditions of the study.

In the EFD study, maternal toxicity (clinical signs, reduced maternal body weight gain) and increased incidences of various visceral and skeletal malformations were seen at ≥0.25 mg/kg/day and a large set of malformations and a slight decrease in foetal body weight were observed at 1.25 mg/kg/day. Based on these findings the NOAEL for effects on embryo-foetal development is 0.01 mg/kg/day

No EFD study was conducted in a second species like the rabbit as recommended in the guideline ICH S5 (R3) to identify human teratogens that have not been detected in rodents. However, as teratogenic effects have already been identified in rat such a study is considered to not add any value. Palovarotene induced malformations when administered to rats during organogenesis at exposures well below the range of clinically relevant exposures and, like other retinoids, should be classified as a human teratogen.

No PPND study has been conducted and no data are available on palovarotene levels in human breast milk. Also, there are no data available on the influence of palovarotene on neurobehavioral development and reproductive performance in animals exposed pre-postnatally to palovarotene.

Due to the teratogenic and embryotoxic effects seen with palovarotene at clinically relevant doses there is apparent risk that the survival will be too low to assess the appropriate endpoints in a PPND study. Based on this and in agreement with 3R principles, it is considered that such a study is not needed. Further, relevant risk minimisation measures are proposed by the applicant.

2.4.4.6. NOAEL

The NOAEL in all the pivotal repeated-dose toxicology and development/reproduction studies is well below the exposure at the intended high clinical dose. The applicant mentioned as the indication for palovarotene is a serious disease one should focus on identifying a dose level that is "acceptably safe," rather than a dose level free of adverse effects. This is true for assessing anti-cancer products were HNSTD (Highest Non-Severely Toxic Dose) is a commonly approach to set a start dose from animal studies.

2.4.4.7. Toxicokinetic data

See sections 2.4.3. Pharmacokinetics and 2.4.4.3. Genotoxicity.

2.4.4.8. Local Tolerance

No studies have been done specifically to evaluate the local toxicity of palovarotene in the gastrointestinal tract when administered orally. However, local tolerance of the GI tract following oral exposure was evaluated in the repeat-dose toxicity studies (section 2.4.4.2.).

2.4.4.9. Other toxicity studies

Two GLP-compliant repeated-dose toxicology studies with the metabolites of palovarotene were conducted in rat and dogs. Palovarotene is metabolised primarily to 6-hydroxy (M2) and 7 hydroxy (M3) metabolites of palovarotene, which are further metabolised to 6 oxo (M4a) and 7-oxo (M4b) metabolites, respectively, in rats, dogs and in humans.

In rats and dogs dosed with the metabolites M2 and M3 clinical observation and histopathological findings were similar to those seen with the parent drug but were milder in severity. After 4-weeks of recovery these findings were more or less resolved or sustained to a milder grade.

2.4.5. Ecotoxicity/environmental risk assessment

The applicant provided an ERA in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use - (EMEA/CHMP/SWP/4447/00 corr 21*, 01 June 2006).

A refined PECSURFACEWATER of palovarotene based on the orphan designations is 0.000006 µg/L, therefore a Phase II assessment is not required.

The log Dow was adequately evaluated in an OECD 123 study. The log Dow ranged from 2.67 to 5.95 at pH range of 5 to 9, indicating potential for bioaccumulation and a PBT-assessment was conducted.

The persistence of palovarotene was adequately evaluated in an OECD 308 study using two different water-sediment systems. The normalised DT50 of palovarotene ranged from 10 to 302 days indicating that palovarotene meets the criteria for classification as very persistent (vP) in aquatic systems. Palovarotene dissipated from the overlying water into sediment where formation of transformation products and bound residues were observed. The DT50 values (12oC) for the M4 transformation product ranged from 87 to 104 days, indicating that M4 is potentially persistent in aquatic systems.

The Applicant has performed an acute toxicity study with palovarotene in the rainbow trout designed according to the OECD 203 Guideline. Due to the poorly water-solubility of palovarotene a modification of the standard method for the preparation of aqueous media was performed. The study was performed as a limit test at a nominal concentration of 100% saturated solution (geometric mean concentration of 0.138 mg/L). There were no mortality or toxic effects at saturation and the 96-h LC50 > 0.1 mg/L. The need for conducting the acute toxicity study of palovarotene in rainbow trout according to the OECD 203 guideline is questioned, because of the result of such a study is not the long-term NOEC that forms the basis for investigating the T-criterion. The (aquatic) T criterion in the PBT assessment is based on the long-term no-observed effect concentration (NOEC) or EC10 for marine or freshwater organisms being less than 0.01 mg/L. Therefore, it cannot be concluded that palovarotene is not T. In addition, palovarotene was found to be teratogenic in reproductive toxicity studies in the rat. Based on the results of all toxicity tests, the T-criterion for the PBT-assessment (in this case the R in the CMR-criterion) is considered fulfilled.

The bioaccumulation potential of palovarotene has been determined in an OECD 305 bioconcentration study in the rainbow trout. The reported steady-state BCF value based on total radioactivity was 506 L/kg and the kinetic BCF was approximately 480 L/kg. The growth corrected kinetic BCF, lipid normalised kinetic BCF, and lipid normalised growth corrected kinetic BCF were 496, 289 and 299 L/kg, respectively indicating that palovarotene is not bioaccumulative (B) or very bioaccumulative (vB). The provided study is not acceptable. Toxic effects appeared from day 11 on. On day 12 the test was terminated without continuing the uptake phase and without performing neither the depuration phase to determine the depuration rate k2 for BCFkinetics, nor the elimination rate or residues at the end of the depuration phase. Furthermore, the uptake can be hampered by toxic effects, resulting in an underestimation of the uptake rate k1.

Therefore, based on the available data, no decision on bioaccumulation potential can be made.

Palovarotene is practically insoluble or insoluble in aqueous buffer and has a log Dow of up to 5.95 at pH 5. The relevance of performing a bioconcentration study with such a test item dissolved in water instead of a dietary study has been discussed. Log Dow values were highest at pH 5 (5.95) but decreased at higher pH values (4.6 and 2.67 at pH 7 and 9 respectively). Since it was not technically feasible to run the test on fish at pH 5 the test was therefore conducted at pH 7.2-7.4. Under these conditions the palovarotene is more soluble and less hydrophobic and therefore an aqueous exposure BCF test in fish is considered adequate. However, a new fish BCF study would still be required.

The applicant in principle agrees to conduct a new OECD 305 bioconcentration study at a lower, non-toxic test concentrations of palovarotene. In view of the critical points regarding sufficient recovery of the radioactivity at an even lower test concentration especially for HPLC analysis in water and the possibility that even at a lower concentration, toxic effects may occur, a phased procedure is proposed. Therefore, the applicant proposed as a first step to conduct a feasibility study as a post-approval commitment using a significantly reduced number of fish (7 fish, in a 20 L tank) at a test concentration of 0.00067 mg/L in a flow-through system under same condition as in the bioconcentration study. The exposure period should be 28 days.

If the results of the feasibility study indicate that an OECD 305 test is practicable at the tested concentration, the applicant would be willing to conduct a further bioconcentration study in fish with a 28-day exposure phase and a 14-day depuration phase as a second step.

Table 1 Summary of main study results

Substance (INN/Invented Name): Palovarotene			
CAS-number (if available): 410528-02-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123 (slow-stirring)	Log D_{ow}= 5.95 at pH 5 Log Dow= 4.30 at pH 7 Log Dow= 2.67 at pH 9	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	OECD 305	pending	Potential B
Persistence	DT50	**Calwich Abbey** Water: 9.6 Total system: 302 **Emperor Lake** Water: nd Total system: 227	vP
Toxicity	CMR	Reprotoxic in mammals (R)	T
PBT-statement :	Pending The compound is considered as vP		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined	0.000006 (refined based on Orphan designation)	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

2.4.6. Discussion on non-clinical aspects

Pharmacology

Primary pharmacodynamic

The applicant has conducted four primary pharmacodynamics studies: i) Binding and transactivation were analysed in *in vitro* assays, ii) Palovarotene inhibition of Smad phosphorylation was studied in Human FOP Fibroblast Cell Line Carrying the R206H ALK2 Mutation, and finally, iii) Palovarotene's effect on HO was investigated in two *in vivo* studies using a mouse model for the disease.

Based on the results, palovarotene can be described as an orally bioavailable RAR agonist, with highest affinity for the gamma subtype of RAR over the other subtypes. However, since the activation of RARγ receptors was 10-fold greater than for RARα receptors but only ≥2.5 fold over RARβ receptors (based on the EC_{50} values), palovarotene is not considered a selective RARγ agonist.

Based on published literature data, humans RARγ showed highest expression levels in oesophagus and skin and in line with this the applicant stated that both organs/tissues have been confirmed to be affected by palovarotene treatment in the toxicology studies. Regarding gene expression regulated via RARγ the applicant pointed out that numerous target genes modulated by RARγ agonists involved in various pathways have been described, but that gene expression following treatment with palovarotene has not been specifically studied. The applicant also stated that molecular mechanism of the link between RARγ and ALK-Receptor signaling has not been fully elucidated for palovarotene specifically, but that published literature supports the hypothesis that RARγ agonists regulate ALK-Receptor mediated reduction of BMP4 signaling via promoting SMAD1/5/8 degradation.

Evaluation of palovarotene inhibition of HO was studied in the ALK2 (Q207D) mouse model of the disease. When administered prior to injury, palovarotene at 5 mg HED reduced HO formation and nearly eliminated HO formation at 10 mg HED and was associated with maintenance of mobility.

Different dosing regimen were studied in the mouse model in a dosing regimen (exploratory study) and this study contains doses higher than what the Dose-response relationship study did. Palovarotene was administered at 10 mg HED once daily, 10 mg twice daily, 20 mg HED once daily or 20 mg HED every second day. Except for the 20 mg HED every second day regimen, treatments with palovarotene statistically significantly reduced heterotopic BV at all dosing regimens compared to vehicle control. It is noted that while the effects on HO at 20 mg HED daily and 10 mg HED twice daily were numerically better compared to 10 mg HED once daily, the difference was not statistically significant. Also, adverse effects on femur length were more pronounced at both 20 mg HED daily and 10 mg HED twice daily compared to 10 mg HED once daily. Findings on bone development and growth were also observed in repeat dose toxicity studies and are further discussed in the Toxicology section. Therefore, the applicant's argument that a dose higher than the highest tested dose (15 mg HED once daily), may provide even greater efficacy in inhibiting HO (~ 6 mg/kg or 20 mg HED once daily is suggested) is not supported as it is considered to be based on few experimental data points and as it remains unclear whether already at 4.41 mg/kg bw in Q207D mice a plateau in efficacy might have been reached. The proposed dosing schedule for patients for the Chronic/Flare-Up regimen is 5 mg palovarotene once daily (chronic treatment), with an increase in dose at the time of flare-up to 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks for a total of 12 weeks (20/10 mg flare-up treatment), even if symptoms resolve earlier.

To assess and compare the effect of treatment with corticosteroids (standard of care for treatment of flare-ups in FOP) versus palovarotene on HO, Q207D mice were administered dexamethasone (synthetic corticosteroid) at 4.4 mg/kg/day for either 4 or 15 days, vehicle or palovarotene. Corticosteroid treatment at 4.4mg/kg for 4 days had no effect on heterotopic BV. When corticosteroid treatment was extended to 15 days, results showed a not statistically significant inhibitory effect on HO.

Secondary pharmacodynamics

The off-target interactions noted in the secondary pharmacodynamics study appear to be unlikely to cause adverse effects in humans.

Safety pharmacology

The effects of palovarotene have been adequately evaluated on CNS, renal, GI and CV systems. The metabolites M2, M3, M4a and M4b were also tested in a hERG assay. No dedicated studies on the

respiratory system have been submitted. As the respiratory is considered a vital organ system, ICH S7A recommends an evaluation prior to first administration in humans. At this stage, the absence of a dedicated study can be replaced by information from toxicology studies and information from clinical studies. In repeat-dose toxicity studies, respiratory effects were indirectly evaluated by way of clinical observations in repeat-dose toxicity studies where palovarotene demonstrated no potential for adversely affecting respiratory system function. In response to a request the applicant summarised clinical study data investigating palovarotene in healthy subjects and patients with chronic obstructive pulmonary disease (COPD), FOP and multiple osteochondromas (MO) which did not raise concerns regarding respiratory safety. Taken together, the data available to date indicate that palovarotene is unlikely to affect respiratory system function in humans and the absence of a dedicated study on the respiratory system is considered acceptable.

The two *in vitro* hERG studies were not performed in compliance with GLP. This is considered acceptable given that the study in HEK293 cells seems well conducted and as two *in vivo* GLP studies of adequate quality were performed.

Pharmacokinetics

Palovarotene was extensively bound to proteins in mouse, rat, dog, monkey and human plasma (mean of 97.5% to 99.0% bound in all species, 97.9 to 99.6% in human) indicating the need to compare free palovarotene when calculating exposure margins. In humans, the relative plasma exposure of metabolite M3 is approximately 10% of total drug-related radioactivity and 50-60% compared to the parent compound and the applicant was asked to better characterise this metabolite and also to determine the fraction unbound for metabolite M3 and M4b in humans and animals *in vitro*.

The applicant conducted a plasma protein binding study to determine the unbound fractions of palovarotene and M3 and M4b metabolites. The results confirmed that palovarotene, M3 and M4b were extensively bound to proteins in rat, rabbit, dog and human plasma. The exposure margins accounting for the unbound fractions in plasma were calculated and presented as requested. Although the margins at some points were below 1 it can be concluded that the M3 and M4b had been sufficiently covered in the toxicology program.

Toxicology

Palovarotene produced skeletal effects in rats. In juvenile animals, adverse bone effects (abnormal bone shape, bone loss and thinning/closure of femur and ulna) was seen at ≥0.5mg/kg/day. Mild chondrodystrophy was seen at the same dose but turned adverse at 1.2 mg/kg/day. In adults, skeletal effects were limited to chondrodystrophy in the epiphyseal growth plate. Skeleton effects were not seen in rabbits and dogs and, as the applicant claims, this reflects the fact that the growth plate remains open in rats well into adulthood, unlike in rabbits, dogs or humans. As seen with other RAR agonists in rats, there was a tendency of increased chondrodystrophy with dose level but not with duration. Therefore, it seems likely that the chondrodystrophy seen in adult rat pose no risk for adult patients. However, for paediatric patients where the growth plates have not closed there seems to be a risk as the intended pharmacological activity of the test-article is to prevent HO by inhibiting chondrogenesis. However, the applicant's proposal to include children, girls from 8 year and boys from 10 years, are not agreed since the safe use of palovarotene in patients with growing skeleton is still not considered sufficiently shown (see section 2.5.8. Clinical Safety).

No PPND study was conducted, and no data are available on palovarotene levels in human breast milk. Also, there are no data available on the influence of palovarotene on neurobehavioral development and reproductive performance in animals exposed pre-postnatally to palovarotene. Due to the teratogenic and embryotoxic effects seen with palovarotene at clinically relevant doses there is apparent risk that the survival will be too low to assess the appropriate endpoints in a PPND study. Based on this and in

agreement with 3R principles, it is considered that such a study is not needed. Further, relevant risk minimisation measures are proposed by the applicant (see section 2.5.8. Clinical Safety).

Skin lesions were observed in all toxicological species. This was manifested by hair loss, reddening/swelling of the facial area, acanthosis, chronic-active skin inflammation, pododermatitis, skin lesions of head, neck, torso, feet and/or ears, hypergranulosis and erosions. The NOAEL for skin lesions occurred at below or at similar exposures compare to the intended clinical dose. Some NOAELS proposed by the applicant may need re-evaluation. Since skin lesions can be monitored in the clinic, they are considered to pose a low risk to human safety.

Toxicity in male reproduction organs occurred in all toxicological species. This was manifested by decreased mean epididymis weight, lower motile and normal sperms, lower mean sperm count in left epididymis in rat and decreased secretory content in the seminal vesicles and marked degeneration of testes in juvenile rats. In rabbits, testicular degeneration/atrophy and hypospermia in the epididymides were observed and multifocal testicular atrophy/degeneration in testes were seen in dogs. In addition, the two hydroxy metabolites (M2 and M3) of palovarotene generated also testicular degeneration and increased incidence of multinucleated giant cells in testes in dogs. The applicant claims that these findings (except those that occurred at 5.0 mg/kg/day in rat) are background findings. The NOAEL for the observed testicular findings corresponds to an exposure with no marginal to the intended clinical dose. However, the testicular findings were found in animals with poor clinical condition and control animals, and were either mild, sporadic, or dissimilar, and it seems likely that the testicular findings are not related to treatment.

No studies have been done to evaluate the carcinogenic hazard posed by palovarotene. A weight-of-evidence analysis was performed indicating that a 2-year rat carcinogenicity study with palovarotene is not likely to add value to the human carcinogenicity risk assessment. This is in line with the draft Addendum to the ICH guideline S1B on testing for carcinogenicity of pharmaceuticals (EMA/CHMP/ICH/272147/2021) and agreed by CHMP.

ERA

Palovarotene PEC surfacewater value is below the action limit of 0.01 µg/L. The log Kow does exceed 4.5 and at present it is not possible to conclude on the PBT assessment. Since significant sediment shifting occurs with a DT50 value over 180 d, palovarotene is classified as very persistent (vP) in sediment and total system (aquatic sediment system).

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of palovarotene to the environment.

The applicant committed to perform the following studies as follow-up measures:

The applicant should conduct a new OECD 305 bioconcentration study at a lower, non-toxic test concentrations of palovarotene in a stepwise procedure. If the results of the feasibility study indicate that an OECD 305 test is practicable at the tested concentration, the applicant is willing to conduct a further bioconcentration study in fish with a 28-day exposure phase and a 14-day depuration phase as a second step.

This is approach could be acceptable provided a positive benefit risk on palovarotene in the treatment of FOP can be concluded.

2.4.7. Conclusion on the non-clinical aspects

Overall, based on the primary pharmacodynamic studies, it is has been shown that palovarotene is a RARγ agonist. The micro CT images of bone in the Q207D mouse model clearly illustrate effect of palovarotene on HO, however, the ability of this model to capture the human disease is uncertain.

The off-target interactions noted in the secondary pharmacodynamics study are unlikely to cause adverse effects in humans.

The toxicological program revealed that palovarotene induced adverse effects on mucocutaneous system (skin, stomach, and oesophagus), male reproductive system, skeleton and female fertility, and that palovarotene have embryotoxic and teratogenic potential, at low exposures compared to that of the intended clinical dose. The effects on skeleton (bones and cartilage) seen in juvenile rats are of specific concerns for paediatric patients with growing bones. The carcinogenicity potential is considered minimal based on a weight-of-evidence approach.

The applicant proposed a post authorisation study to allow definite conclusion on the potential risk of palovarotene to the environment. This proposal could have been acceptable should the benefit-risk of the product be considered positive. In view of the negative CHMP opinion, this post authorisation study cannot be requested.

With the post-authorisation study proposed, the non-clinical part could have been considered acceptable.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical 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)

Study Number (Phase)	Design	Population	Dose/Treatment	Number of Subjects per Dose
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 1: oral QD 10 mg for 2 weeks, then 5.0 mg for 4 weeks, or placebo	Cohort 1: 12 active; 4 placebo
		Cohort 2: FOP subjects with active flare-ups age ≥6 years	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 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).

Study Number (Phase)	Design	Population	Dose/Treatment	Number of Subjects per Dose
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)

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Palovarotene is a highly lipophilic compound with a molecular weight of 414.54 g/mol. The molecule is a benzoic acid which is negatively charged at physiological pH in blood.

Characterisation of the *in vivo* pharmacokinetics of palovarotene was based on 12 completed Phase 1 clinical pharmacology studies in healthy subjects. Palovarotene was administered orally (once-daily) as an immediate-release capsule formulation. Intravenous PK parameters have not been determined in humans.

Pharmacokinetic data in the target patient population were collected in three multiple-dose studies in subjects with FOP (Study PVO-1A-201, Study PVO-1A-202, Study PVO-1A-301), and in the Phase 2 study in subjects with MO (Study PVO-2A-201). Pharmacokinetic results from studies in subjects with COPD were also submitted. A population pharmacokinetic model was developed for palovarotene using data obtained after single- and multiple-dose oral administration to healthy volunteers and subjects with COPD, FOP, and MO.

Methods

- *Analytical methods*

Plasma concentrations of palovarotene and its metabolites M2, M3, M4a and M4b were quantified with validated LC-MS/MS methods.

- *Pharmacokinetic data analysis*

Pharmacokinetic evaluation of plasma concentration data from individual studies was performed using standard non-compartmental methods.

The population PK analysis was mainly performed to support the proposed weight-adjusted posology in children below 14 years of age (skeletally immature children).

The objectives of the population pharmacokinetic (popPK) analysis were to:

- develop a popPK model to describe the time course of palovarotene in plasma after oral administration to healthy volunteers and to patients with COPD, FOP and MO.
- estimate between and within patient variability and explore and quantify the potential influence of covariates that contribute significantly to the between subject differences in the PK parameters.
- apply the popPK model in a simulation study to assess the appropriateness of weight-based dosing of palovarotene in a paediatric population.

Initially, a popPK model was developed based on exposure data in healthy volunteers (study nos. RB16327, NP17584, NP17726, PVO-1A-101, RB16328, NP17055, NP21025 and PVO-1A-102) and patients with symptomatic emphysema secondary to COPD (study nos. NA17598, NP17124 and NB18332), FOP (study nos. PVO-1A-201, PVO-1A-202 B and C and PVO-1A-301) and MO (study no. PVO-2A-201). Henceforth, this model is called the "original popPK model". After the original analysis, two model updates (model Updates 1 and 2) were performed based on additional data collected in healthy volunteers and FOP and MO subjects.

The analyses were performed using Nonlinear mixed effects modelling (NONMEM, Version 7.4.3). Monte Carlo Importance Sampling Expectation Maximization (EM) (IMP) was the method of parameter estimation. "Mu Referencing" was used to improve the efficiency of computations.

9088 concentration records from 701 subjects were included in the popPK dataset (observations after data exclusions). 11% (including 673 post-dose BLQ concentrations) palovarotene concentrations were excluded from the analysis. The majority of the post-dose BLQ concentrations came from studies RB16327 and RB16328, which had a higher lower limit of quantification (LLOQ) (0.02 and/or 0.2 ng/mL) compared to all other studies (LLOQ of 0.01 or 0.0005 ng/mL). The handling of the post-dose BLQ concentrations was assessed in the initial models in the original popPK analysis by implementing the M3 method.

Demographic data for all subjects included in the original, update 1 and update 2 analyses are summarised in Table 2.

Table 2: Summary of Subject Demographics in popPK Analysis

Covariate	Statistic	Original	Overall Update 1	Overall Update 2
	Number of Subjects	577	638	701
Age (yrs)	Median (Min-Max)	47.0 (2.00-85.0)	44.0 (2.00-85.0)	42.0 (2.00-85.0)
Weight (kg)	Median (Min-Max)	71.0 (12.7-130)	69.4 (12.6-149)	68.2 (12.5-149)
Albumin (g/dL)	Median (Min-Max)	4.40 (3.34-5.50)	4.48 (3.34-5.50)	4.50 (3.34-5.50)
ALP (U/L)	Median (Min-Max)	73.0 (22.0-878)	76.0 (22.0-878)	77.0 (22.0-878)
ALT (U/L)	Median (Min-Max)	19.0 (5.00-90.0)	18.0 (5.00-90.0)	17.0 (5.00-90.0)
AST (U/L)	Median (Min-Max)	21.0 (6.00-76.0)	21.0 (6.00-76.0)	21.0 (6.00-76.0)
Bilirubin (mg/dL)	Median (Min-Max)	0.500 (0.0994-2.07)	0.500 (0.0994-2.07)	0.468 (0.0994-2.07)
Creatinine (mg/dL)	Median (Min-Max)	0.803 (0.200-1.60)	0.800 (0.200-1.60)	0.800 (0.200-1.60)
Gender, N (%)	Female	199 (34)	223 (35)	251 (36)
	Male	378 (66)	415 (65)	450 (64)
Race, N (%)	Asian	22 (4)	26 (4)	28 (4)
	Black	29 (5)	31 (5)	41 (6)
	White	489 (85)	536 (84)	583 (83)
	Other	16 (3)	22 (3)	24 (3)
	Unknown	21 (4)	23 (4)	25 (4)
Health Status, N (%)	COPD	198 (34)	198 (31)	198 (28)
	FOP	123 (21)	132 (21)	133 (19)
	HV	238 (41)	238 (37)	269 (38)
	MO	18 (3)	70 (11)	101 (14)
Smoking Status, N (%)	Unknown	141 (24)	150 (24)	151 (22)
	No	370 (64)	422 (66)	484 (69)
	Yes	66 (11)	66 (10)	66 (9)
Administration Method[a, b], N (%)	Sprinkled on food	77 (13)	106 (17)	125 (18)
	Swallowed whole	526 (91)	553 (87)	597 (85)
	Sprinkled on food & Swallowed whole	1 (0)	2 (0)	2 (0)
	Unknown	1 (0)	6 (1)	6 (1)
Prednisone Flag[d], N (%)	No	569 (99)	629 (99)	693 (99)
	Yes	59 (10)	62 (10)	62 (9)
Fed[e] N (%)	No	41 (7)	41 (6)	41 (6)
	Yes	565 (93)	626 (98)	689 (98)
Formulation[c], N (%)	Powder-filled hard gelatin capsule	207 (36)	268 (42)	331 (47)
	Solution-filled hard gelatin capsule	84 (15)	84 (13)	84 (12)
	Soft gelatin capsule	286 (50)	286 (45)	286 (41)
	Tablet	12 (2)	12 (2)	12 (2)

ALP = Alkaline Phosphatase, ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, HV = healthy volunteer, COPD=chronic obstructive pulmonary disease, FOP=fibrodysplasia ossificans progressiva, MO=multiple osteochondromas

[a] The same subject may have had more than one method of administration.

[b] Tablet, solution filled hard-gelatin capsule and soft gelatin capsule studies are flagged as swallowed whole.

[c] Subjects in study NP17584 received both tablet and soft gelatin capsule formulations

[d] The same subject may have had prednisone administered for not all PK concentrations so in both no and yes groups.

[e] The same subject may have had palovarotene administered in both fasted and fed conditions.

The following covariates were evaluated for their impact on the PK of palovarotene: age, body weight, sex, race, smoking status, health status (healthy volunteer, COPD patient, FOP patient, or MO patient),

co-administration with food, formulation (soft gelatin capsule, powder-filled hard gelatin capsule, solution/suspension filled hard gelatin capsule, tablet), method of administration (sprinkled on food or swallowed whole), administration of prednisone, albumin, ALT, AST, ALP, creatinine and bilirubin.

Results

The final popPK model was a two-compartment model with first-order absorption (six transit compartments were used to describe the delay in absorption) and first-order elimination. The model included differences in both mean transit time (MTT) and bioavailability under fasted conditions, and difference in MTT when the palovarotene powder in the capsule was sprinkled onto food. In addition, body weight was included as a covariate on CL/F, Vc/F, Q/F and Vp/F (estimated allometric constants).

Final popPK parameter estimates are shown in Table 3.

Table 3: Parameter Estimates of Updated Final PopPK Model (Run 082) in Update 2

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.

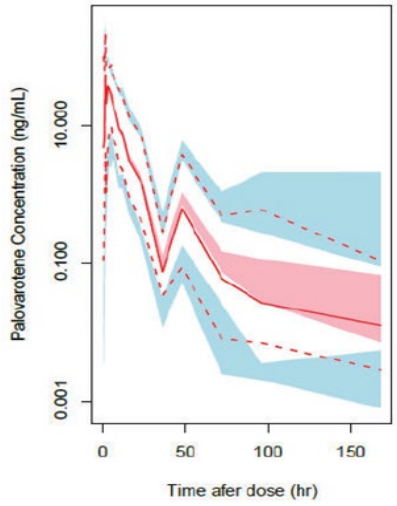
Abbreviations: CL/F = apparent total clearance, Vc/F = apparent volume of central compartment, Vp/F = apparent volume of peripheral compartment, Q/F = inter compartment clearance between central and peripheral compartments, Ka=first order absorption, MTT=mean transit time, F=bioavailability, IIV = inter-subject 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.

Source: 082.cnv/ext, 082mcmcbay.csv

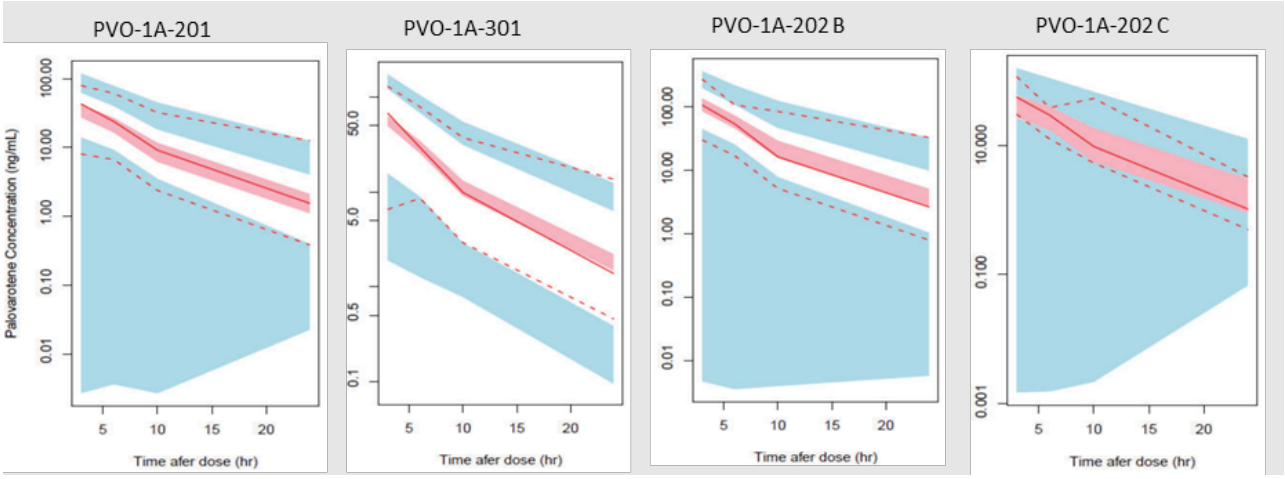
The shrinkages of individual random effects were estimated to 8% for CL/F, 25% for Vc/F, 18% for Q/F, 22% for Vp/F, 39% for Ka and 27% for MTT. Prediction-corrected VPCs (pcVPC) are shown in Figure 2 and Figure 3.

Figure 2: PcVPC for the Updated Final PK Model from Update 2 – All studies



Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th percentile of observed concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th percentiles of Predicted Concentrations
Source: 082VPC.tab

Figure 3: PcVPC for the Updated Final PK Model from Update 2 - FOP patients



Linear X Scale
Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th Percentile of Observed Concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th Percentiles of Predicted Concentrations
Source: 082VPC.tab

Body weight, fed status and powder-filled hard gelatin capsule sprinkled compared to swallowed whole were identified as significant covariates on palovarotene pharmacokinetics. The effect of capsule sprinkled on food compared to swallowed whole was not considered to be clinically relevant. For further information regarding these covariate effects, see sections *Absorption* and *Special populations*.

Absorption

Palovarotene has low solubility and high *in vitro* permeability and does not appear to be a substrate for P-gp or BCRP.

Bioavailability

The oral bioavailability of palovarotene in humans has not been determined. The estimated clearance

of palovarotene after oral administration (20 L/h) represents 20-25% of liver blood flow which indicate a low first-pass hepatic extraction ratio. The observed dose-linear PK suggests that the extent of absorption is not solubility limited. Peak plasma concentrations of palovarotene were typically observed at about 4 hours after administration.

Bioequivalence

No studies were performed to assess the relative bioavailability between the soft gelatin capsules used (in most of) the early studies and the current powder-filled hard gelatin capsule formulation. The objective of most of the Phase 1 studies using the soft gelatin capsules was to explore a relative difference in the exposure, e.g. with and without a perpetrator drug. Population PK analysis confirmed that there was no obvious difference in the clearance estimate between studies, regardless of the formulation used or the population studied (healthy or patients).

Influence of food

Sohonos is intended to be taken with food, preferably at the same time each day, according to the proposed posology. The results from a food-effect study with palovarotene hard gelatine capsules showed that $AUC_{0-\infty}$ and C_{max} were 40% and 16% higher, respectively, following a high-fat, high-calorie breakfast than after palovarotene administration under fasted conditions. Under fed conditions, there was no statistically significant difference in bioavailability between the palovarotene capsule swallowed whole and the capsule contents sprinkled onto food. A population PK analysis supported the results and conclusions from the *in vivo* study. No food effect study has been performed with the soft gelatine capsule formulation. Except for two food interaction studies, all other Phase 1 and Phase 2/3 studies have been conducted under fed conditions.

Distribution

The apparent volume of distribution following intravenous administration has not been determined. Based on population PK analysis, the apparent volumes of the distribution of the central (V_1/F) and peripheral (V_2/F) compartments are estimated at 36.2 and 77.3 L, respectively. The reported volume of distribution during the terminal phase (V_z/F) following repeated oral dosing was 319 L. The apparent volume of distribution (V_z/F) following an oral single dose (20 mg in the fasted state) was 237 L.

Palovarotene is highly bound to plasma proteins, i.e. *ca* 99%. The plasma protein binding of [^{14}C]-palovarotene was determined *in vitro* by a dextran coated charcoal adsorption method over the concentration range 6-1000 ng/mL. The fraction bound was high and ranged between 97.9 to 99.6%. In a new plasma protein binding study, albumin was identified as the major binding protein in human plasma. The plasma protein binding of the metabolites, M3 and M4b, were >99% in humans.

The blood-to-plasma ratios of palovarotene *in vitro* in humans (at 100 and 1000 ng/mL) was 0.62, indicating that palovarotene did not partition into erythrocytes. In the oral mass balance study with [^{14}C]-radiolabelled palovarotene, the mean whole blood to plasma radioactivity ratio was 0.61.

The distribution of palovarotene into seminal fluid in males was evaluated following 5-day treatment with 20 mg QD. The maximal amount of palovarotene in a single ejaculate was 33 ng or *ca* 0.00017% of the daily dose administered.

Elimination

The estimated clearance of palovarotene after oral administration (CL/F) is 20 L/h. The mean terminal half-life following 20-mg palovarotene once daily oral dosing was 8.7 hours.

Excretion

An oral single dose mass balance study with [^{14}C]-radiolabelled palovarotene showed that the drug-related radioactivity almost exclusively was excreted in faeces (97%) with a very low proportion recovered in urine (3%). The total recovery was complete, i.e. 100%.

Metabolism

Palovarotene showed a very low metabolic stability *in vitro* in human liver microsomes. In human hepatocyte incubations, 43.4% of palovarotene was transformed into five identified metabolites: M1 (0.729%), M2 (14.1%), M3 (12.8%), M4 (11.7%) and M5 (0.568%), where M5 is a carboxyl β-glucuronide of the parent compound. These results indicated a significant NADPH-oxidative metabolism of palovarotene and also β-glucuronide formation of the parent compound. No UGT-dependent metabolism was observed *in vitro*. A new *in vitro* study with ^{14}C-palovarotene in human hepatocytes was performed aiming to further elucidate the biotransformation pathways. A new *in vitro* study with ^{14}C-palovarotene in human hepatocytes was performed aiming to further elucidate the biotransformation pathways. The proposed metabolic pathways of palovarotene are shown in Figure 4.

In vitro studies to assess the CYP isoform(s) responsible for the oxidative biotransformation strongly suggest that palovarotene primarily is metabolised by CYP3A4 (98% turnover) and to a minor extent by CYP2C19 (14% turnover) and CYP2C8 (4% turnover). In the incubation with human recombinantly expressed CYP3A4, palovarotene was converted to the mono-hydroxylated metabolites M2 and M3 (6- and 7-hydroxy, respectively) which were further transformed to the oxo metabolites M4a and M4b (6- and 7-oxo, respectively).

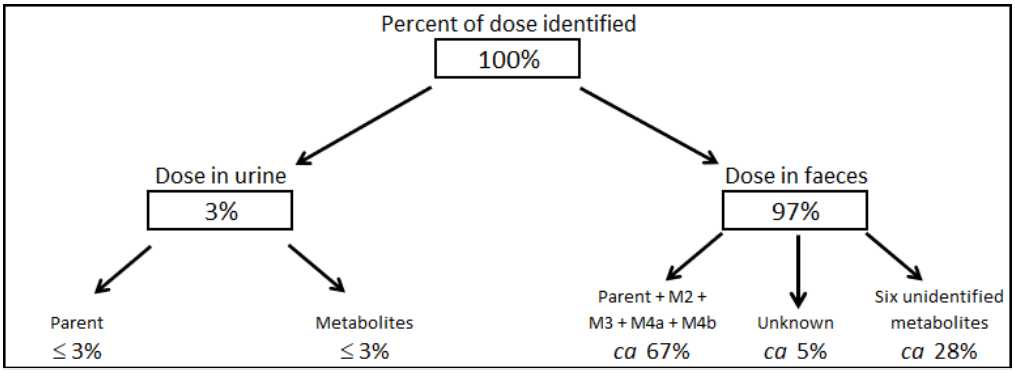
The plasma pharmacokinetics of the metabolites M2, M3, M4a and M4b was characterised in healthy volunteers (and in COPD patients), both following single and repeated dose administration of palovarotene. All four metabolites had a slower elimination rate than the parent compound with plasma half-lives in the range 16 to 30 hours, as compared to palovarotene's $t_{1/2z}$ of ca 8 hours. Metabolite M3 had the highest plasma exposure (50-60% of the palovarotene AUC) followed by M4b. Metabolite M4b had the longest half-life, i.e. 29.7 hours which is close to that estimated for the drug related [^{14}C]-palovarotene radioactivity in the massbalance study (36.6 hours).

The $AUC_{0-\tau}$ ratios (metabolite/parent) for each metabolite were consistent across studies and appeared to be dose proportional between 1 and 5 mg doses of palovarotene. The four mentioned metabolites were not quantified in the clinical studies in FOP (and MO) patients.

The *in vitro* potency of the metabolites with the highest plasma exposure, i.e. M3 and M4b, was 1.7% and 4.2%, respectively, of the activity of palovarotene which suggest that none of the identified metabolites will contribute to the pharmacological effect *in vivo* in humans.

Metabolite profiling was performed in plasma, urine and faeces samples collected in the oral single dose mass balance study with [^{14}C]-radiolabelled palovarotene. In urine, metabolites were unsuccessfully profiled because of the low amount of radioactivity. In faeces samples, palovarotene and four of its identified metabolites together accounted for 67.2% of the dose while six other unidentified metabolites accounted for 28.4%. Two of these six unidentified metabolites accounted for 28.4%. Two of these six unidentified metabolites were reported to represent >5%, i.e. 6% and 10%, respectively, of the radioactivity in faeces Figure 4.

Figure 4 Results from the [^{14}C]-radiolabelled palovarotene oral massbalance study (Study NP17056)



In plasma, the AUC of palovarotene constituted 14% of the total radioactivity AUC exposure. The corresponding relative exposure of the identified palovarotene metabolites was: M3 10% > M4b 7% > M2 5% > M4a 4%. Hence, overall ca 60% of the drug-related radioactivity in plasma was not characterised, which raises concerns. The analytical protocol (the mass balance study was conducted in 2003) describes the metabolic profiling as exploratory and appears only to have been performed in pooled plasma samples collected at early time points where it was found that unknown chromatographic peaks accounted for 24% at 2 hours and 13% at 4 hours. Based on the information in the study report, the sum of the parent compound and the four metabolites constituted ca 60% of the radioactivity at those time points. In the new *in vitro* metabolism study in human hepatocytes aside from the main metabolites identified in the mass balance study (M2, M3, M4a and M4b) and metabolites detected in *in vitro* studies (M1a, M1b and M5), 8 previously unknown metabolites (M7, M8, M6a, M6b, M1c, M1d, M9 and M10) were identified. The newly identified metabolites do only represent a minor share. The *in vitro* study also supports that the unknown chromatographic peaks in pooled plasma at 2 and 4 hours in the mass balance study is most likely caused by an overloaded HPLC column and did not present a specific single metabolite.

Dose proportionality and time dependencies

Palovarotene appeared to exhibit dose-linear pharmacokinetics within the clinically relevant dose range.

There was no indication of time dependent PK following repeated administration. In accordance with a half-life of <10 hours, the degree of accumulation following once-daily oral administration was low.

Intra- and inter-individual variability

The inter-individual variability (CV%) in the PK of palovarotene in the clinical studies in FOP patients was high, generally between 30-50% for the oral clearance (CL/F) and 40-50% for C_{max}. In the population PK analysis, the inter-individual variability was estimated to 34% for CL/F and *ca* 90% for the volume parameters. The inter-occasion (IOV) variability was approximately 45% for k_a and MTT.

Pharmacokinetics in target population

The pharmacokinetics of palovarotene was assessed based on semi-sparse data in the three multiple-dose studies in subjects with FOP (one completed Phase 2 study [Study PVO-1A-201], one ongoing Phase 2 study [Study PVO-1A-202], and one ongoing Phase 3 study [Study PVO-1A-301]), and one Phase 2 study in subjects with MO (Study PVO-2A-201). Concurrent oral medication identified as strong inhibitors or strong inducers of CYP3A4 were excluded.

The pharmacokinetics in the target population appeared to be dose proportional across dose range studied (2.5-20 mg). The PK estimates during flare-up treatment were similar whether the chronic dosing had been administered prior to flare-up dosing or not. Peak plasma concentrations of

palovarotene were typically observed at 3 hours after dosing and then declined with a half-life of 4-5 hours. The half-life estimates may be slightly underestimated due to the semi-sparse sampling schedule. Generally, the inter-individual variability (CV%) in PK was high, ranging between 30-50% for CL/F and 40-50% for $C_{max,ss}$. Overall, considering the differences in the applied sampling schedule, the pharmacokinetics in the patient population appeared similar to that in healthy volunteers (Table 4).

Table 4 Summary of Steady-State Exposures (50% Median [90% Prediction Interval]) Following 5, 10 and 20 mg Palovarotene in the Paediatric Population by Weight Category

Dose	Weight Category	Dose	$C_{max,ss}$ (ng/mL)	$C_{min,ss}$ (ng/mL)	$AUC_{0-\tau}$ (ng·h/mL)
5 mg once daily	<20 kg	2.5 mg	50.6 (47.1-54.0)	0.769 (0.645-0.866)	263 (243-282)
	20-40 kg	3 mg	40.0 (38.2-42.2)	0.931 (0.829-1.05)	237 (225-248)
	40-60 kg	4 mg	36.7 (34.3-39.0)	1.27 (1.11-1.45)	242 (228-254)
	≥60 kg	5 mg	35.9 (32.8-39.6)	1.58 (1.30-1.91)	252 (232-277)
10 mg once daily	<20 kg	5 mg	101 (94.1-108)	1.54 (1.29-1.73)	527 (485-563)
	20-40 kg	6 mg	80.0 (76.3-84.4)	1.86 (1.66-2.10)	474 (450-495)
	40-60 kg	7.5 mg	68.8 (64.4-73.2)	2.38 (2.09-2.72)	454 (428-476)
	≥60 kg	10 mg	71.9 (65.7-79.1)	3.16 (2.61-3.82)	504 (464-554)
20 mg once daily	<20 kg	10 mg	202 (188-216)	3.07 (2.58-3.46)	1054 (971-1126)
	20-40 kg	12.5 mg	167 (159-176)	3.88 (3.46-4.37)	988 (938-1032)
	40-60 kg	15 mg	138 (130-146)	4.76 (4.17-5.44)	909 (856-952)
	≥60 kg	20 mg	144 (131-158)	6.32 (5.22-7.65)	1008 (928-1107)

Source: Module 2.7.2 Table 40

Special populations

Sex, race, age, body weight

In the population PK analyses, there was no evidence that gender, race, or age affected the pharmacokinetics of palovarotene. Body weight was identified as a clinically relevant covariate. From simulations in adult subjects, derived $AUC_{0-24,ss}$ and $C_{max,ss}$ were 8% and 12% higher for a 51-kg subject (5^{th} percentile of weight from adults in analysis) and 18% and 26% lower for a 98-kg (95^{th} percentile of weight from adults in analysis), respectively, compared with a 70-kg typical subject. Dose adjustments based on weight is proposed in patients ≤14 years of age (presumed to have skeletal maturity <90%).

Children

Weight-adjusted dosing is proposed in children ≤ 14 years of age. In the clinical studies in FOP and MO patients (Phase 2 and Phase 3 studies) weight-adjusted doses were used in skeletally immature subjects for the weight categories 10 to<20 kg, 20 to <40 kg, 40 to <60 kg, and ≥60 kg.

Pharmacokinetics interactions studies

A number of *in vitro* studies were performed to assess whether palovarotene is a substrate, inhibitor and/or inducer of metabolising enzymes, and a substrate and/or inhibitor of various transporters. In addition, *in vivo* drug-drug interaction studies were performed with rifampicin (a strong inducer of CYP3A4), ketaconazole (a strong inhibitor of CYP3A4) and prednisone (a weak inhibitor of CYP3A4 inhibitor), respectively. As a response to a request during the assessment, the applicant provided a

PBPK model to predict the effect on palovarotene exposure in the presence of moderate CYP3A4 inhibitors and inducers.

In vitro CYP450 enzyme inhibition

Palovarotene is considered not to pose a clinically relevant risk for inhibition (direct or time-dependent) of CYPs 1A2, 3A4, 2B6, 2C8, 2C9, 2C19 and 2D6 systemically, or of CYP3A4 intestinally, *in vitro*.

The metabolites of palovarotene (M1a, M1b, M2, M3, M4a and M4b) showed a low potential for inhibition of CYP3A4. A new *in vitro* CYP inhibition study was performed with M3 and M4b. M3 and M4b did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 at clinically relevant concentrations.

In vitro CYP450 enzyme induction

Palovarotene showed no potential for induction of CYP1A2, CYP2C8, CYP2C9 and CYP2C19 *in vitro*, whereas a risk for induction of CYP3A4 and 2B6 could not be excluded. This was further assessed *in vivo* for CYP3A4 (see below) but not for CYP2B6. Based on *in vitro* data, it is considered that CYP2B6 induction by palovarotene *in vivo* cannot be excluded.

In vitro UGTs inhibition

Palovarotene did not appear to be a significant substrate or an inhibitor of human UGTs (i.e. 1A1, 1A3, 1A4, 1A6, 1A9 and 2B7) *in vitro*. Hence, the risk for palovarotene inhibition of UGT-dependent elimination of other drugs is predicted to be low.

In vitro transporter substrate identification and inhibition

Based on the submitted data, palovarotene did not appear to be a substrate of the transporters P-gp, BCRP, OATP1B1, OATP1B3, or OCT1 *in vitro*. However, these experiments were performed at higher test concentrations than those recommended in the EMA Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**).

Palovarotene as a substrate for renal transporters (OAT1, OAT3, OCT2, MATE 1 and MATE2-K) has not been investigated, which is acceptable considering the negligible contribution of renal clearance.

Based on *in vitro* data, palovarotene is not an inhibitor of P-gp, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 or MATE2-K *in vitro* and considered not pose a clinically relevant risk to inhibit BCRP, OCT1 or BSEP.

In vivo DDIs with CYP3A4

The DDI risks for palovarotene as a victim drug were evaluated *in vivo* with the strong CYP3A4 inhibitor ketoconazole, with the considered weak CYP3A4 inhibitor prednisone, and with the strong CYP3A4 inducer rifampicin. The systemic exposure of palovarotene increased substantially, 3-fold for $AUC_{0-\tau}$ and 2-fold for C_{max}, in the presence of ketoconazole, which implicate that palovarotene should

not be co-administered with strong inhibitors of CYP3A4. No clinically relevant effect on the palovarotene pharmacokinetics was observed in the study with prednisone.

The systemic exposure of palovarotene decreased substantially, 10-fold for $AUC_{0-\tau}$ and 5-fold for C_{max}, in the presence of rifampicin, which clearly shows that co-administration of palovarotene with strong inducers of CYP3A4 should be avoided.

The DDI risks for palovarotene as a perpetrator drug, i.e. as a CYP3A4 inhibitor or inducer, were also evaluated *in vivo*. The two clinical studies with midazolam showed that palovarotene is not expected to affect the PK of other drugs metabolized by CYP3A4.

No *in vivo* interaction studies between palovarotene and hormonal contraceptives have been performed, although this is required according to the regulatory guidelines, most importantly since palovarotene is considered teratogenic.

PBPK model

A PBPK model for palovarotene was developed and used to assess the impact of moderate CYP3A4 reversible inhibition and mechanism-based inhibition on palovarotene PK.

When co-administered with a moderate CYP3A4 inhibitor (erythromycin), the PBPK model predicted 1.6 and 2.5 higher C_{max} and AUC of palovarotene, respectively, as compared to palovarotene alone.

Using the qualified PBPK palovarotene model, weak CYP3A4 inhibition was assessed using cimetidine, a weak CYP3A4 inhibitor. There was no discussion regarding the therapeutic window of palovarotene, and it is unclear how large increase in drug exposure that can be acceptable without clinical consequences. The simulations indicated a slight increase in the C_{max} and AUC of palovarotene (approximately 10% increase), when co-administered with cimetidine as compared to alone.

Exposure relevant for safety evaluation

Simulations from a population pharmacokinetic model predict that the median C_{max} and AUC_{0-24h} values at the highest proposed clinical dose of 20 mg/day range from 138 to 202 ng/mL and 909 to 1054 ng·h/mL, respectively. A C_{max} of 200 ng/mL corresponds to an unbound C_{max} of 2 ng/mL (fu=0.01).

2.5.2.2. Pharmacodynamics

Mechanism of action

Palovarotene is a highly lipophilic low molecular weight compound that pharmacologically acts as a retinoic acid receptor gamma (RARγ) agonist.

Through binding to RARγ, palovarotene decreases signalling through the bone morphogenetic protein pathway, leading to an inhibition of SMAD1/5/8. These signalling pathways are deeply involved in the pathogenesis of myositis ossificans, hence in FOP, and by interfering with these processes, palovarotene would prevent chondrogenesis and ultimately HO.

In animal models of FOP and injury-induced HO, palovarotene reduced new HO. It reduced mast cell infiltration and fibroproliferative response at the site of muscle injury in a damaged muscle. Palovarotene also inhibited chondrogenesis and therefore new HO by decreasing Smad signalling. Through this, palovarotene enables normal muscle tissue repair or regeneration to take place and reduces damage to muscle tissue.

Primary and Secondary pharmacology

Primary

The primary pharmacodynamics of palovarotene were evaluated in a series of *in vitro* and *in vivo* studies to characterise the RAR binding affinity and transactivation potential of palovarotene and its metabolites, to describe palovarotene mechanism of action on chondrogenesis and HO and, to evaluate palovarotene efficacy in various injury-based and spontaneous animal models of HO and FOP (see section Non-clinical pharmacology 2.4.2.).

Results from the dose-finding studies in patients are described in the clinical efficacy section 2.5.5.1.

An exploratory analysis was conducted to describe the relationship between palovarotene exposure and six response measures (change in HO volume, change in FOP-Physical Function Questionnaire (FOP-PFQ) score, changes in investigator- and patient-reported global assessment of movement (GAM) scores, and changes in numeric rating scale scores for pain and swelling) in subjects with FOP from three clinical studies (Studies PVO-1A-001, PVO-1A-201 and PVO-1A-202). Changes were computed as the difference for each response measure between baseline and Day 84 of each flare-up occasion. Empirical Bayes estimates (EBEs) of individual model-derived PK parameters and individual dosing histories were used to compute palovarotene exposure over each flare occasion. Exposure metrics included the average daily dose, AUC, and the cumulative dose of palovarotene. Exposure response trends were assessed graphically and by linear regression. Ordered logistic regression analysis was also used for GAM scores. The results indicated no ER trends.

Secondary

No formal examination of the PK/PD relationship for safety was undertaken in the popPK analysis. The relationship between palovarotene exposure and premature physeal closure (PPC) was assessed. Given that palovarotene exposure (as the product of AUC and the days of dosing) was similar in subjects with and without PPC, no palovarotene exposure threshold could be established below which skeletally immature subjects were at no risk of developing closure. There was a slight trend for longer duration and greater total (mg) palovarotene flare-up treatment exposure in the <8/10 years population with PPC compared with those without PPC

A thorough QT study PVO-1A-103 was conducted to evaluate the effect of a therapeutic (20 mg) and a supratherapeutic (50 mg) dose of palovarotene on the QT interval in 32 healthy adult subjects. This was a Randomized, Partially Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study. The subjects were administered single doses of 20 and 50 mg palovarotene, placebo for palovarotene, and 400 mg moxifloxacin.

Mean change-from-baseline HR (ΔHR) on active treatment followed the pattern observed on placebo and mean placebo-corrected ΔHR (ΔΔHR) ranged from -1.6 to 3.4 bpm across postdose time points at both dose levels of palovarotene.

Mean change-from-baseline QTcF (ΔQTcF) on palovarotene closely followed the placebo pattern across postdose time points, and mean placebo-corrected ΔQTcF (ΔΔQTcF) ranged from -2.1 ms (10 hours postdose on 20 mg) to 2.4 ms (1 hour postdose on 20 mg), without a pattern of dose-dependency. There were no subjects with QTcF >450 ms and ΔQTcF >30 ms. There were no treatment-emergent T-wave morphology changes or U-waves.

The predicted ΔΔQTcF, using a linear model, were 0.97 ms (90% CI: -0.80, 2.74) and 0.95 ms (90% CI: -0.98, 2.89) for palovarotene 20 mg (geometric mean C_{max}=134 ng/mL) and palovarotene 50 mg (geometric mean C_{max}=314 ng/mL), respectively. Based on concentration-QTc analysis, an effect on ΔΔQTcF exceeding 10 ms can be excluded within the range of observed palovarotene plasma concentrations up to ~500 ng/mL.

2.5.3. Discussion on clinical pharmacology

The clinical pharmacology characteristics of Sohonos are based on clinical pharmacology phase I studies in healthy subjects.

Initially, the applicant proposed that the oral posology included once-daily administration at doses from 5 mg up to a maximum of 20 mg with a (immediate-release) powder-filled capsule formulation. The dosing regimens were proposed to be adjusted for weight in children <14 years of age. During the assessment, the applicant proposed a weight-based posology for all patients. Based on popPK simulations, the proposed dosing appears to result in a similar exposure in all weight groups but higher fluctuations in the smaller children.

Pharmacokinetics

The PK parameters have been well characterised and are presented in the PK results section.

The submitted pharmacokinetic data showed that the PK of palovarotene following oral administration was described by a two-compartment model with a mean terminal half-life of 8.7 hours. The accumulation following repeated dosing was marginal and the plasma pharmacokinetics was considered linear to dose. The binding to plasma proteins is high, ca 99%. Palovarotene is predominantly cleared by metabolism via CYP3A4 followed by excretion by the bile. Two of the metabolites (M3 and M4b) showed a relatively high plasma exposure. Only the parent compound is considered to contribute to the pharmacological activity. There was no obvious difference in apparent clearance (CL/F) between healthy volunteers and patients. The inter-individual variability (CV%) in plasma exposure in the intended target population was high, generally between 30-50%. Of note, an exposure-response analysis using data from the FOP program found no consistent trends and no palovarotene exposure threshold with respect to safety could be established.

In plasma, the AUC of palovarotene constituted 14% of the total radioactivity AUC exposure. The corresponding relative exposure of the identified palovarotene metabolites was: M3 10% > M4b 7% > M2 5% > M4a 4%. Hence, overall *ca* 60% of the drug-related radioactivity in plasma was not characterised.

According to the *Guideline on the investigation of drug interactions Appendix V (CPMP/EWP/560/95/Rev. 1 Corr. 2):* "Effort should be made to identify as much of the dose related material as possible. It is generally recommended that metabolites contributing to >10% of the AUC of drug related material (e.g. radioactivity in a mass-balance study) are structurally characterised."

The applicant was requested to discuss the fact that a large part of the metabolites in plasma was unknown, and in the light of the proposed biotransformation pathways of palovarotene with possible metabolites circulating as glucuronides/conjugates, discuss the risk for and the clinical implications of potential unidentified relevant metabolite(s). A question was also raised if the unidentified radioactivity was present as a number of minor peaks or if there were any major unidentified chromatographic peak.

The applicant therefore performed a new *in vitro* study in human hepatocytes with ^{14}C-paloverotene to elucidate as much as possible of the biotransformation pathways. Totally, 15 metabolites were detected and were characterised to a certain level. Aside from the main metabolites identified in the mass balance study (M2, M3, M4a and M4b) and metabolites detected in *in vitro s*tudies (M1a, M1b and M5), 8 previously unknown metabolites (M7, M8, M6a, M6b, M1c, M1d, M9 and M10) were identified. The newly identified metabolites do only represent a minor share. The applicant also clarified that the large unknown peak was observed in the metabolite profiling of plasma samples (24% at 2 hours and 13% at 4 hours) in one of three analytical set ups (three analytical methods, HPLC methods 1-3 were used). The new *in vitro* study supports that these unknown peaks, is most likely

caused by an overloaded HPLC column (saturation of the stationary phase and decrease of the column performance). Overall, based on the results from the metabolite profiling in plasma samples and the *in vitro* metabolism study, the metabolic pattern of palovarotene appears to be sufficiently clarified, and seem to support that no additional major metabolite will be evident in plasma. Thus, no new clinical study with radiolabelled drug is required.

Pharmacokinetics in the target population

The pharmacokinetics in the target population appeared to be dose proportional across the dose range studied (2.5-20 mg) and not different to that in healthy volunteers. The PK estimates during flare-up treatment were similar whether the chronic dosing had been administered prior to flare-up dosing or not. Generally, the inter-individual variability in PK was high.

Pharmacokinetics in special populations

Based on population PK analysis, no dose adjustments are required depending on gender, race or age whereas body weight was identified as a clinically relevant covariate (see below).

The impact of renal impairment on the pharmacokinetics of palovarotene has not been investigated in a dedicated renal impairment PK study. Due to the negligible contribution of renal clearance to the overall elimination from the body, this is maybe considered acceptable. The popPK analysis also showed no effects on the pharmacokinetics in patients with mild and moderate renal impairment. However, normally, a study in severe renal impairment is expected also for hepatically cleared drugs, as severe renal impairment may influence drug metabolism and transport. Overall, it can be concluded that no dose-adjustments are needed in patients with mild or moderate renal impairment. Use in patients with severe renal impairment is not recommended.

No study in subjects with hepatic impairment has been performed which raises concerns. Palovarotene is almost exclusively metabolically cleared, primarily via CYP3A4, and the fact that ketoconazole as a perpetrator drug caused a 3-fold increase in palovarotene exposure strongly suggest that hepatic impairment can lead to higher plasma exposure of palovarotene and probably, depending on severity of the impairment, call for dose adjustments in this population.

Given the small patient population and the rarity of liver dysfunction in the patient population, though, it is considered acceptable that a study in subjects with impaired liver function has not been performed. The results from an explorative analysis on the effect of hepatic status on palovarotene PK (based on data from the popPK model) support that no dose-adjustments are needed in subjects with mild hepatic impairment. Only a few subjects with moderate hepatic impairment and no subjects with severe hepatic impairment were included in the clinical studies. The applicant provided PBPK simulations to support that palovarotene should be used in caution in patients with moderate hepatic impairment. However, the PBPK model cannot be used to support these SmPC recommendations. The use of palovarotene in patients with moderate and severe hepatic impairment is not recommended**.**

It should be noted that if the application is extended to other indications, a hepatic impairment study may be required.

Population PK analysis and proposed body weight-adjusted dosing

The population PK analysis was performed to support the weight-adjusted posology initially proposed in paediatrics below 14 years of age. The population PK model seems to describe the pharmacokinetics of palovarotene reasonably well.

In the first round of assessment, a major objection was raised regarding the proposed posology. The reference target exposure had not been defined and presented in the simulations introducing an uncertainty of whether the targeted exposure is corresponding to an efficacious and safe dosing

regimen. It was also unclear how the steady-state exposures (C_{max}, C_{min} and $AUC_{(0-24)}$) were between the different body weight cohorts. There were also concerns regarding the proposed posology in adults and adolescents > 14 years of age, as it was unclear why the weight-based dosing is not applied in this group which may result in higher exposure in subjects with a lower body weight. This major objection was not further pursued since the clinical effect of palovarotene in the treatment of adult and paediatric patients with FOP has not been established (see clinical efficacy), and therefore the therapeutic exposure range is unknown. In addition, the upper target concentration range is questioned due to the different safety profile between children and adults (for instance growing children are considered at risk for Premature physeal closure, PPC). However, based on the simulations provided, the proposed dosing appears to result in a similar exposure in all weight groups but higher fluctuations in the smaller children. Potential clinical relevance of increased fluctuation is not possible to assess, since the clinical effect of palovarotene in the treatment of patients with FOP has not been established, and therefore the therapeutic interval is uncertain.

The overall benefit-risk assessment with the proposed posology must be based on the efficacy and safety data from patients included in the clinical studies. A similar posology as proposed was used in the main clinical studies. The weight-adjusted posology was however only given to skeletally immature patients.

Drug-drug interactions

Palovarotene is considered not to pose a clinically relevant risk for inhibition of CYPs 1A2, 3A4, 2B6, 2C8, 2C9, 2C19 and 2D6 systemically, or of CYP3A4 intestinally, *in vitro*. No information was provided on whether pre-incubation with the investigational drug alters the inhibitory potential of the drug. An *in vitro* study assessing potential time-dependent inhibition of CYPs by palovarotene has been performed. Palovarotene is not considered to be a time dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.

The metabolites of palovarotene, M1a, M1b, M2 and M4a, showed a low potential for inhibition of CYP3A4. In addition, M3 and M4b do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 at clinically relevant concentrations.

Palovarotene showed no potential for induction of CYP1A2, CYP2C8, CYP2C9 and CYP2C19 *in vitro*, whereas a risk for induction of CYP3A4 and 2B6 could not be excluded. This was further assessed *in vivo* for CYP3A4 (see below) but not for CYP2B6. Based on *in vitro* data, it is considered that CYP2B6 induction by palovarotene *in vivo* cannot be excluded. An adequate warning has been included in the SmPC about co-administration with sensitive CYP2B6 substrates. Also, although there is no well-documented probe-drug for CYP2B6 induction at the present time, should be the benefit risk balance of palovarotene be positive, the applicant is encouraged, as a post authorisation measure study, to monitor literature / regulatory guidance for an adequate probe drug for an *in vivo* study and to conduct such a study should an adequate probe drug become available.

The risk for palovarotene inhibition of UGT-dependent elimination of other drugs is predicted to be low.

The applicant considered palovarotene not to be a substrate of the transporters P-gp, BCRP, OATP1B1, OATP1B3, or OCT1 *in vitro*. However, the design of the performed study does not allow firm conclusions to be drawn since transporters active at low concentrations may have been saturated at the test concentrations studied (1 to 100 μM). The applicant argued that no additional experiments will be performed since the LLOQ of the bioanalytical method did not allow testing lower concentrations, and also states that 1 μM is believed to be an acceptable concentration for testing interaction with renal and hepatic transporters. However, since palovarotene is predominantly cleared by metabolism followed by excretion in the bile, the applicant should as minimum requirement find a way to evaluate the interaction between palovarotene and the hepatic uptake transporters OATP1B1, OATP1B3, e.g. by

using radiolabeled test compound which will allow a lower limit of quantification, using test concentrations according to the Guideline on the investigation of drug interactions Appendix III (CPMP/EWP/560/95/Rev. 1 Corr. 2). The applicant agrees to perform the OATP1B1/B3 *in vitro* study as a post approval commitment. This could have been acceptable should the benefit risk of palovarotene be concluded positive. In view of the CHMP negative opinion, this remains to be addressed in a future procedure.

Palovarotene as a substrate for renal transporters (OAT1, OAT3, OCT2, MATE 1 and MATE2-K) was not investigated by the applicant. This is found acceptable since the degree of urinary excretion of palovarotene and its metabolites is very low.

Palovarotene was shown not to be an inhibitor of P-gp, OAT1, OAT3, OCT2, MATE1 or MATE2-K *in vitro*. For the other transporters tested, BCRP, OATP1B1, OATP1B3, OCT1 and BSEP, the applicant initially concluded that palovarotene does not pose a clinically relevant risk with respect to the inhibition of any of these. Previously a clinically relevant inhibition of OTP1B1/B3 could not be excluded but based on a new cut off provided by the applicant it was concluded that that inhibition of OATP1B1/B3 *in vivo* is unlikely. Therefore, a clinical drug-drug interaction study with OATP1B1/B3 substrates is no more required.

The DDI risks for palovarotene as a perpetrator drug, i.e. as a CYP3A4 inhibitor or inducer, were evaluated *in vivo* with midazolam. The two clinical studies with midazolam showed that palovarotene is not expected to affect the PK of other drugs metabolized by CYP3A4.

Based on the results from the interaction study with midazolam palovarotene did not appear to be an inducer of CYP3A4. However, this does not rule out the possibility that palovarotene may affect the PK of oral contraceptives. According to the *Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2)*: "It should be noted that there may still be mechanisms of induction which presently are unknown. Therefore, a potential human teratogen (definition given in EMEA/CHMP/203927/2005) needs to be studied *in vivo* for effects on contraceptive steroids if the drug is intended for use in fertile women*".* During the assessment, the applicant proposed to perform a clinical DDI study with oral contraceptives as a post authorisation measure study. In the absence of *in vivo* data updates to the SmPC has been made. These proposals could have been acceptable should a positive benefit risk be concluded. In view of the CHMP negative opinion, this remains to be addressed in a future procedure.

The applicant developed a PBPK model to predict the effect on palovarotene exposure in the presence of moderate CYP3A4 inhibitors and inducers. The model is considered to have high regulatory impact. The PBPK model seems qualified for its purpose with regards to CYP3A4 inhibition (palovarotene as victim). The PBPK platform is not considered sufficiently qualified in accordance with the EMA PBPK guideline (EMA/CHMP/458101/2016) to reliably predict different levels of CYP3A induction (i.e., with strong/moderate/mild CYP3A inducers) and palovarotene as the "victim" drug.

When co-administered with a moderate CYP3A4 inhibitor (erythromycin), the PBPK model predicted 1.6 and 2.5 higher C_{max} and AUC of palovarotene, respectively, as compared to palovarotene alone. Therefore, concomitant use of a moderate or strong CYP3A4 inhibitor with palovarotene is not recommended.

An issue was raised regarding the effect on palovarotene exposure when co-administered with a weak CYP3A4 inhibitor. The applicant provided PBPK simulations for palovarotene when co-administered with a weak CYP3A4 inhibitor, cimetidine. There was no discussion regarding the therapeutic window of palovarotene, and it is unclear how large increases in drug exposure can be acceptable without clinical consequences. The simulations indicated a slight increase in the C_{max} and AUC of palovarotene (approximately 10% increase), when co-administered with cimetidine as compared to alone. It would

have been preferable if simulations for more than one weak CYP3A4 inhibitor were provided. In the EMA DDI guideline, it is stated that a weak inhibitor can increase the systemic exposure up to two-fold for a sensitive substrate. Since palovarotene is mainly metabolised by CYP3A4, the applicant should provide information on the upper range of the therapeutic interval, in terms of safety, and discuss the clinical consequences following a two-fold fold higher systemic exposure (worst-case scenario) when concomitantly treated with a mild CYP3A4 inhibitor. Alternatively, the applicant can provide PBPK simulations with other mild CYP3A4 inhibitors and discuss the clinical consequences of the predicted increase in exposure.

Considering a relatively large induction effect observed in the clinical DDI study with strong CYP3A inducer rifampicin (i.e. 10-fold decrease in palovarotene exposure), it can be expected that a similarly large DDI effect could be observed even when co-administering palovarotene with moderate CYP3A inducers. Therefore, concomitant use of a strong or moderate CYP3A4 inducer is not recommended.

Pharmacodynamics

An exploratory analysis was conducted to describe the relationship between palovarotene exposure and six clinical flare-up related endpoints in subjects with FOP. Analyses indicated no exposure response trends. No PK/PD analysis for safety was performed. The thorough QT study showed that palovarotene at the studied doses (20 and 50 mg) had no clinically relevant effects on studied ECG parameters.

2.5.4. Conclusions on clinical pharmacology

The plasma pharmacokinetics of palovarotene has been adequately characterised in the intended target patient population. Study results implicated that palovarotene should not be co-administered with strong and moderate CYP3A4 inhibitors or inducers, and that the use in patients with moderate and severe hepatic impairment is not recommended. Overall, also the ADME characteristics have been well characterised.

The proposed dosing appears to result in a similar exposure in all weight groups but higher fluctuations in the smaller children.

2.5.5. Clinical efficacy

2.5.5.1. Dose response studies

The clinical program included two dose finding studies: PVO-1A-201 and PVO-1A-202 (Part A, B, C).

Study PVO-1A-201

This was a multicenter, randomised, double-blind (investigator and subject), sponsor-unblinded, placebo-controlled phase 2 study to evaluate the efficacy and safety of episodic treatment with palovarotene at the time of a flare-up in adult and paediatric subjects with FOP.

The effect of flare-up-based treatment with palovarotene on HO formation relative to placebo was evaluated in 40 subjects with FOP. Subjects were randomised (3:3:2) to receive either 10 mg palovarotene daily for 14 days followed by 5 mg daily for 28 days (10/5 mg); 5 mg palovarotene for 14 days followed by 2.5 mg for 28 days (5/2.5 mg); or placebo for 42 days. After the 6-week treatment period, subjects began a 6-week follow-up period during which no study drug was administered. This dosing regimen is referred to as **"flare-up only"** albeit differing from the flare-up posology proposed in the current application as significantly lower dosed have been used.

Results:

The primary endpoint was the proportion of responders (defined as subjects with no or minimal new HO at the flare-up site as assessed by plain radiograph) at Week 6. Using this definition, the percent of subjects classified as responders was 88.9% in the placebo group, 88.9% in the 5/2.5 mg palovarotene group, and 100% in the 10/5 mg palovarotene group (p=0.1664).

Examination of both Primary Read and Global Read imaging showed that plain radiographs were not as sensitive as CT scans to measure new HO formation.

The secondary efficacy endpoint results are presented in the Table 5.

Table 5 Volume of New HO at Week 12 by CT Scan (PP Population – Subjects with New HO from Screening/Baseline Volume >0 mm3, Primary Read)

	Placebo	PVO 5/2.5 mg	PVO 10/5 mg
Volume (mm^3) from the Primary Read[1] at Week 12			
n	3	2	4
Mean ±SD	53939 ±68914	5332 ±6089	16396 ±21822
Median	29512	5332	8551
Min, Max	565, 131739	1027, 9638	62, 48422
Flare-up locations	2 hips 1 knee	1 shoulder/elbow 1 knee	3 hips 1 knee

Source: Table 14.2.2.4.4a, Listings 16.2.4.6 and 16.2.6.3.3

[1] HO volumes were calculated from CT scans during the Primary Read process. Therefore, values do not include one subject in the placebo group and two subjects in the 5/2.5 mg palovarotene group identified with new HO from the Global Read process. In addition, values include the volume (61.5 mm^3) observed on the Primary Reads from one subject in the 10/5 mg palovarotene group that was deemed not to be new HO on the Global Reads.

CT = computed tomography, max = maximum; min = minimum, PP = per protocol; PVO = palovarotene, SD = standard deviation

Study PVO-1A-202

This was a phase 2, open-label extension, efficacy and safety study of palovarotene in the treatment of pre-osseous flare-ups in subjects with FOP.

Study PVO-1A-202 was an extension of Study PVO-1A-201 in which subjects were enrolled at the time of an active flare-up. This study explored different dosing regimens of palovarotene in adult and paediatric subjects with FOP. The study had three parts: Part A (completed July 2017), Part B (completed October 2018), and Part C (ongoing).

Approximately 60 subjects were planned for enrollment and 54 subjects were enrolled.

This study included 2 modes of treatment: chronic (5 mg palovarotene daily) and flare-up based (treatment for up to 12 weeks, starting as soon as possible after the beginning of a flare-up). Flare-up-based treatment was used in all 3 study parts, and chronic treatment was used in Part B (for patients >90% skeletally mature) and Part C. Flare-up regimens are listed below. Doses were weight adjusted.

Part A: Part A evaluated the long-term safety and efficacy of prior palovarotene treatment after an additional 12 months of follow-up and obtained additional efficacy and safety data of the 10/5-mg flare-up only palovarotene regimen. (Palovarotene 10 mg daily for 2 weeks followed by 5 mg daily for 4 weeks).

Part B: In Part B, additional palovarotene dosing regimens included, in subjects with at least 90% skeletal maturity, chronic daily doses (5 mg) in the absence of a flare-up. During a flare-up, all subjects received higher dose/longer duration treatment with palovarotene (20 mg for 4 weeks

followed by 10 mg for 8 weeks, with continuation of treatment in 4-week increments for persistent symptoms).

Part C: The study included subjects who had prior participation in Part B and were able to undergo low-dose WBCT scan. The primary efficacy endpoint for Part C was the annualised change in new HO volume (as assessed by low-dose WBCT scan, excluding head).

Chronic dosing is included for skeletally immature subjects as well as skeletally mature subjects. Additionally, substantial high-risk traumatic events qualified for flare-up treatment as well as restarting flare-up treatment for intercurrent flares. This dosing regimen is referred to as "chronic/flare-up". As chronic treatment, subjects are receiving 5 mg palovarotene once daily. Only one symptom is required to define a flare-up in Part C. Flare-up based treatment (20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks; could be extended by 4-week intervals until flare-ups (including intercurrent flare-ups) or major traumatic event(s) resolved.)

The primary efficacy endpoint for Part C was similar to the main study PVO-1A-301: the annualised change in new HO volume (as assessed by low-dose WBCT scan, excluding head). The change in new HO total volume was compared to baseline where the baseline value is performed prior to the initiation of chronic dosing (in Part B or Part C). The WBCT HO total volume was calculated as the sum of the volumes for each location of the WBCT assessment. If there is no HO, 0 was assigned for analysis.

Results:

Part A and B

The primary efficacy analysis in Part A and B was the incidence of flare-ups with no new HO at Week 12 (relative to baseline) as assessed by CT scan (or by plain radiograph for subjects unable to undergo CT scan). A secondary analysis also included the volume of HO as determined from CT scans at each scheduled visit.

"Annualised change in new HO volume" was the primary endpoint for Part C.

Table 6 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.

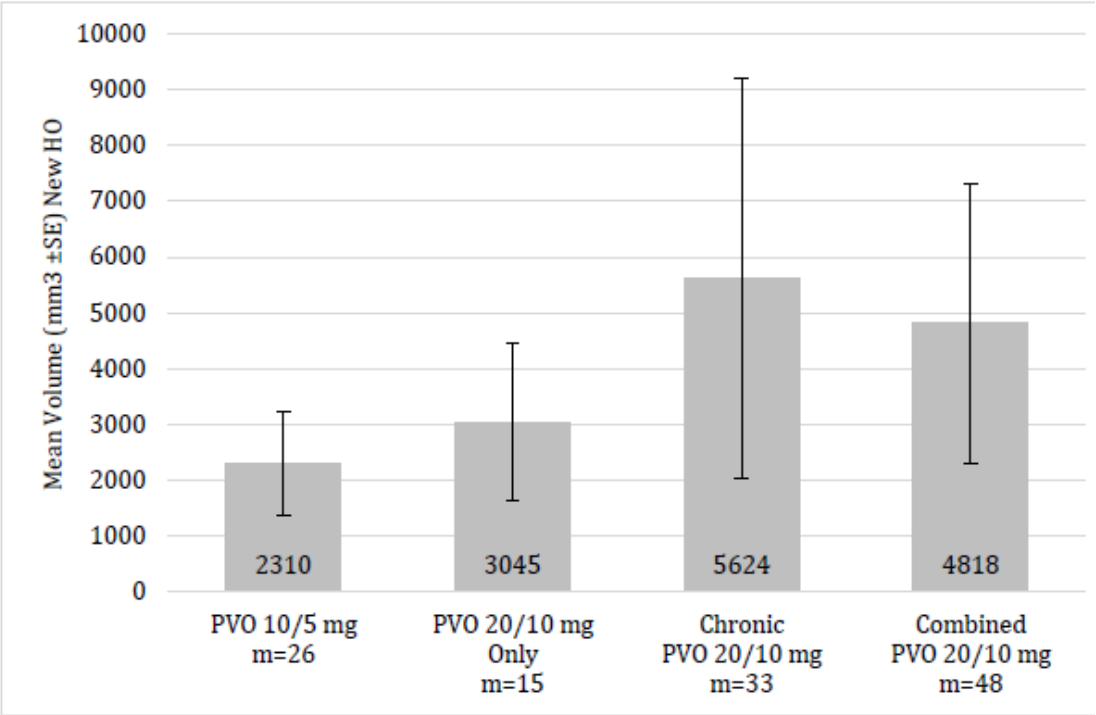
6 Part A only.

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

Across Part A and B, most flare-ups did not form bone as assessed by flare-up site-specific CT scan. In Part A, the increase in flare-ups with new HO from Week 6 (25%) to Week 12 (36%) may reflect the end of PVO administration after 6 weeks in this treatment group. In Part B, flare-ups treated in the chronic/PVO 20/10 mg group, had the lowest incidence of new HO (21%) of all treatment groups at Week 12.

Table 7 Mean Volume (mm^3) of New HO at Week 12 by CT Scan for All Imaged Flare-ups (Part A Efficacy Population, Part B Flare-up Population)



Source: Tables 14.2.4.1 and 14B.2.3.1
CT = computed tomography, HO = heterotopic ossification, PVO = palovarotene, SE = standard error

The mean (SD) volume of new HO (including those flare-ups with new HO and those with no new HO) at Week 12 across all treatment groups was numerically higher with the chronic/PVO 20/10 mg group (5,624 mm^3, 20,663) than in the PVO 10/5 mg group (2,310 mm^3, 4,739) or the PVO 20/10 mg group (3,045 mm^3, 5,453). Individual flare-up volume for all evaluable flare-ups shows that the data are highly variable, with two high volume flare-ups in the Part B chronic/PVO 20/10 mg group contributing substantially to the results of chronic/PVO 20/10 mg dosing.

Part C (ongoing)

For updated results after clinical hold, please see subheading Long-term data with cut off 30 July 2021 below.

According to the interim clinical study report (data cut-off 28 February 2020): in Part C, a total of 6 (60.0%) subjects at Month 12, 18 (54.5%) subjects at Month 24, and 16 (61.5%) subjects at Month 36 had new HO relative to baseline in the PVO Total group. Change from baseline in mean volume of new HO was 9,332, 62,857, and 89,487 mm^3 for Months 12, 24, and 36.

The whole-body burden of new HO was assessed by WBCT (excluding head) in Part B (in subjects who received chronic PVO 5 mg once daily) and Part C (in all subjects enrolled into Part C). The change from baseline in the volume of total new HO is summarised in Table 8.

Table 8 Volume of New HO by WBCT in PVO-1A-202

	Part B WBCT Population	Part C Enrolled Population
	PVO Total[1,2] (N=37)	PVO Total[1,2] (N=46)
Total Whole Body HO[3] (mm^3)		
Screen/Baseline		
n	37	43
Mean (SD)	454891 (357621)	423171 (353605)
Median	348780	322630
Min, Max	89660, 1727760	53480, 1727760
Total Whole Body New HO[3] (mm^3)		
New HO at Month 12 – change from baseline		
n	36	10
Mean (SD)	28386 (89918)	9332 (32401)
Median	0	2870
Min, Max	-50900, 403045	-55290, 58900
Subjects with new HO,[4] n (%)		
New HO	15 (41.7)	6 (60.0)
No new HO	21 (58.3)	4 (40.0)
Not evaluable	1 (2.6)	0
New HO at Month 24 – change from baseline		
n	1	33
Mean (SD)	193150 (-)	62857 (136761)
Median	193150	4655
Min, Max	193150, 193150	-94990, 533820
Subjects with new HO,[4] n (%)		
New HO	1 (100.0)	18 (54.5)
No new HO	0	15 (45.5)
New HO at Month 36[5] – change from baseline		
n		26
Mean Total New HO (SD)		89487 (198749)
Median		13503
Min, Max		-100660, 701780
Subjects with new HO,[4] n (%)		
New HO		16 (61.5)
No new HO		10 (38.5)

[1] PVO Total includes subjects who had at least one dose of PVO treatment. Note that: One subject is included in Part B (Screening and Month 12) column but was not treated in Part C and therefore is not included in Part C column.
One subject did not receive treatment in Part B or Part C and therefore is not included in either column.
One subject was not included in Part B or Part C as this subject only had one unscheduled WBCT scan.

[2] For subjects from Part B continuing chronic treatment into Part C (ie, subjects who received at least one dose of chronic treatment in both Part B and Part C), baseline was from the assessment prior to the first chronic treatment in Part B. For subjects who did not receive chronic treatment in Part B but started chronic treatment during Part C, baseline was from the assessment prior to the first chronic treatment in Part C.

[3] Total WBCT new HO volume (mm^3) is defined as total WBCT HO volume at a visit – total WBCT HO volume at screening, where total WBCT HO volume is calculated as the sum of HO across all regions. If there was no new HO for a specific region, then 0 was assigned for the volume of new HO of the given region.

[4] New HO and No New HO incidence are based on the total New HO volume (across all regions) at each visit. New HO is defined as total WBCT new HO volume >0. No New HO is defined as total WBCT new HO volume ≤0. Only includes Part B scans for subjects that had a post-baseline visit in Part C.

[5] The last WBCT assessed in Part B was at Month 24. Part C Month 36 data were collected from subjects who started chronic treatment during Part B and continued into Part C

HO=heterotopic ossification; max=maximum; min=minimum; SD=standard deviation; WBCT=whole body computed tomography.

	Part B WBCT Population	Part C Enrolled Population
	PVO Total[1,2] (N=37)	PVO Total[1,2] (N=46)

During the evaluation (at Day 120 LoQ), the applicant was asked to present the results from PVO-1A-202/204 annualised change in new HO volume, side by side with corresponding results from the NHS. The annualised new HO volumes in Part B and C were numerically higher compared to untreated subjects in PVO-1A-001, as show in the Table 9. The mean annualised new HO was 27967 mm^3 in Study PVO-1A-202/Part B, 24290 mm^3 in Part C and 23720 mm^3 in the NHS.

Table 9 Summary of Demographics and Estimated Annualised New Whole-Body HO Volume for Treated Subjects in Study PVO-1A-202/Parts B and C and Study PVO-1A-001

	Study PVO-1A-202		Study PVO-1A-001
	Part B[a]	Part C[a]	
Variable	**(N=37)**	**(N=32)**	**(N=111)[c]**
Age, years			
Mean (SD)	22.6 (7.5)	21.5 (8.4)	17.5 (9.8)
Total WBCT HO volume, baseline, mm^3			**(N=109)[c]**
Mean (SD)	454891 (357621)	407133 (289853)	306135.3 (364077.2)
Median	348780	333998	194330.0
Min, max	89660, 1727760	90710, 1396120	0.0, 1906210.0
Annualized new HO, last postbaseline visit[b], mm^3			**(N=101)[c]**
Mean (SD)	27967 (82436)	24290 (63290)	23720.2 (48741.9)

a For PVO-1A-202/Part B: subjects who received chronic treatment before flare-up treatment and had WBCT volume at both screening and Month 12 are included.
For PVO-1A-202/Part C: subjects who received treatment and had at least 2 WBCT volume assessments after the first dose of palovarotene are included. For Part C, baseline is defined as the first WBCT scan assessment collected while the subjects was on Part C.

b Annualized new HO (mm^3) = (Total HO at latest postbaseline visit – total HO at baseline visit)/postbaseline years. Postbaseline years = (date of the latest post-visit scan – date of the baseline scan)/365.25.

c N=111 represents the Principal Safety Set, N=109 represents the Progression Analysis Set, and N=101 represents the Full Analysis Set (based on Study PVO-1A-301 criteria) from Study PVO-1A-001

HO=heterotopic ossification; SD=standard deviation; WBCT=whole-body computed tomography.

Long-term data with cut off 30 July 2021

Updated information from Study 202 Part C involving 26 subjects who restarted palovarotene after pausing as of the data cut off of 30 July 2021 was presented by the applicant as response to the Day 120 LoQ. Only subjects >14 years of age could restart palovarotene.

The mean observed annualised new HO volume from original baseline to the time of the palovarotene pause was 23411 mm^3 in patients who restarted. This is slightly lower than the mean observed annualised new HO volume from restart baseline to the last WBCT which was 26105 mm^3 (N=19). For these subjects, the mean timeframe from the restart baseline WBCT to the last WBCT represents approximately 17 months, of which approximately 7 months were untreated.

In summary, the annualised new HO volumes seem to remain in the same range in actively treated patients in study PVA-1A-202 as in the NHS.

Long-term data with cut off September 2022

During the oral explanation on 13 December 2022, the applicant presented new data analysis from study start to last-patient-last-visit (sept 2022 data cut-off). These included HO measurements during treatment interruptions (average time off treatment ~ 7 months) and "comparable" baseline WBCTs for Study 202 Part C. The mean annualised new HO volume was 19,555 mm^3/year in Study 202 C (N=29), 13,316 mm^3/year (N=97) in Study 301 compared to 23,656 mm^3/year in the NHS study (N=101).

Excluding certain patients from the analysis of Study 202 Part C is not supported as this seems data-driven. Post-hoc defined variables were chosen for matching and patients with missing values for matching variables were excluded. In addition, all new post hoc analysis presented by the applicant included negative values. This is not in line with the pre-defined primary endpoint of the studies that was measurement of "new HO volume" in new regions where new HO was identified. Change in existing volumes were not systematically measured and therefore negative values are considered as likely measurement errors. Any analysis including negative values is therefore of very limited confirmatory value in assessing palovarotene efficacy.

2.5.5.2. Main study

Study PVO-1A-301 (MOVE) and Natural History Study (NHS) PVO-1A-001

The main study (study PVO-1A-301 – MOVE) was a multicentre, open-label, single-arm, phase 3 study in 107 adult and paediatric subjects with FOP to evaluate the efficacy and safety of palovarotene in decreasing HO in subjects with FOP. The study duration was planned up to 48 months but the majority of data from this study is limited to about 1 year duration. The results were compared with data collected from natural history study (NHS) cohort, Study PVO-1A-001.

Study PVO-1A-001, was a 3-year, longitudinal, non-interventional NHS describing FOP disease characteristics, prospectively evaluating disease progression, and illuminating the impact of flare-ups on FOP outcomes in 114 subjects with FOP due to the R206H mutation.

Both studies were conducted separately.

Study PVO-1A-301 was still ongoing at time of initial marketing authorisation application, and therefore the evaluation is based on the interim clinical study report with data cut-off 28 February 2020.

Based on the serious identified risk of premature physeal closure (PPC), a partial clinical hold was implemented on subjects <14 years old on 04 December 2019 in this main study (PVO-1A-301). The sponsor paused dosing for all remaining subjects (14 years and older) in the FOP palovarotene program on 24 January 2020 due to futility. After that, the sponsor became unblinded to all study data. Analyses of all efficacy endpoints presented by the sponsor include assessments collected on or before these interruptions, unless otherwise specified (see also paragraph "Conduct of the study").

After post-hoc analysis of the efficacy data, the sponsor has decided to reinitiate dosing in subjects 14 years and older and the study is still ongoing.

Methods

Study Participants

Main inclusion criteria

Study PVO-1A-301 (MOVE)	***Study PVO-1A-001 (NHS)***
1. Male or female at least 4 years of age. 2. Previous participation in Study PVO-1A-001; or clinically diagnosed with FOP, with the R206H ACVR1 mutation or other FOP variants reported to be associated with progressive HO (who have not previously participated in any sponsored study); or participants in Study PVO-1A-202 or Study PVO-1A-204 who cannot currently receive the chronic/flare-up regimen due to country of residence or those traveling long distances to participate in the Phase 2 study. 3. No flare-up symptoms within the past 4 weeks, including at the time of enrolment. 4. Must be accessible for treatment and follow-up and be able to undergo all study procedures. including low-dose WBCT (excluding head) without sedation.	1. Male or female ≥18 years of age for Part A and male or female ≤65 years of age for Part B. 2. Clinically diagnosed with FOP with documented R206H mutation or believed to carry the R206H mutation.

Exclusion criteria

Study PVO-1A-301	***Study PVO-1A-001 (Natural History)***
1. Weight <10 kg. 2. If currently using vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, or herbal preparations, fish oil, and unable or unwilling to discontinue use of these products during palovarotene treatment. 3. Exposure to synthetic oral retinoids other than palovarotene within 4 weeks prior to screening. 4. Concurrent treatment with tetracycline or any tetracycline derivatives due to the potential increased risk of pseudotumor cerebri. 5. History of allergy or hypersensitivity to retinoids, gelatin, or lactose (note that lactose intolerance is not exclusionary). 6. Concomitant medications that are strong inhibitors or inducers of cytochrome	1. Unable or unwilling to complete the study or all study-related procedures, including the radiographic assessments. 2. Participation in an interventional clinical research study within the 4 weeks prior to enrolment.

P450 (CYP450) 3A4 activity; or kinase inhibitors such as imatinib. 7. Amylase or lipase >2x above the upper limit of normal (ULN) or with a history of chronic pancreatitis. 8. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5x ULN. 9. Fasting triglycerides >400 mg/dL with or without therapy. 10. Female subjects who are breastfeeding. 11. Subjects with uncontrolled cardiovascular, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease. 12. Subjects experiencing suicidal ideation (Type 4 or 5) or any suicidal behavior within the past month as defined by the Columbia-Suicide Severity Rating Scale (C-SSRS). 13. Simultaneous participation in another interventional clinical research study (other than palovarotene studies) within 4 weeks prior to Screening; or within five half-lives of the investigational agent, whichever is longer. 14. Any reason that, in the opinion of the Investigator, would lead to the inability of the subject and/or family to comply with the protocol.	

Treatments

PVO-1A-301: All subjects enrolled in this study received palovarotene; the study did not include a control group.

This study included 2 modes of treatment: chronic (palovarotene 5 mg daily) and flare up based (palovarotene 20 mg daily for 4 weeks, starting as soon as possible after the beginning of a flare up, followed by palovarotene 10 mg daily for 8 weeks, for a total of 12 weeks). All doses were weight adjusted for skeletally immature subjects. If a subject experienced an intercurrent flare-up or traumatic event at any time during flare-up-based treatment, the 12-week dosing regimen was restarted.

Subjects received chronic treatment for up to 24 months (Part A) and flare up-based treatment when they experienced an eligible flare up or a substantial high-risk traumatic event likely to lead to a flare

up as confirmed by the Investigator. Of note, in the submission, data at 24 months is available for one subject only (see paragraph "numbers analysed"). In part B, the study treatment is being extended and additional 24 months to a total of 48 months of treatment. No data from part B is included in the submission.

PVO-1A-001 (NHS): This was a non-interventional study and no subjects received treatment.

Objectives

Study PVO-1A-301

The *primary objectives* were:

- To evaluate the efficacy of palovarotene in **decreasing 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 from FOP NHS (Study PVO-1A-001).
- To evaluate the **safety** of palovarotene in adult and paediatric subjects with FOP.

Secondary/exploratory objectives included:

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

Outcomes/endpoints

Study PVO-1A-301

Primary Efficacy Endpoint

- The **annualised change in new HO volume** as assessed by low-dose WBCT, excluding head.

Secondary Efficacy Endpoint

- Proportion of subjects with any new HO at Month 12 (key secondary endpoint).
- Number of body regions with new HO at Month 12.
- Proportion of subjects reporting flare-ups at Month 12.
- Flare-up rate per subject-month exposure through Month 24.

Exploratory Endpoints

- Change from Baseline in ROM assessed by CAJIS through Month 24 in Study PVO-1A-301 and Study PVO-1A-001.
- Change from Baseline in physical function through Month 24 in Study PVO-1A-301 and Study PVO-1A-001, using age-appropriate forms of the FOP-PFQ.

- Change from Baseline in physical and mental function for subjects ≥15 years old and mental function for subjects <15 years old using age appropriate forms of the PROMIS Global Health Scale, through Month 24 in Study PVO-1A-301 and Study PVO-1A-001.
- Incidence and volume of catastrophic HO per year, ie, new HO of at least >50,000 mm^3 and >30,000 mm^3 at Months 12 and 24. (added after results were disseminated)

Sample size

The sample size in the PVO-01-301 study was calculated to detect an overall 65 % relative reduction on the volume of new HO.

Randomisation and Blinding (masking)

The PVO-1A-301 study was an open-label study and did not involve randomisation or study drug blinding.

The PVO-1A-001 was a non-interventional study and did not involve randomisation.

Statistical methods

The interim Clinical Study report (CSR, dated 19 Mar 2021) was authored based on the analysis performed on data cut-off from 28 February 2020.

Three versions of the SAP were submitted: version 1.0 (13 Sep. 2019), version 1.1 (9 Apr 2020) and the final version 1.2 (9 Sep 2020).

In order to address the prolonged interruptions in dosing in subjects <14 years old upon US Food and Drug Administration's (FDA) institution of a partial clinical hold due to PPC on 04 December 2019 and interruptions in dosing for the remaining subjects on 24 January 2020 due to the crossing of the futility boundary at IA2 (see section conduct of the study below), analyses of all efficacy endpoints presented include assessments collected on or before these interruptions, unless otherwise specified.

Analysis populations:

The Principal Enrolled Population (Principal EP) included all subjects with the R206H ACVR1 mutation who had not previously been treated with palovarotene and who signed the informed consent form and met all eligibility criteria of the MOVE Trial. For the NHS, the Principal EP included all subjects enrolled.

The Principal Full Analysis Set (Principal FAS) included all enrolled subjects in the Principal EP who had a baseline HO volume measurement and at least one post baseline HO volume measurement in the MOVE trial. For efficacy comparisons to the NHS, the Principal FAS also included subjects enrolled in the NHS with available baseline and at least one post-baseline HO volume measurement.

The efficacy endpoints were to be analysed using the Principal FAS.

Primary analysis:

The primary efficacy endpoint is the annualised change in new HO volume (as assessed by WBCT). The change in new HO volume is calculated by summing the increase in HO volume across all body regions for which new HO has occurred, where the increase in HO volume per region is defined as the square root of the volumetric increase in that region. The square root transformation is used to reduce the influence of outliers. The change in new HO volume is modelled using a Bayesian compound Poisson distribution of the number of body regions with new HO and the new HO volume per region where new HO has occurred. The model is thoroughly described in the SAP; it accounted for potential correlation in measurements from the same subject and included covariates sex and age (<18 years; ≥ 18 years old) to adjust for potential explained differences in the rate of new HO based on the subject's sex and age at time of scan.

The primary efficacy analysis is performed by calculating the ratio of the annual mean change in HO volume in palovarotene treated subjects to untreated subjects using the Principal FAS and assuming missing at random.

New HO is deemed to be present in a body region if the volume of net new HO is greater than zero, i.e. the change in volume of HO in a region between two timepoints is positive. (Volumes of individual lesions are not assessed; the net volume of HO in a body region is reported.) The measurement procedure starts with the central imaging laboratory readers performing a qualitative assessment of whether there is new HO within each body region compared to baseline (or the previous scan). If the qualitative assessment is that there is new HO in any individual region, then the HO within all the regions is measured, and the change from baseline represents the amount of new HO.

Any regions with amounts of new HO<0 mm^3, i.e. reductions in the volume of HO over time (which can happen due to bone remodelling or measurement error), are represented as having no new HO and the volumes are set to zero in the analysis.

Missing data:

Missing timepoints for subjects, i.e. assessments not conducted, assessments conducted but not evaluable for the presence of HO or volume of HO, or assessments for which HO volume for at least 50% of body regions is not evaluable or not available, are not imputed. Body regions with non-evaluable HO volume at a timepoint are represented as having no new HO and the volumes are set to zero in the analysis.

Interim analyses:

Three interim efficacy analyses and one final analysis were planned in Part A using group sequential methods. The first interim analysis (IA1) was planned to be conducted when 35 subjects completed 1 year of follow-up, and the second (IA2) and third interim analyses (IA3) when all subjects enrolled in the Principal Enrolled Population completed (i.e., had WBCT data) 12 months and then 18 months of follow-up, respectively.

A futility analysis was planned at the second and third interim analyses to assess whether the study should be stopped due to insufficient evidence of efficacy. The study should be stopped for futility if the posterior probability that g <0.7 (at least a 30% reduction in annualised new HO volume) is less than 5%.

A futility analysis was conducted at IA2 to assess whether the study should be stopped due to insufficient evidence of efficacy. At the IA2 Data Monitoring Committee (DMC) meeting on 15 January 2020 futility was declared for Study PVO-1A-301 and the sponsor paused dosing, as required in the protocol, for all subjects in the FOP palovarotene program. After the DMC communicated to the sponsor that the prespecified futility boundary had been crossed, the sponsor became unblinded to all study data. After unblinding and review of the post-hoc efficacy analyses that found evidence of clinically meaningful benefit of palovarotene in the overall population, the DMC recommended that palovarotene be continued in skeletally mature children ≥14 years. This age recommendation was due to the SAEs of PPC.

Results from IA3 were evaluated by the DMC on 26 May 2020 and yielded findings consistent with those from IA2. The IA3 analysis included 24% longer total follow-up for palovarotene-treated subjects than at IA2. Because the futility boundary was crossed at the IA2, all subsequent analyses of efficacy data were supplied without applying thresholds for success or futility, as these thresholds were no longer relevant.

Multiplicity:

The alpha level threshold used to determine treatment effect significance at each analysis was derived using the Lan-DeMets alpha-spending function with O'Brien-Fleming parameterisation and assuming a one-sided, overall type I error rate of 2.5%. The one-sided significance thresholds are 0.0058, 0.0103, 0.0156, and 0.0190 for the first, second and third interim analyses and the final analysis, respectively, in the scenario with following expectation on accrual rates and total planned accrual in the Principal EP:

Table 10 Observed MOVE follow-up

Analysis	Observed MOVE follow-up	Percentage of follow-up available
Interim #1	35 subjects with 12 months *45 subjects with 6 months	66%
Interim #2	*80 enrolled subjects with 12 months *35 subjects with 18 months	80%
Interim #3	*80 enrolled subjects with 18 months *35 subjects with 24 months	92%
Final	80 enrolled subjects with 24 months	100%

The one-sided significance thresholds for the Lan-DeMets alpha spending function with an O'Brien-Fleming boundary was to be recalculated at the time of each interim analysis based on the estimate of the information fraction.

The critical p-value for the final analysis was to be set such that the remaining alpha is spent. Study success was to be declared if the posterior probability that palovarotene reduces the change in new HO volume is greater than 1 minus the one-sided significance threshold. For example, the posterior probability that palovarotene reduces the annualised change in new HO volume must be greater than 0.9810 to declare study success at the final analysis in the scenario above.

Secondary efficacy endpoints were not adjusted for multiplicity.

Post-hoc analyses:

The applicant claims that the most appropriate analysis for these data is the simpler wLME (weighted linear mixed effect) analysis without square-root transformation, which was the original protocol-specified primary efficacy analysis before the Bayesian analysis with the square-root transformation was substituted for it in Amendment 1 of the protocol. With square-root transformation, the sponsor believes that the Bayesian analysis is biased against palovarotene due to differences in assessment schedule between the two groups. Even without square-root transformation, while the overall assessment of efficacy in the Bayesian analysis is shown via simulation to be unbiased, it is the product of two parameters, the estimates of each of which is biased, but the biases are in opposite directions and offset.

Additional post-hoc supportive analyses for differences at Month 12 using Fisher's exact test and negative binomial regression, respectively, were also performed.

The flare-up rate per subject-month of exposure was also analysed using a post-hoc negative binomial regression. In the Study PVO-1A-001, events were considered flare-ups when two or more flare-up symptoms were reported; in Study PVO-1A-301, the flare-up definition required one or more flare-up symptoms. To allow direct comparison, the analysis restricted flare-ups from Study PVO-1A-301 to

those events that matched the Study PVO-1A-001 definition. Therefore, only Study PVO-1A-301 flare-ups with two or more flare-up symptoms were to be included in the above secondary efficacy analyses.

The proportion of subjects reporting flare-ups was compared between Studies PVO-1A-301 and PVO-1A-001 using a post-hoc Fisher's exact test. As with the flare-up rate analysis, this analysis restricted flare-ups from Study PVO-1A-301 to those meeting the definition for Study PVO-1A-001.

Change from the pre-specified analyses:

Changes prior to the interim analyses

The method for the primary efficacy analysis (a Bayesian analysis of a compound Poisson distribution) described in Protocol Amendment 1 and the SAP version 1.0 is different from the method included in the original protocol dated 10 July 2017 (weighted linear mixed effects model). The method and accompanying power simulations in the original protocol were based on a March 2017 evaluation of the available NHS 12-month WBCT data. In a subsequent dataset, increased variability in the change from baseline in new HO resulted in a substantive power decrease for the weighted linear mixed effects model. Therefore, additional modeling and simulation work was undertaken to assess whether alternative models or transformations would be more appropriate methods of analysing the data, and thus maintain the power of the MOVE Trial. This resulted in changes to the primary efficacy analysis method as well as the simulations underlying sample size determination. Additionally, the Lan-DeMets alpha-spending function with Pocock parameterisation was revised to O'Brien-Fleming parameterisation based on FDA scientific advice.

Changes after the 2nd interim analysis

The Applicant performed interim analyses assessing annualised new HO volume in the chronic/flare-up regimen in the Phase 3 study (PVO-1A-301). The results are compared with those from untreated subjects in Study PVO-1A-001. The prespecified interim data analysis used a Bayesian compound Poisson model that describes the likelihood of an HO growth event and the volume of HO growth per event. The model for the primary analysis incorporated a square-root transformation of HO volume per region and required that new HO volumes be non-negative (i.e. that negative new HO values, which can happen due to bone remodelling or measurement variability, are set to zero). Square-root transformation of new HO volume per event was intended to reduce variability and increase the power of the study.

At the DMC meeting to discuss the results from the second interim analysis (IA2) on 15 January 2020, the Applicant was notified that the prespecified analysis using a Bayesian compound Poisson model with square-root transformation demonstrated that the futility boundary (<5% posterior probability of at least a 30% reduction in annualised new HO volume) had been crossed. Given this finding the Applicant interrupted dosing, as required in the protocol, for all subjects in the FOP palovarotene program. Data were "unblinded" in order to confirm the futility findings and to perform additional post-hoc analyses.

These post-hoc analyses included the Bayesian model applied without square-root transformation and a weighted linear mixed effect model (wLME) with and without square-root transformation.

The statistical analysis described in the SAP version 1.1 and 1.2 are by the CHMP considered post-hoc as the study results were disseminated prior to these versions. Specific changes from the original SAP were:

SAP version 1.1

• wLME analysis (which was designated as the primary efficacy analysis in the original clinical protocol) reintroduced as a supportive analysis in Protocol Amendment 4;

• Introducing several age (years) by sex partitions for use in subgroup analyses, including <8 for Females and<10 for Males vs. ≥8 for Females and≥10 for Males; and <13 for Females and<15 for Males vs. ≥13 for Females or ≥15 for Males. These are intended to inform the benefit/risk assessment for younger subjects at risk of PPC;

• Addition of a subgroup of Asian subjects (to support interactions with global regulatory authorities);

• Sensitivity analysis in which the impact of the difference in WBCT visit schedules between MOVE and NHS is assessed by analysing the data as if the WBCT assessments in MOVE were conducted annually rather than biannually. This is intended to investigate whether the differences in visit schedules introduced bias, with and without use of the square-root transformation;

• Exploratory endpoints of incidence and volume of "catastrophic HO" based on the observation – made after unblinding the second interim analysis – that a minority of subjects develop large amounts of HO in a year; post-hoc cut-offs of at least 50,000 mm^3 and 30,000 mm^3 of new HO are used;

• After crossing futility boundary at IA2, no predefined efficacy rules for success or futility will be used in subsequent analyses of efficacy data.

SAP version 1.2 includes further clarifications on the Bayesian compound Poisson analysis, wLME analysis method and sensitivity analyses, additions of summaries of dosing compliance, growth velocity, subgroups etc.

Results

- **Participant flow**

Table 11 Subject disposition for palovarotene-treated and untreated subjects.

	Study PVO-1A-301 Palovarotene	Study PVO-1A-001 Untreated
Enrolled	107	114
Principal enrolled population	99	114
Supplementary enrolled population	8	NA
Principal safety set	99 (92.5)	111 (97.4)
Ongoing in study	88 (82.2)	2 (1.8)
Completed study	0	31 (27.2)
Discontinued study	19 (17.8)	81 (71.1)
Adverse event	6 (5.6)	0
Death	0	1 (0.9)
Noncompliance	0	2 (1.8)
Sponsor request	2 (1.9)	0
Withdrawal by subject	11 (10.3)	9 (7.9)
Lost to follow-up	0	1 (0.9)
Subject enrolled in interventional study	NA	52 (45.6)
Subject enrolled in interventional study at time of flare-up	NA	9 (7.9)
Other: Subject did not want to travel	0	1 (0.9)
Other: Subject enrolled in an interventional study not listed in Edc	0	1 (0.9)
Other: Subject enrolled in another interventional study	0	3 (2.6)
Other: Subject enrolled in another non-Clementia interventional study	0	1 (0.9)
Other: Worsening of clinical condition and impossibility to move to the center	0	1 (0.9)

Source: Table B1A.

Note: The Principal Enrolled Population includes all subjects with the R206H *ACVR1* mutation who have not previously been treated with palovarotene and who sign the informed consent form and meet all eligibility criteria of Study PVO-1A-301. For Study PVO-1A-001, three enrolled subjects were not included in the Principal Enrolled Population because it was determined after enrollment that two subjects did not have the R206H mutation and one subject did not have FOP.

Note: Subjects who do not have the R206H *ACVR1* mutation or who have received previous treatment with palovarotene will comprise the analogous supplementary populations in Study PVO-1A-301.

Note: The Principal Safety Set for Study PVO-1A-301 includes all enrolled subjects receiving at least one dose of palovarotene. The Principal Safety Set for Study PVO-1A-001 includes subjects enrolled with available post-baseline follow-up for the purposes of comparison to Study PVO-1A-301, where applicable.

Edc=electronic data capture; NA=not applicable.

- **Recruitment**

PVO-1A-301

Date of first patient screened: 30 November 2017 (first subject signed informed consent form).

Date of last patient screened: No subjects had competed the study by the data cut-off date.

Data cut-off for subjects aged <14 years: 4 December 2019

Data cut-off for subjects aged ⩾14 years: 24 January 2020

Data cut-off for interim clinical study report: 28 February 2020

PVO-1A-001 (Natural History)

First subject enrolled: 18 December 2014

Last subject completed: 09 April 2020

- **Conduct of the study**

PVO-1A-301

US FDA instituted a partial clinical hold on dosing of palovarotene due to PPC for subjects <14 years of age on December 4, 2019; as of the finalisation of this SAP amendment, dosing has not yet resumed for these subjects.

Dosing on all other subjects not subject to US FDA's partial clinical hold was interrupted following the January 21, 2020 DMC meeting while the protocol amendment allowing the continuation of the study after the futility outcome and incorporating the additional analyses requested by the DMC was reviewed by regulatory agencies, IRBs, and investigational sites. These subjects had palovarotene dosing interrupted on or around January 24, 2020.

Based on additional post-hoc analyses presented to the DMC on January 21, 2020, the DMC noted that using the square-root transformation of the data in the primary analysis appears to have moved the statistical conclusion from significant therapeutic benefit to showing futility of the treatment. The DMC also noted that the dilemma created by these highly disparate results precludes a confident conclusion about futility.

The sponsor allowed dosing to resume as of March 26, 2020 in subjects over 14 years provided each individual site had obtained Ethics Committee approval to do so and the site was able to fulfil regulatory and operational requirements. Subjects were expected to restart dosing over a span of weeks due to these logistical considerations.

As a consequence of the FDA partial clinical hold subjects remained off treatment for a prolonged period of time. As such a significant gap in dosing occurred which would render any further data to inform additional benefit/risk uninterpretable in this patient population. Part C was added to ensure continued collection of safety data off treatment for subjects <14 years of age and any subjects who were skeletally immature at the time of their EOS visit.

Shortly after, the futility boundary was crossed at the second interim analysis, signifying that the prespecified Bayesian compound Poisson distribution model with square-root transformation indicated that the trial was unlikely to show sufficient evidence of benefit. The independent DMC informed the sponsor of this outcome on January 15, 2020, and the efficacy assessments were subsequently unblinded to the sponsor.

No subject discontinued the study due to a protocol deviation. A total of 25 subjects experienced at least one significant protocol deviation.

PVO-1A-001 (Natural History)

There were five protocol amendments. The major changes affecting the clinical conduct of the study was:

- The paediatric FOP-PFQ was added to assess physical function in paediatric subjects.

- Start of Part B: WBCT scan, excluding head, was specified as the optimal imaging modality of total HO for subjects in Part B.

- Subjects aged <2years were added to inclusion criteria.

- Analyses were added.

- Sample size was increased (from ~50 up to 100)

- **Baseline data**

A tabular summary of demographic characteristics for the palovarotene treated patients (N=99) and the untreated patients in the Natural History Study (N=111) is presented in Table 12.

Most subjects in both groups were younger than 18 but with a higher percentage in the palovarotene (76%) than in the untreated group (60%).

Table 12 Demographic and baseline characteristics for palovarotene-treated and untreated subjects

	Palovarotene (N = 99)	**Untreated (N = 111)**
Age (years)		
Mean (SD)	15.1 (9.6)	17.5 (9.8)
Median (Min, Max)	13.0 (4, 61)	15.0 (4, 56)
Age category, n (%)		
<18 years	75 (75.8)	66 (59.5)
≥18 years	24 (24.2)	45 (40.5)
Sex, n (%)		
Male	53 (53.5)	60 (54.1)
Female	46 (46.5)	51 (45.9)
Race, n (%)		
White	70 (70.7)	81 (73.0)
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)

Source: Module 5.3.5.1 Report PVO-1A-301 Table B2A.
Note: The Principal Safety Set for PVO-1A-301 includes all enrolled subjects receiving at least one dose of palovarotene. The Principal Safety Set for PVO-1A-001 includes subjects enrolled with available post-baseline follow-up for the purposes of comparison to PVO-1A-301, where applicable.

Baseline values regarding FOP history are presented in Table 13.

Table 13 FOP History for palovarotene-treated and untreated subjects

	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)

Source: Table B3.
FOP=fibrodysplasia ossificans progressiva; max=maximum; min=minimum; SD=standard deviation.

The flare-up history for patients entering both studies are presented in Table 14.

Table 14 Flare-up history for palovarotene-treated and untreated subjects

	Palovarotene (N = 99)	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)

Source: Module 5.3.5.1 Report PVO-1A-301 Table B5.
1. Time since last flare-up (months)-calculated as [(ICF- Last flare-up start date)/30.4375]+1.
ICF=informed consent form; LOM=loss of movement; max=maximum; min=minimum; PSS=Principal Safety Set; SD=standard deviation.

Table 15 Baseline Heterotopic ossification (HO) palovarotene-treated and untreated subjects.

Treatment group (N)	**Palovarotene (97)**	**Untreated (101)**
Mean (SD) in mm^3	231211.2 (292496.0)	312453.3 (373609.7)
Median	127240.0	195420.0
Min; Max	0; 1382040	0; 1906210

The available data indicate differences in baseline variables between palovarotene treated (study PVO-1A-301) and untreated (study PVO-1A-001) participants.

- **Numbers analysed**

Number of participants in each study included in each analysis is presented in Table 16.

Table 16 Palovarotene-treated and untreated subjects with available visits.

	Study PVO-1A-301 Palovarotene	Study PVO-1A-001 Untreated
Screening	97	101
Month 6	94	2
Month 12	92	90
Month 18	64	11
Month 24	1	63

Source: Table E30.1.
Untreated subjects had data at Months 30, 36 and 42 that are not displayed since no subjects on palovarotene have data for these visits.

- **Outcomes and estimation**

Primary endpoint

The primary endpoint was the annualised change in new HO volume as assessed by low-dose WBCT, excluding head.

The prespecified primary analysis utilised the Bayesian model with square-root-transformed values. Quantitative assessment was performed in case of positive qualitative assessment that there is new HO in any individual region. The change in new HO volume is calculated by summing the increase in HO volume across all body regions for which new HO has occurred where the increase in HO volume per region is defined as the square-root of the volumetric increase in that region. The square-root transformation is used to reduce the influence of outliers.

The table below presents the mean observed annualised new HO volumes and weighted linear mixed effect (wLME) analysis for annualised new HO with square-root transformation and negatives values zeroed out by body region. This is the wLME analysis most similar to the prespecified primary analysis.

The Principal FAS population was further focused to include only those subjects who meet the ≥50% of regions evaluable (5 out of 9) criteria. This analysis population (N=97 for PVO-1A-301 and N=101 for PVO- 1A-001) provides the basis for the analyses performed in IA3. For PVO-1A-001, all available data up to 28 February 2020 were included.

Table 17 wLME for annualised new HO volume with square-root transformation and negatives zeroed out by body region for palovarotene-treated and untreated subjects (principal FAS).

		Palovarotene (N=97)	Untreated (N=101)
Number of subjects analysed		97	101
New HO (mm^3)	Mean (SEM)	140.2 (23.6)	149.8 (19.4)
	% reduction (palovarotene vs untreated)	6.4%	
	LSmean (SEM)	137.0 (20.7)	129.5 (15.7)
	% reduction (palovarotene vs untreated)	-5.9%	
		wLME estimate (95% CI)	p-value
	Intercept	100.3 (58.50, 142.16)	<0.0001
	Baseline total HO/Baseline age	0.002 (0.0002, 0.0038)	0.002
	Treatment	7.6 (-45.17, 60.32)	0.7727
Wilcoxon test	p-value	0.5165	

	Palovarotene (N=97)	Untreated (N=101)

Note: The new HO weighted linear mixed effect (wLME) LSMEAN estimate and SEM are from a mixed model with dependent variable annualised new HO and independent variables including fixed effects of treatment and baseline total HO/baseline age and a random subject effect.
FAS=full analysis set; HO=heterotopic ossification; LSMEAN=least square mean; SEM=standard error of the mean; wLME=weighted linear mixed effect.

As presented in Table 17, the primary analyses do not suggest differences in the mean observed annualised new HO volume (square root transformed data zeroed out by body region).

The mean observed annualised new HO volume was numerically 6.4% lower for PVO (140 mm^3) versus untreated (150 mm^3) subjects, with square-root transformed data zeroed out by body region. The wLME LS mean (SEM) of new HO was even numerically 5.9% higher 137.0 mm^3 in study PVO-1A-301 compared to NHS 129.5 mm^3.

The results are mainly consistent with the primary analysis, in that the credible interval in the Bayesian analysis and the confidence interval for the wLME both are wide, showing no treatment effect. The Bayesian analysis with square-root transformation fit a 6% reduction on the square-root scale of the volume of annualised new HO. The Wilcoxon rank-sum test, which depends only on the numeric rank order of the observed volumes of new HO rather than their magnitudes and is thus less influenced by extreme values, does not suggest a difference.

The available data on mean values of primary endpoint is presented descriptively in Table 18. These values are untransformed and negative values (regions where new HO occurred according to qualitative assessment but the calculated volume was negative) are included.

Table 18 Volume of new HO (mm3) by visit in principal FAS with no square root transformation and negatives included before Dec 4 2019/Jan. 24 2020. (Adopted from table E30.1)

		MOVE Trial / Palovarotene		NHS / Untreated	
Analysis visit	**Statistics**	**Value**	**Change from Baseline**	**Value**	**Change from Baseline**
Baseline	N	97		101	
	Mean (SD)	231211 (292496)		312453 (373610)	
	Min; Max	0 ; 1382040		0 ; 1906210	
Month 6	N	94	94	2	2
	Mean (SD)	240579 (298845)	3561 (15233)	69345 (23667)	26510 (37321)
	Min; Max	0 ; 1432530	-45700 ; 88890	52610;86080	120; 52900
Month 12	N	92	92	90	90
	Mean (SD)	242078 (302552)	6680 (22432)	316741 (357717)	22624 (62818)
	Min; Max	115 ;1432530	-45130 ; 89190	0 ; 1906210	-91300 ; 391730
Month 18	N	64	64	11	11
	Mean (SD)	240522 (280301)	8799 (24342)	292803 (258066)	21266 (16934)
	Min; Max	115 ; 1432530	-45130 ; 79160	46460 ; 916430	0 ; 52290
Month 24	N	1	1	63	63
	Mean (SD)	508645	149385	349434 (423935)	31669 (71403)
	Min; Max	508645 ; 508645	149385 ; 149385	0 ; 1906210	-91790; 403850
Month 30	N			9	9
	Mean (SD)			212288 (412368)	22489 (31235)
	Min; Max			4220 ; 1295230	0 ; 77150
Month 36	N			32	32
	Mean (SD)			451392 (502919)	70370 (118109)
	Min; Max			13160 ; 1906210	-113340 ; 502450
Month 42	N			4	4
	Mean (SD)			495575 (224849)	55920 (56085)
	Min; Max			262710 ; 749500	22380 ; 139500
Annualized New HO (last-first)	N		97		101
	Mean (SD)		9427 (30374)		23720 (48742)
	Min; Max		-30245 ; 236804		-37945 ; 339328

As presented in Table 21 above, the mean HO volume at baseline was higher in the NHS (312000000 mm^3) than in the PVO-1A-301 study (231000 mm^3).

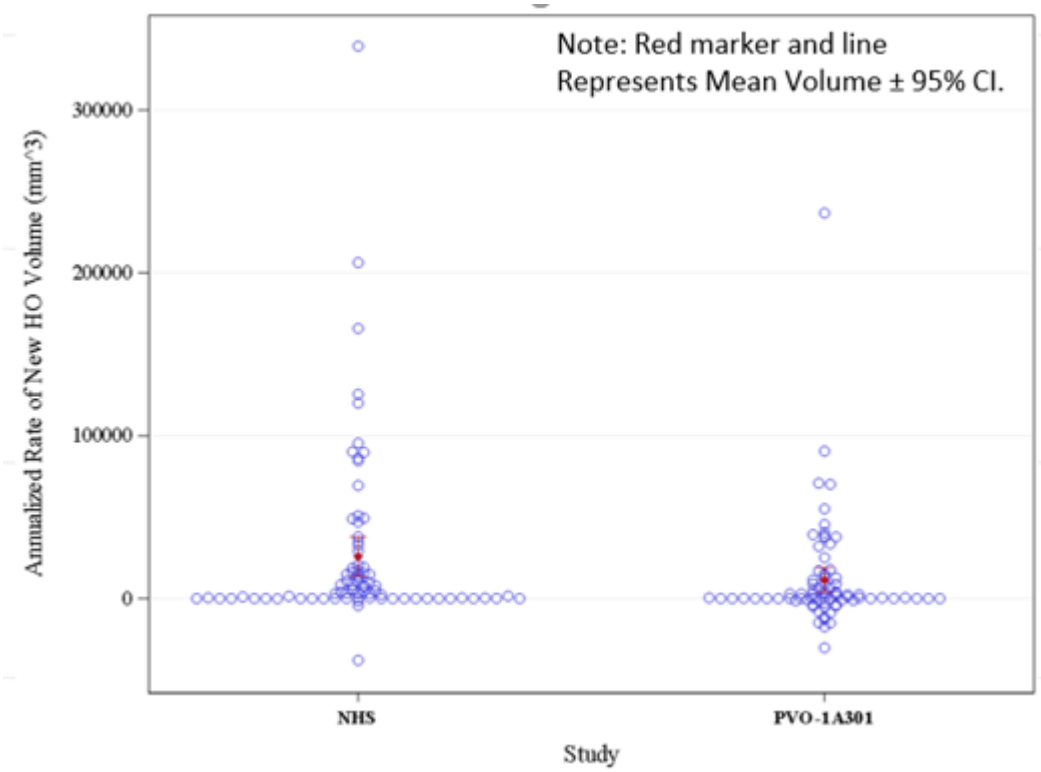
The annualised new HO values were 9400 mm^3 in the palovarotene study (approx 4 % increase) and 24000 mm^3 (approx. 8% increase) in the NHS. There was a considerable variability within the groups.

Only one subject had new HO data at a later time point of observation than 18 months. In NHS, approximately 60% had values at month 24 and 30% at month 36.

At month 12, when >90% of the subjects had available measurements in both cohorts, the mean HO in available measurements had increased in both studies; to 240000 mm^3 in the PVO-1A-301 study and to 317000 mm^3 in NHS.

However, the change from baseline (in available paired readings) was numerically larger in NHS.

Figure 5 Annualised rate of new HO volume (mm^3) by study: all subjects exclude visits that after clinical hold dates: peds 04 Dec 19 and Adults 24 Jan 20.



Secondary endpoint

- ***Proportion of subjects with any new HO at month 12***

Table 19 Proportion of subjects with any new HO at month 12

Treatment group	**Palovarotene**	**Untreated**
Number of subjects with data	92	90
Subjects with new HO since baseline, n (%)	59 (64.1%)	56 (62.2%)

There was no difference in the portion of subjects with any new HO (volume >0 mm^3) between the palovarotene treated subjects (64%) and in the untreated subjects in the NHS (62%).

- ***Number of body regions with new HO at month 12***

Table 20 Number of body regions with new HO at month 12

Treatment group	**Palovarotene**	**Untreated**
Number of subjects with data	92	90
Number of body regions with new HO since baseline per subject, mean (SD)	1.3 (1.4)	1.5 (1.6)

There was no substantial difference in the number of new body regions with new HO between the palovarotene treated subjects (1.3) and the subjects in the NHS (1.5).

- ***Proportion of subjects reporting flare-ups at month 12***

Most instances of new HO are preceded by subject report of flare-up symptoms. The most common symptoms include localised pain, swelling, erythema, warmth, decreased range of motion, and stiffness.

In PVO-1A-001, events were considered flare-ups when two or more flare-up symptoms were reported and within 14 days of flare-up initiation. In contrast, PVO-1A-301 defined a flare-up as an event with one or more flare-up symptoms, and regardless of flare-up symptom onset. The analysis of the proportion of subjects reporting flare-ups restricted PVO-1A-301 flare-ups to those events that matched the PVO-1A-001 study definition. Therefore, only PVO-1A-301 flare-ups with two or more flare-up symptoms were to be included in the secondary efficacy analyses.

Table 21 Proportion of subjects reporting flare-ups at month 12

Treatment group	**Palovarotene**	**Untreated**
Number of subjects with data	99	111
Subjects reporting flare-ups at month 12, n (%)	64 (64.6%)	60 (54.1%)

The proportion of subjects reporting flare-ups at month 12 was 65 % in the palovarotene treated study and 54 % in the NHS. There was no improvement in number of flare-ups with the treatment with palovarotene.

- ***Flare-up rate through month 24***

Only one subject was exposed to palovarotene for 24 months. Therefore, flare-up rate per subject-month exposure is more informative than rate through month 24.

Table 22 Flare-up rate through month 24

Treatment group	**Palovarotene**	**Untreated**
Flare-up rate per subject-month exposure (95% CI)	0.13 (0.09, 0.17)	0.07 (0.05, 0.08)
Ratio (palovarotene/untreated)	1.88	

The flare-up rate per month was higher in the palovarotene treated study than in the natural history study where subjects were untreated.

Of note, of the 69 subjects treated for at least one flare-up in PVO-1A-301, 37 (54%) were treated for at least one intercurrent flare-up during at least one flare-up cycle.

Exploratory efficacy endpoints

- ***Change from baseline in ROM assessed by Cumulative analogue joint involvement scale (CAJIS) through month 24***

Month 12 is presented as it is the post-baseline timepoint with the most consistent amount of follow-up data per group.

Table 23 Change from baseline in ROM assessed by cumulative analogue joint involvement scale (CAJIS) through month 24

Treatment group	**Palovarotene**	**Untreated**
Number of subjects	86	99
CAJIS score, baseline, mean (SD)	10.0 (6.1)	11.8 (7.0)
Change in score, month 12, mean (SD)	0.5 (2.0)	0.6 (2.4)

A physician assessment of body movement has been developed for FOP, the Cumulative Analogue Joint Involvement Scale (CAJIS) Ref. Kaplan et al, Bone. 2017. The CAJIS assesses range of motion of 12 joints, and three body regions with each joint/region as essentially normal or not involved (<10% deficit, score of 0), partially impaired or partially involved (10-90% deficit, score of 1); functionally ankylosed or completely involved (score of 2). The total score range is calculated as a sum of all scores of all joints/regions and ranges from 0 (normal function) to 30 (functionally ankylosed across all regions).

The CAJIS score (range 0-30) was slightly higher in the NHS at baseline. Both palovarotene treated subjects and untreated subjects had small numerical increase in CAJIS (clinical worsening) from baseline to month 12.

- ***Change from baseline in physical function through month 24, using age-appropriate forms of the FOP-PFQ (FOP-Physical function questionnaire).***

Table 24 Baseline and mean changes in FOP-PFQ values over time for palovarotene-treated and untreated subjects

Visit	Palovarotene (N = 99)	Untreated (N = 111)
Chronic Baseline		
N	98	100
Mean (SD)	44.28 (26.86)	46.97 (28.06)
Median (min, max)	42.79 (0.0; 98.2)	45.84 (0.0; 100.0)
Mean Change at Month 6		
N	82	76
Mean (SD)	2.53 (9.62)	3.18 (9.34)
Median (min, max)	0.96 (-17.3; 52.9)	1.79 (-18.8; 47.3)
Mean Change at Month 12		
N	71	82
Mean (SD)	2.76 (7.77)	4.50 (8.88)
Median (min, max)	1.92 (-17.3; 27.9)	3.71 (-23.1; 27.7)
Mean Change at Month 18		
N	64	56
Mean (SD)	4.19 (12.31)	4.11 (10.08)
Median (min, max)	1.79 (-47.3; 37.5)	1.34 (-13.5; 29.8)

Source: Table S40.1.
FOP-PFQ=Fibrodysplasia Ossificans Progressiva-Physical Function Questionnaire; max=maximum; min=minimum; SD=standard deviation.

The FOP-PFQ was developed by the Applicant to assess the relationship between patient reports of physical impairment and total body burden of HO. Age-appropriate forms provide a measure of functional impairment experienced by subjects. The total score across each of the age forms is different due to the differences in the number of questions included. Therefore, raw scores were transformed to the percentage of the total possible score in order to normalise across all subjects and instruments (adult and paediatric), with higher percentages representing greater functional impairment. The Applicant states that the tool is not sufficiently sensitive to detect change over 1 to 2 years.

At baseline, the NHS scored somewhat higher (47%) in the FOP-PFQ than subjects in study PVO-1A-301 (44%). In the palovarotene treated subjects the change from baseline at months 6 and 12 seems to be numerically slightly less (2.8%) than in the untreated subjects (4.5%). This difference did not persist at month 18.

- ***Change from baseline in physical and mental function for subjects ≥ 15 years old and mental function for subjects <15 years old using age appropriate forms of the PROMIS Global health scale, through month 24.***

The 10-item adult tool assesses general health in the areas of global physical health (quality of life, mental health, satisfaction with social activities and emotional problems). A similar instrument for the paediatric population, a part for self-report by children aged 8 to 17 years and a parent proxy tool for children aged 5 to 17 years. Due to the different scoring in the adult and paediatric versions the data were summarised by age group.

Table 25 Summary of PROMIS- Adult self-completed global physical health T-score over time in Study PVO-1A-301 and NHS subjects (Principal Safety Set)

Analysis visit	Statistics	MOVE Trial / Palovarotene		NHS / Untreated	
		Value	Change from Baseline	Value	Change from Baseline
Baseline	N	36		57	
	Mean (SD)	43.15 (7.93)		43.35 (8.66)	
	Min; Max	23.5 ; 61.9		23.5 ; 67.7	
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)
	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)

Table 26. Summary of PROMIS- Paediatric Total T-Score Over Time in Study PVO-1A-301 and the NHS subjects (Principle Safety Set)

Analysis visit	Statistics	MOVE Trial / Palovarotene		NHS / Untreated	
		Value	Change from Baseline	Value	Change from Baseline
Baseline	N	58		40	
	Mean (SD)	46.10 (9.15)		44.05 (9.01)	
	Min; Max	29.4; 66.1		24.4; 66.1	
Month 12	N	41	41	31	31
	Mean (SD)	43.86 (8.49)	-2.60 (7.34)	44.18 (10.72)	-0.60 (4.44)
	Min; Max	27.7; 63.2	-24.0; 11.4	21.0; 63.2	-11.9; 8.0
Month 18	N	23	23	21	21
	Mean (SD)	45.73 (11.18)	-1.00 (6.78)	45.96 (9.17)	0.12 (5.73)
	Min; Max	26.1; 63.2	-11.4; 15.9	29.4; 63.2	-10.3 ; 10.9

With the adult and paediatric PROMIS score, small changes from baseline were seen in palovarotene-treated subjects at all post-baseline time points, and the results were similar to those reported in untreated subjects.

- ***Incidence and volume of Catastrophic HO per year, ie, new HO of at least >50,000 mm^3 and >30,000 mm^3 at months 12 and 24***

Table 27 Catastrophic HO for palovarotene-treated and untreated subjects (Principal FAS).

	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

Source: Table E40.1.
FAS=Full Analysis Set; HO=heterotopic ossification.

SAP Version 1.1 (after unblinding of the second interim analysis) defined exploratory endpoints of incidence and volume of "catastrophic HO". In these post-hoc comparisons the percentage of subjects with catastrophic new HO was numerically lower in palovarotene-treated subjects than in untreated subjects at Month 12 and at the last timepoint assessed (the last timepoint at which a subject had available data).

- **Ancillary analyses**

Long term follow-up data were submitted during the evaluation (answers to the Day 120 LoQ) and are present thereafter:

Study PVO-1A-301: For the 45 subjects that restarted treatment following the pause and contributed WBCT data at restart baseline and post restarting palovarotene, the mean observed annualised new HO volume (square-root transformation and negatives zeroed out, predefined analysis) from the original baseline to the time of the palovarotene pause was 112.6 mm^3. In comparison, the mean observed annualised new HO volume from restart baseline to the last WBCT was, 200.1 mm^3 (N=18). For these subjects, the mean timeframe from the restart baseline WBCT to the last WBCT represents approximately 16 months, of which approximately 7 months were untreated. Nevertheless, it should be noted that the reported annualised HO of 200.1 mm^3 is more than reported for untreated patients in NHS 143.8 mm^3.

In the analysis using post-hoc analysis of the data, the increase in new HO after re-start is even more clear. For the 45 subjects, the mean observed annualised new HO volume (with no square-root transformation and negatives included) from the original baseline to the time of the palovarotene pause was 5 488 mm^3. In comparison, the mean observed annualised new HO volume from restart baseline to the last WBCT was, 36 915.9 mm^3 (N=18). For these subjects, the mean timeframe from the restart baseline WBCT to the last WBCT represents approximately 16 months, of which approximately 7 months were untreated. Nevertheless, it should be noted that the reported annualised HO of 36 916 mm3 is numerically considerably more than reported for untreated patients in NHS (approximately 24 000 mm3) and also more than in Study PVO-1A-202/204 Part C (22 000 mm^3 from original baseline and after restart 26 000 mm3)

The data on HO volumes after restart of treatment in study PVO-1A-301 do not support effect of Palovarotene in decreasing HO volume.

Study PVO-1A-202/204 Part C: Updated information of Study 202 Part C involving 26 subjects who restarted palovarotene after pausing as of the data cut off of 30 July 2021 was presented. Only subjects >14 years of age could restart palovarotene.

The mean observed annualised new HO volume from original baseline to the time of the palovarotene pause was 23411 mm^3 in patients who restarted. This is slightly lower than the mean observed annualised new HO volume from restart baseline to the last WBCT which was 26105 mm^3 (N=19). For these subjects, the mean timeframe from the restart baseline WBCT to the last WBCT represents approximately 17 months, of which approximately 7 months were untreated.

In summary, the annualised new HO volumes seem to remain in the same range in actively treated patients in Study 202 as in the NHS.

Flare-ups

Patients had comparable rate of flare-ups both during treatment and during off treatment in both studies Study PVO-1A-301 (0.05-0.1 per subject/ month) and Study PVO-1A-202/204 Part C (0.2-0.3 per subject/ month). The data do not indicate that PVO treatment would have any effect on flare-up rate. In contrast, numerically lowest flare-up rate 0.05 in Study PVO-1A-301 was reported during dosing interruption. For comparison, the flare-up rate was 0.07 per subject/ month in the NHS.

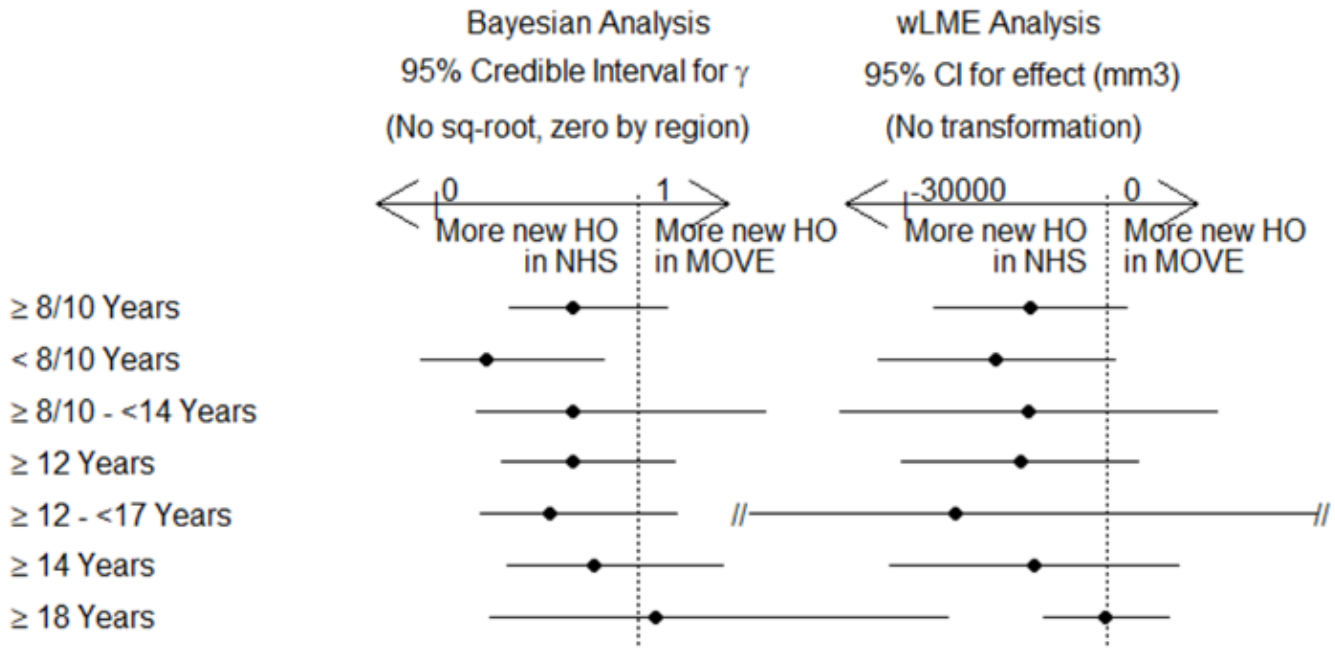
Subgroup analyses

As palovarotene safety data demonstrated increased risk of PPC in some skeletally immature paediatric subjects, additional analyses were performed on the subgroups in whom the potential benefit might outweigh the identified risks.

Subgroup analyses were performed for all efficacy endpoints to examine the consistency of the estimated treatment effect by age (≥12, ≥14, ≥18, ≥12 – <17 years), age by sex (<8 years for females or <10 years for males; ≥8 – <14 for females or ≥10 – <14 years for males), sex (male, female), and race (white versus other).

Age

Figure 6 Forest Plot for Bayesian and wLME Analyses for Age Subgroups (post-hoc analysis methods without sq root transformation)



Sex and race

Among subjects who received PVO, there was a 73% reduction in the mean annualised new HO volume in males (8,353 mm^3; N=51) compared to untreated subjects (31,276 mm^3; N=56) and a 26% reduction in females (10,618 mm^3; N=46) compared to untreated subjects (14,317 mm^3; N=45). The greater percent reduction in HO volume in male subjects may be explained by differences in the response of individual subjects.

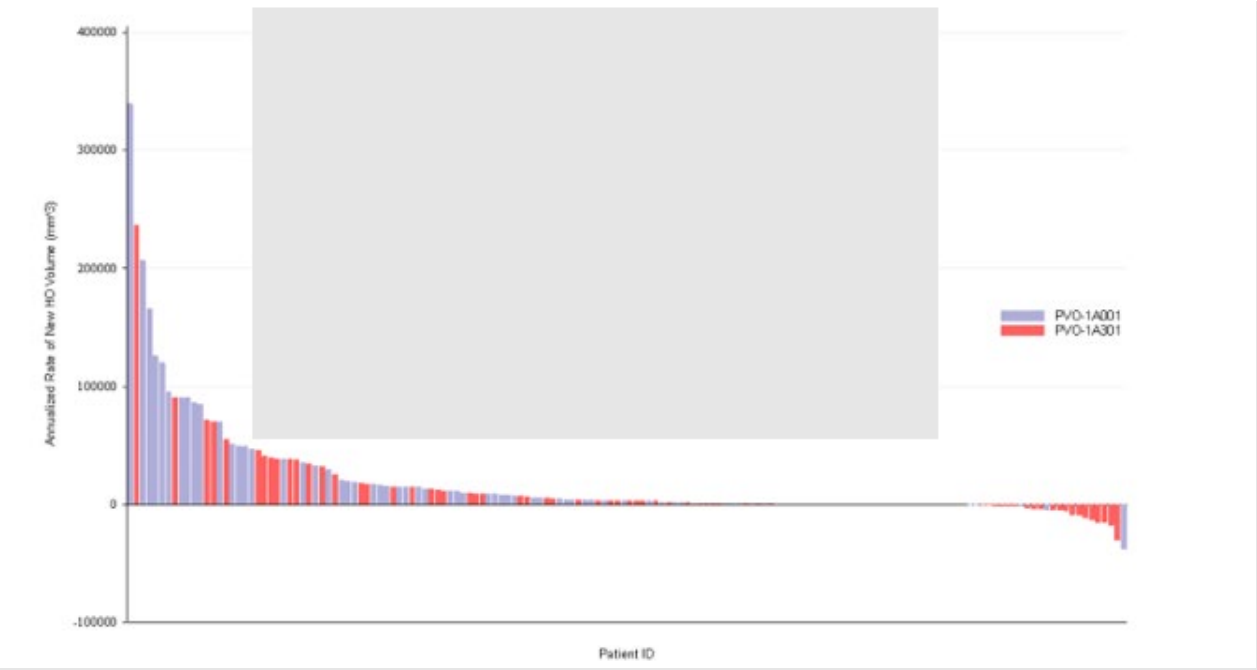
Reduction in annualised new HO was similar in White and Other subjects.

Negative new HO volume from baseline (new HO volume <0 mm^3)

FOP is characterised by cumulative and irreversible HO formation resulting in progressive loss of physical function. However, radiographic assessment of HO volumes obtained during the FOP clinical program suggests that some regression of new HO may occur, although measurement variability could also explain a component of the observed degree of negative HO reported. Another potential cause of negative new HO may be related to the subjectivity of outlining HO within a CT axial slice. In cases of HO that encompass many large cranial to caudal regions (and thus across multiple axial slices), small differences outlining HO at each axial slice can translate into large differences in total HO measured. Analysis of negative WBCT HO by region demonstrated that the upper body, including chest, neck,

shoulder (left and right), and mid torso were the most common regions identified with negative new HO. These represent large body regions in which it may be more challenging to quantify HO compared to the lower body.

Figure 7 Annualised rate of new HO volume (mm^3) at last visit by subject/study. Excludes visits that after clinical hold dates: peds 04 Dec 19 and Adults 24 Jan 20.



Further Ancillary analyses: Post hoc analysis of the primary endpoint

After that studies were announced futile and data was unblinded, the Applicant performed several post-hoc analysis on the new HO volume endpoint, including following:

a) wLME analysis was used instead of Bayesian

b) negatives values were zeroed by overall instead of per region as in the primary analysis

c) negatives included

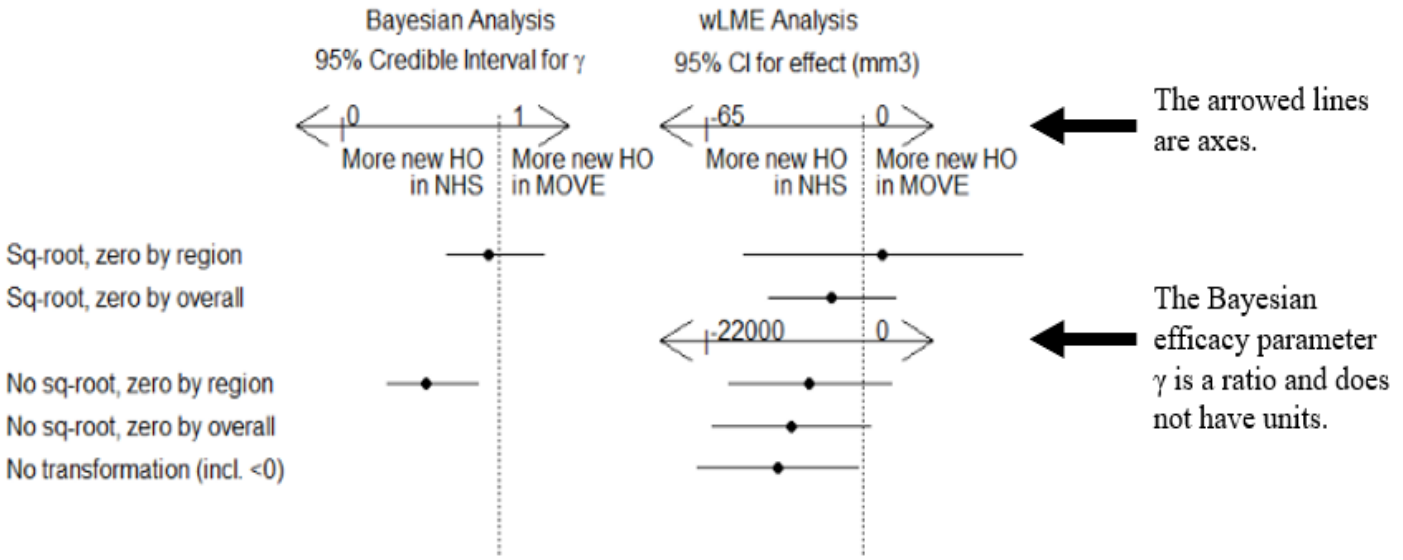
d) in contrast to primary analysis, no square root transformation was used

e) combinations of above

The Figure 9 shows a forest plot of the 95% credible intervals for the median posterior distribution γ for the Bayesian analyses and the 95% confidence intervals (CI) for the treatment effect for the wLME analyses of the annualized volume of new HO in the overall population.

The spe-specified Sq-root, zero by region analyses indicate no difference between NHS and interventional MOVE study. However, wLME analysis using not transformation provides a nominally statistically significant result favoring MOVE.

Figure 8 Forest Plot for Bayesian and wLME Analyses for Palovarotene-treated and Untreated Subjects.



[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= PVO-1A-301; NHS=natural history study PVO-1A-001; wLME=weighted linear mixed effect.

According to the initial application, the Bayesian analysis with square-root transformation fit a 7% reduction on the square-root scale in the volume of new HO (i.e, change from baseline in HO volume) with palovarotene treatment. WLME analysis indicated more new HO with palovarotene.

The Bayesian analysis without square-root transformation fit a 38% reduction in the volume of new HO. However, utilising the non-square-root transformed raw data that includes all observed data – including reductions in HO, i.e negative new HO, a reduction in the mean annualised new HO volume of 60% was observed in palovarotene-treated (9,427 mm^3) versus untreated (23,720 mm^3) subjects in the overall population. A wLME using these non-transformed annualised new HO volumes yielded a nominally statistically significant 54% reduction in the overall population (nominal wLME p-values <0.05).

Table 28 wLME for Annualised New HO Volume with No Square-root Transformation and Negatives Included for Palovarotene-treated and Untreated Subjects (Principal FAS).

		Palovarotene (N=97)	**Untreated (N=101)**
Number of subjects analyzed		97	101
New HO (mm3)	Mean (SEM)	9427.1 (3084.0)	23720.2 (4850.0)
	% reduction (palovarotene vs untreated)	60.3%	
	LSmean (SEM)	9366.8 (4101.7)	20273.0 (3266.6)
	% reduction (palovarotene vs untreated)	53.8%	
		wLME estimate (95% CI)	p-value
	Intercept	16174.1 (7470.37, 24877.88)	0.0003
	Baseline total HO/Baseline age	0.3 (-0.10, 0.66)	0.1440

		Palovarotene (N=97)	Untreated (N=101)
	Treatment	-10906.2 (-21240.69, -571.63)	0.0392
Wilcoxon test	p-value	0.0003	

Note: The new HO weighted linear mixed effect (wLME) LSMEAN estimate and SEM are from a mixed model with dependent variable annualized new HO and independent variables including fixed effects of treatment and baseline total HO/baseline age and a random subject effect.
HO=heterotopic ossification; LSMEAN=least square mean; MOVE=PVO-1A-301; NHS=natural history study (PVO-1A-001); SEM=standard error of the mean; wLME=weighted linear mixed effect.

The applicant claims that the most appropriate analysis for these data is the wLME analysis without square-root transformation, which was the original protocol-specified primary efficacy analysis before the Bayesian analysis with the square-root transformation was substituted for it in Amendment 1 of the protocol. With square-root transformation, the Applicant claims that the Bayesian analysis is biased against palovarotene due to differences in assessment schedule. The wLME analysis without square-root transformation has the added advantage that it accommodates the annualised new HO as reported, including any observed reductions in HO volume over time.

Across all methodologies, with the square-root transformation reducing the influence of subjects with unusually large amounts of new HO, analyses with square-root transformation are expected to be less powerful relative to the analyses without the square-root transformation.

Several sensitivity analyses were performed without square-root transformation. Overall, the estimated treatment effects were similar when using additional covariates including fixed effects of treatment, baseline HO volume divided by age, baseline age, sex, baseline month since last flare-up and baseline CAJIS and a random subject effect and propensity score quartile as a covariate.

Subjects who contributed follow-up for both Studies PVO-1A-301 and PVO-1A-001

An analysis (wLME for Annualised New HO Volume with No Square-root Transformation and Negative Values Included) was performed in the 38 untreated subjects in Study PVO-1A-001, who transitioned to the palovarotene treatment in Study PVO-1A-301. In the analysis provided in the initial application, subjects who first participated in Study PVO-1A-001 and then commenced palovarotene treatment in Study PVO-1A-301 (n=38), demonstrated a 61% lower annualised new HO volume during chronic/PVO 20/10 mg administration in Study PVO-1A-301 compared to no treatment in Study PVO-1A-001. The wLME favored palovarotene with a 57% reduction (nominal wLME p=0.0438). The prespecified analysis (Square-root Transformation and Negative Values zeroed) was not presented.

Assessment of the Impact of the Difference in Length of Follow-up Between Subjects in Studies PVO-1A-301 and PVO-1A-001

The mean observed annualised new HO volumes and wLME analysis for annualised new HO volume (with no square-root transformation and negatives included) through Month 12 and 24 were presented by the Applicant. Overall, the results of both analyses are similar to those using all follow-up data. The prespecified analysis (Square-root Transformation and Negative Values zeroed) was not presented.

Assessment of Missing Data in Study PVO-1A-301

A tipping point analysis for missing data through Month 18 in palovarotene-treated subjects from Study PVO-1A-301 was presented by the Applicant. The data included in untreated subjects from Study PVO-1A-001 are unchanged from the wLME with no square-root transformation and negatives included; no imputation is performed for missing data in this population. The wLME fitted reduction in annualised new HO volume ranged from 61% (p=0.0064) to 52% (p=0.0190) in palovarotene-treated subjects as compared with untreated subjects across the 10 datasets if the observed treatment effect retained ranges from 100% to 0%, respectively. The prespecified analysis (Square-root Transformation

and Negative Values zeroed) was not explored. Of note, impact of missing data from the NHS study was not explored.

Assessment of the Impact of Extreme Values for Annualised New HO Volumes in the Studies PVO-1A-301 and PVO-1A-001

To determine whether extreme values for annualized new HO volumes in Studies PVO-1A-301 and PVO-1A-001 unduly influence the described treatment effect, any annualized new HO value >100,000 mm^3 was set to 100,000 mm^3. The results remained essentially similar. The Applicant concludes that the results demonstrated does not depend solely on the magnitude of the small number of subjects with extremely large, annualized new HO volume.

Additional Analyses of the Primary Efficacy Analysis with No Square-root Transformation and Negatives Included)

Four additional analyses of annualized new HO using the wLME method with no square-root transformation and negatives included were performed to determine outcomes in subjects who reported at least one vs. no flare-ups:

- subjects in Studies PVO-1A-301 and PVO-1A-001 with no flare-ups at Month 12
- subjects in Studies PVO-1A-301 and PVO-1A-001 with flare-ups at Month 12
- subjects in Study PVO-1A-301 with no flare-ups vs. flare-ups at Month 12
- subjects in Study PVO-1A-001 with no flare-ups vs. flare-ups at Month 12

Support for the chronic component of the Chronic/Flare-up regimen comes from the analysis of annualized new HO in palovarotene-treated subjects who reported no flare-ups (and thus received only chronic palovarotene treatment, N=33) compared with untreated subjects who reported no flare-ups (N=44). In this population, mean annualized new HO volume was 48% lower in palovarotene (3,183 mm^3) versus untreated subjects (6,150 mm^3). Support for the flare-up component of the Chronic/Flare-up regimen comes from the analysis of annualized new HO in palovarotene-treated subjects who reported flare-ups (and thus received the Chronic/Flare-up regimen, N=64) compared with untreated subjects who reported flare-ups (N=46). In this population, mean annualized new HO was 69% lower in palovarotene-treated subjects with reported flare-ups (11,661 mm^3) versus untreated subjects (37,380 mm^3).

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 29 Summary of efficacy for trial PVO-1A-301

Title: A Phase 3, Efficacy and Safety Study of Oral Palovarotene for the Treatment of Fibrodysplasia Ossificans Progressiva (FOP)		
Study identifier	Protocol number: PVO-1A-301 EudraCT number: 2017-002541-29 NCT number: NCT03312634	
Design	This is an ongoing Phase 3, multicenter, open-label study in adult and paediatric subjects with FOP, conducted in two parts: Part A, the main phase; and Part B, the extension. Sources of subjects eligible for enrollment include: (1) subjects from Study PVO-1A-001; (2) additional subjects clinically diagnosed with FOP with the *R206H* activin receptor type IA (*ACVR1*) mutation or other FOP variants reported to be associated with progressive HO; and (3) subjects from Phase 2 studies PVO-1A-202 or PVO-1A-204 who could not receive the chronic/flare-up regimen due to their country of residence or who were traveling long distances to participate in the Phase 2 trial. Up to 110 subjects were to be enrolled (up to 99 with the *R206H* mutation and no previous exposure to palovarotene, and up to 11 with other mutations or previous participation in the Phase 2 trials). This study included 2 modes of treatment: chronic (palovarotene 5 mg daily) and flare-up based (palovarotene 20 mg daily for 4 weeks, starting as soon as possible after the beginning of a flare-up, followed by palovarotene 10 mg daily for 8 weeks, for a total of 12 weeks). All doses were weight adjusted for skeletally immature subjects. All subjects enrolled in this study received palovarotene; the study did not include a control group. Untreated subjects in Study PVO-1A-001 were used as an untreated comparison group. **Part A:** Subjects received chronic treatment for up to 24 months and flare-up-based treatment when they experienced an eligible flare-up or a substantial high-risk traumatic event likely to lead to a flare-up as confirmed by the Investigator. Remote visits occurred at Week 6 and at Study Months 3, 9, 15, and 21 unless the Investigator deemed that a site visit was necessary. **Part B:** Palovarotene was administered for an additional 24 months at the same regimens as in Part A. No new subjects were enrolled into Part B.	
	Duration of main phase	Stopped for futility. Clinical hold due to safety issues. Restart after post-hoc analyses.
Hypothesis	Not applicable	

Treatment groups	**Group Name**		**Description**	**Number of Subjects**
	PVO-1A-301 Palovarotene		Subjects in Study PVO-1A-301 who received palovarotene	107
	PVO-1A-001 Untreated		Subjects in Study PVO-1A-001 who did not receive palovarotene, used as a comparison group	114
Endpoints and definitions	Primary endpoint	Annualised change in new HO volume, excluding head, as assessed by low-dose WBCT		
	Key secondary endpoint	Proportion of subjects with any new HO at Month 12		
	Secondary endpoint	Number of body regions with new HO at Month 12		
	Secondary endpoint	Proportion of subjects reporting flare-ups at Month 12		
	Secondary endpoint	Flare-up rate per subject-month of exposure through Month 24		
Database lock	Final database lock has not yet occurred. This summary is based on a database cutoff date of 28 February 2020 and includes assessments collected on or before the dosing interruption on 04 December 2019 for subjects <14 years old (pause due to a partial FDA clinical hold) and 24 January 2020 for subjects ≥14 years old not affected by the partial clinical hold but paused due to futility analysis.			
Results and Analysis: Summarised from interim Clinical Study Report dated 19 March 2021. Results were updated according to Day 120 Major Objection from Clinical Study Report dated 04 April 2022.				
Analysis population	Principal Full Analysis Set	All subjects enrolled in Study PVO-1A-301 with the *R206H ACVR1* mutation who had not previously been treated with palovarotene and who signed the informed consent form and met all eligibility criteria, who had a baseline HO volume measurement and at least one post-baseline HO volume measurement in Study PVO-1A-301. For efficacy comparisons to Study PVO-1A-001, the Principal FAS also included subjects enrolled in Study PVO-1A-001 with available baseline and at least one post-baseline HO volume measurement.		
Analysis description	**Primary Analysis**			
Descriptive statistics and estimate of variability	New HO volume (mm^3), with square-root transfor-mation and negatives zeroed out	Treatment group	**Palovarotene**	**Untreated**
		Number of subjects with data	97	101
		Mean (SEM)	140.2 (23.6)	149.8 (19.4)
		% reduction (palovarotene vs untreated)	6.4%	

	by body region	LSmean (SEM)	137.0 (20.7)	129.5 (15.7)
		% reduction (palovarotene vs untreated)	-5.9%	
Analysis description	**Secondary Analyses**			
Descriptive statistics	Treatment group		**Palovarotene**	**Untreated**
	Proportion of subjects with any new HO at Month 12	Number of subjects with data	92	90
		Subjects with new HO since baseline, n (%)	59 (64.1%)	56 (62.2%)
	Number of body regions with new HO at Month 12	Number of body regions with new HO since baseline per subject, mean (SD)	1.3 (1.4)	1.5 (1.6)
	Proportion of subjects reporting flare-ups at Month 12	Number of subjects	99	111
		Subjects reporting flare-ups at Month 12, n (%)	64 (64.6%)	60 (54.1%)
	Flare-up rate through Month 24	Flare-up rate per subject-month exposure (95% CI)	0.13 (0.09, 0.17)	0.07 (0.05, 0.08)
		Ratio (palovarotene/ untreated)	1.88	

2.5.5.3. Clinical studies in special populations

The clinical FOP studies included a large number of paediatric patients. Studies in other indications are described in the safety section but are not relevant for efficacy.

2.5.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

Annual and bi-annual endpoint data (i.e, non-flare-up based outcome data) from PVO-1A-202/Parts B and C were not pooled with data from PVO-1A-301 and PVO-1A-001. The rationale by the Applicant is that PVO-1A-202/Parts B and C are components of an extension study of PVO-1A-201 in which subjects were enrolled at the time of an active flare-up. However, according to the CHMP, for the long-term results, the time of enrolment should not be reason for not pooling the data. As only one patient had available 24-month data in study PVO-1A-301, longer-term results from the NHS can only be compared with study PVO-1A-202/Parts B and C.

The proposed target population is ≥8 years for females and ≥10 years for males (referred to as ≥8/10). Analyses of the primary endpoint of annualised new HO include the Bayesian analysis without square-root and with negatives zeroed out by region, and wLME without square-root and negatives included, as these are the methods on which the conclusion of efficacy by the Applicant in the overall population is based. The prespecified analysis (Square-root Transformation and Negative Values zeroed) was not presented.

In these post-hoc analysis presented in the initial application, there was a 57% reduction in the mean annualised new HO volume in PVO (10,655 mm^3) compared with untreated subjects (24,777 mm^3). When covariates and follow-up-based weights are considered in the wLME, there was a 51% reduction in the model-fitted mean annualised new HO volume in PVO subjects (10,572 mm^3) compared with untreated subjects (21,617 mm^3) (nominal wLME p=0.0953). The proportion of subjects in the target population with any new HO overall was similar in PVO (61%) and untreated subjects (57%) at Month 12 (Fisher's exact test p=0.7333).

Flare-up outcome data

The flare-up outcomes from the Phase 2 studies and PVO-1A-001 (NHS) were presented by the applicant to provide evidence of efficacy of the flare-up only regimen as a standalone regimen, to support the recommendation that this regimen may be prescribed for those subjects who cannot tolerate chronic PVO 5 mg daily.

The data obtained in the PVO groups are compared to pooled data from placebo-treated flare-ups in PVO-1A-201 and untreated flare-ups from PVO-1A-001.

In the target population, the proportion of flare-ups with new HO at Week 12 was lower in the 20/10 mg chronic/flare-up group (21%) and higher in the 20/10 mg only group (44%). The rates in the 5/2.5 mg (29%), 10/5 mg (28%), and combined 20/10 mg (28%) groups were similar to the PBO/untreated (30%) group.

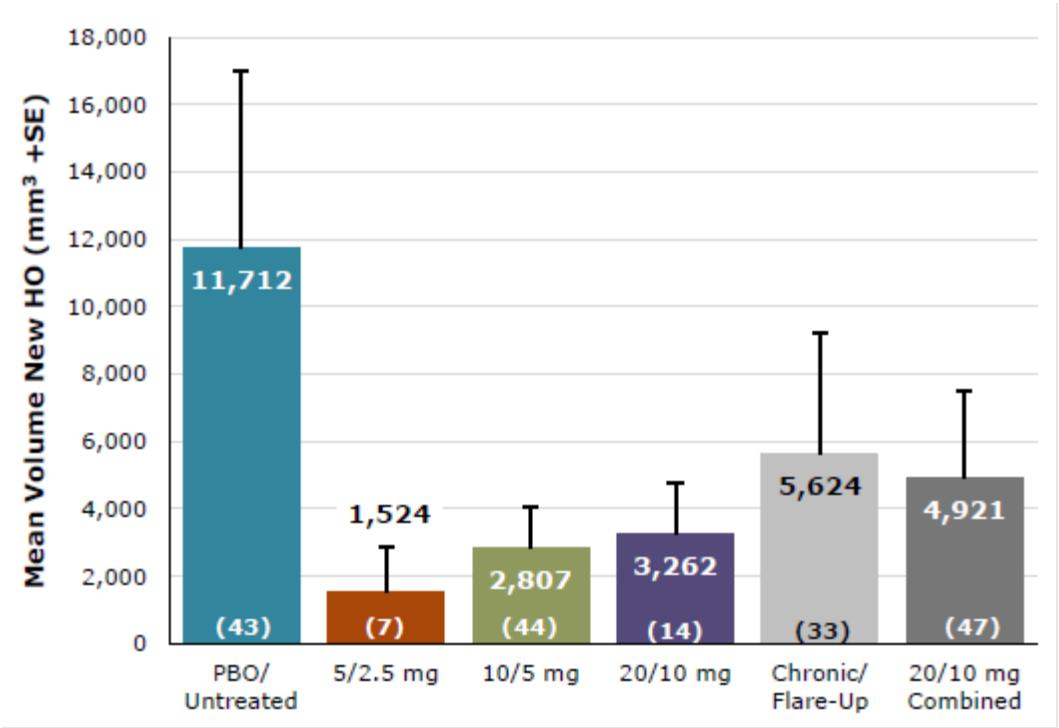
Table 30 Flare-up New HO at Week 12 for the Placebo/Untreated and Palovarotene Treated Flare-ups in the Target Population (IF-FAS)

	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)

Source: Module 5.3.5.3 ISE Table 14.2.11.2.1.
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.

Flare-up new HO volumes at Week 12 in target population is presented in Figure 10; flare-up new HO volumes at Week 12 was higher in the chronic/flare-up group than in the 20/10 mg, 10/5 mg, and 5/2.5 mg groups with volume descending with PVO dose.

Figure 9 Flare-up New HO at Week 12 for the Placebo/Untreated and Palovarotene-Treated Flare-ups in the Target Population (IF-FAS)



Regarding annual data, the Applicant stated that pooling of phase 2 study data with PVO-1A-001 is not possible due to possible baseline differences. For flare-up outcomes the Applicant claims that similarities in demographics and disease characteristics support pooling. This does not seem to have a scientific rationale and is considered likely as a post-hoc data driven strategy. Furthermore, regarding flare-up reporting in NHS vs pivotal phase 3 study, the Applicant concluded that the reporting of flare-ups may differ depending on it the patients are on an active flare-up based regimen or not. Therefore, whereas pooling of the annual data would seem to be appropriate, pooling of available flare-up data where data from placebo patients (flare-ups treated with placebo n=3) and NHS are combined is questionable.

The applicant claims that in the target population, PVO 20/10 mg (3,262 mm^3) provided the strongest evidence of a treatment effect with an approximate 72% reduction in new HO relative to the PBO/untreated group (11,712 mm^3). This interpretation of the figure above is not shared as the lower dose regimens 5/2.5mg and 10/5mg seemed to result in numerically lower volumes of new HO.

Numeric Rating Scale for Pain and Swelling

Table 31 Change in Numeric Rating Scale for Pain and Swelling from Day 1 (Baseline) to Week 12 for the Target Population (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)
Pain						
Baseline						
m	46	7	46	16	34	50
Mean (SD)	3.8 (2.9)	3.7 (3.0)	4.4 (2.6)	3.5 (2.8)	3.2 (2.4)	3.3 (2.5)
Median (min, max)	3.5 (0, 10)	3 (0, 9)	4 (0, 10)	4.5 (0, 7)	3 (0, 8)	3.5 (0, 8)
Change at Week 12						
m	46	7	46	16	34	50
Mean (SD)	-2.0 (3.1)	-2.1 (2.7)	-2.9 (2.8)	-2.2 (2.4)	-2.4 (2.4)	-2.3 (2.4)
Median (min, max)	-1 (-10, 4)	-2 (-7, 1)	-3 (-10, 2)	-1.5 (-7, 1)	-2 (-7, 2)	-2 (-7, 2)
Swelling						
Baseline						
m	46	7	46	16	34	50
Mean (SD)	3.1 (3.0)	3.6 (2.8)	3.5 (2.9)	2.8 (2.5)	3.2 (2.9)	3.1 (2.8)
Median (min, max)	2 (0, 10)	3 (0, 7)	3 (0, 10)	3.5 (0, 7)	3 (0, 10)	3 (0, 10)
Change at Week 12						
m	46	7	46	16	34	50
Mean (SD)	-2.0 (2.7)	-2.4 (2.4)	-2.6 (3.1)	-1.8 (2.3)	-2.6 (2.8)	-2.3 (2.6)
Median (min, max)	-2 (-10, 3)	-2 (-7, 0)	-2 (-10, 5)	-1 (-6, 2)	-2 (-10, 2)	-2 (-10, 2)

The mean changes in the NRS pain and swelling were similar across the groups. The acute flare-up symptoms improved over 12 weeks regardless of treatment or not.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Design

Study PVO-1A-001 was a 3-year, longitudinal, non-interventional NHS describing FOP disease characteristics, prospectively evaluating disease progression and the impact of flare-ups on FOP outcomes in 114 subjects with FOP due to the R206H mutation.

Study PVO-1A-201 was a placebo-controlled Phase 2 study to evaluate episodic treatment with palovarotene at the time of a flare-up in adult and paediatric subjects with FOP. Sparse data from 9 participants who developed heterotopic ossification (HO; presence of bone in soft tissue where bone normally does not exist) by week 12 is available.

Study PVO-1A-202 was an extension of PVO-1A-201 without a placebo group and had three parts. Part A evaluated flare-up only palovarotene regimen further. In Part B, chronic daily doses (5 mg) in the absence of a flare-up were added. During a flare-up, subjects received palovarotene 20 mg for 4 weeks followed by 10 mg for 8 weeks. Similar doses were used in part C but the definition of flare-up qualifying for treatment was made broader. The primary efficacy endpoint for Part C was the annualised change in new HO volume (as assessed by low-dose WBCT scan, excluding head). Part C has longer follow-up than the pivotal phase 3 study, used similar dosing and primary endpoint, which makes the results of interest for the application.

PVO-1A-301, which was meant to be the main study, is a multicentre, open-label, single arm, phase 3 study in 107 adult and paediatric subjects with FOP to evaluate palovarotene treatment for up to 48 months. Dosing was similar to PVO-1A-202 Part B. The results are compared with data collected from

the NHS. The study was designed to evaluate if exposure to palovarotene could prevent the formation of HO in subjects with FOP.

Conduct

Based on the serious identified risk of PPC, a partial clinical hold in the palovarotene program was implemented on subjects <14 years old on 04 December 2019. Shortly after, the sponsor paused dosing for all remaining subjects (14 years and older) in the FOP palovarotene program on 24 January 2020 due to futility in interim analysis of main study PVO-1A-301. After that, the sponsor became unblinded to all study data. Analyses of all efficacy endpoints in this application included assessments collected on or before as well as after these interruptions. After post-hoc analysis of the efficacy data, the sponsor decided to reinitiate dosing in subjects 14 years.

During the assessment, new data from the ongoing PVO studies: PVO-1A-301 and Study PVO-1A-202/204 Part C was submitted by the applicant, including 45 patients from study 301 and 26 patients from 202. The available longer term new efficacy data from these studies do not indicate that PVO treatment would have an effect in decreasing new HO volume. The numbers reported are similar or higher compared to those from the natural history cohort.

Furthermore, PVO treatment has no effect on flare-up rates as numbers reported during on-and off treatment periods were similar.

Inclusion/exclusion criteria

The NHS study had minimal inclusion and exclusion criteria. Basically, the patients should have been clinically diagnosed with FOP (believed to carry the R206H mutation) and be willing to participate. The interventional PVO-1A-301 study had somewhat more rigorous criteria. As the comparisons are not based on randomisation, several sources of bias cannot be excluded. For example, patients with flare-up symptoms within the past 4 weeks were to be excluded in PVO-1A-301 that might have led to exclusion of the patients with most active disease. In contrast, subjects in Study PVO-1A-201 were enrolled at the time of flare-up.

The age for inclusion was discussed in a CHMP scientific advice, in which the exclusion of children at ages below 4 years of age was not considered acceptable at that time as the disease is present from birth. The currently proposed indication is from 8 (female)/10 (male) years due to safety. Despite no upper age restriction, no patients >65 were recruited in study PVO-1A-301.

Efficacy data and additional analyses

Dose finding studies

The first dose finding study PVO-1A-201 did not meet its primary responder endpoint, nearly all participants had no or minimal new HO at week 6. Very sparse data from 9 participants (from 10/5 mg, 5/2.5 mg and placebo groups) who developed HO by week 12 indicated, however, that palovarotene could have an effect on new HO volume and this endpoint was chosen for further development.

In study PVO-1A-202, patients from all modes of treatment continued to develop new HO (21-41% at 12 weeks). The mean volume of new HO at week 12 was higher in the chronic+20/10 mg palovarotene group than the other two treatment groups (PVO 10/5 mg and PVO 20/10 mg only at flare-ups). In summary, the 12-week flare-up outcome data did not demonstrate a dose response across the flare-up doses utilised in the Phase 2 program and did not justify the chronic 5 mg dosing. In Part B, change from baseline in mean volume of new HO at Month 12 was 28,386 mm^3. In Part C, change from baseline in mean volume of new HO was 9,332, 62,836, and 89,487 mm^3 for Months 12, 24, and 36 respectively. Using the "without square-root transformation negatives included" approach, no reduction

of annualised new whole-body HO volumes was seen in PVO-1A-202/204 Parts B and C compared to NHS. HO volumes in this study were numerically even higher compared to untreated subjects. The mean annualised new HO was 27.967 mm^3 in Study PVO-1A-202/Part B, 24.290 mm^3 in Part C and 23.720 mm^3 in the NHS.

During the oral explanation on 13 December 2022, the applicant presented new data analysis including only patients with comparable WBCT (September 2022 data cut-off). Excluding certain patients from the analysis of Study 202 Part C is not supported as this seems data-driven.

Main study PVO-1A-301

In study PVO-1A-301, no subjects had completed the study by the data cut-off date. At the time of futility stop, of the 107 subjects who were enrolled and treated, 88 remained in the study and 19 subjects had discontinued, the majority due to subject withdrawal or adverse events.

A total of 114 untreated subjects with FOP caused by the R206H mutation and with baseline data were enrolled in the PVO-1A-001 study (NHS); 81 (71%) subjects discontinued; the majority due to enrolment into an interventional study.

Primary endpoint

There was no difference in the radiological endpoint, mean observed annualised new HO volume, as assessed by low-dose WBCT, in the prespecified analysis (square root transformed data zeroed out by body region). The LS mean (SEM) of new HO was even numerically 5.9% higher (137.0 mm^3) in study PVO-1A-301 compared to NHS (129.5 mm^3). This is in line with the futility conclusions at the prespecified interim analysis that led to decision to interrupt the study.

The mean HO volume at baseline was higher in the NHS (312000 mm^3) N=101 than in the PVO-1A-301 study (231000 mm^3) N=97. This could indicate more severe disease in subjects included in NHS. At month 12, the mean HO increased in both PVO-1A-301 study (to 242000 mm^3) N=92 and in NHS (to 317000 mm^3) N=90 in available measurements (101 measurements at baseline, 90 at month 12). There was a considerable variability within the groups. The individual HO volumes had a high variability and there is a high degree of overlap between study PVO-1A-301 and NHS, except 3 more outliers in NHS. Negative annualised new HO volumes were seen more often in PVO-1A-301 (28%) than untreated subjects (6%). According to the Applicant, negative new HO may be related, in part, to bone remodeling or to measurement variability associated with the increased frequency of WBCT scans in PVO-1A-301 compared to NHS. Another potential cause of negative new HO may be related to the subjectivity of outlining HO within a CT axial slice. In cases of HO that encompass many large cranial to caudal regions (and thus across multiple axial slices), small differences outlining HO at each axial slice can translate into large differences in total HO measured.

The primary (and secondary objectives) of the main study PVO-1A-301 were agreed upon in a previous CHMP scientific advice. The overall relevance of the primary radiological endpoint and the association with function is out of doubt. However, quantification of which magnitude of HO volume reduction may be of clinical relevance could not be demonstrated by the applicant. The images were measured by two independent radiologists with adjudication by a third radiologist if needed in a blinded way. A qualitative determination of the presence of any new HO (yes/no) since prior timepoint was made, per region. If "yes", then total HO was outlined in the region(s) with qualitative new HO, using each axial slice and semi-automated segmentation tools with lower HU range threshold of 150. Intra- and interindividual variability were assessed by a secondary read process. The intra-read discrepancies from quantitative HO volume and from qualitative new HO account for 12% of assessed regions in 58% of assessed timepoints in 78% of assessed subjects. When comparing data across all readers, 7% of regions from 38% of timepoints in 100% of subjects had at least one region with a different

qualitative result of Yes, No, or NE for presence of new HO in at least one timepoint. This degree of variability makes the interpretation of results further challenging.

Secondary endpoints:

There was no difference in the portion of subjects with any new HO (volume >0 mm^3) between the palovarotene treated subjects (64%) and in the untreated subjects in the NHS (62%).

There was no substantial difference in the number of new body regions with new HO between the palovarotene treated subjects (1.3) and the subjects in the NHS (1.5).

The proportion of subjects reporting flare-ups at month 12 was 65 % in the palovarotene treated study and 54 % in the NHS i.e. the flare-up rate per month was numerically higher in the palovarotene treated study than in the natural history study where subjects were untreated. It is possible that untreated subjects in study PVO-1A-001 may have been less motivated to report flare-ups because flare-ups would not be treated. The magnitude of this potential is unclear bias which is one of the drawbacks of the chosen single arm study design.

Exploratory endpoints

The CAJIS score (range 0-30) was slightly higher in the NHS (11.8) than in the PVO-1A-301 study (10.0) at baseline. This could be a reflection of the higher age at inclusion in the NHS or higher disease activity. Both palovarotene treated subjects and untreated subjects had small numerical increase in CAJIS (clinical worsening) from baseline to month 12 (0.5 and 0.6 respectively). At baseline, the NHS scored somewhat higher (47%) in the FOP-PFQ than subjects in study PVO-1A-301 (44%). In the palovarotene treated subjects the change from baseline at months 6 and 12 seems to be numerically slightly less (2.8%) than in the untreated subjects (4.5%) but this difference did not persist at month 18. It is not known what difference in the FOP-PFQ scoring that would be considered clinical meaningful. It seems that there is not a sustained difference with treatments vs natural history.

In summary, the PRO measures FOP-PFQ and PROMIS did not give support for palovarotene efficacy in study PVO-1A-301. Data is presented only for 12 months and 18 months respectively. According to the applicant, it is possible that the CAJIS and PRO measures are not sufficiently sensitive to detect progression over only one year.

An additional exploratory endpoint that was defined post hoc was incidence and volume of catastrophic HO per year. The percentage of subjects with catastrophic new HO was numerically lower in palovarotene-treated subjects than in untreated subjects mainly due to 4 subjects more in NHS who experienced very large volumes. Of note, this was an explorative endpoint defined post-hoc. High-volume flare-ups occurred also in PVO-1A-202/204.

Post-hoc analyses of the primary endpoint:

The prespecified interim data analysis used a Bayesian compound Poisson model that describes the likelihood of an HO growth event and the volume of HO growth per event. The model for the primary analysis incorporated a square-root transformation of HO volume per region and required that new HO volumes be non-negative (ie, that negative new HO values, which can happen due to measurement variability, are set to zero). Square-root transformation of new HO volume per event was intended to reduce variability and increase the power of the study.

The applicant now believes that the most appropriate analysis for these data is the wLME analysis without square-root transformation. In the "best case" post hoc analysis by the applicant, also negative values were included. In this analysis the annualised new HO values of 9427 mm^3 in the palovarotene study and 23720 mm^3 in NHS, reduction of new HO by approximately 60% was

concluded with high nominal statistical significance in contrast to non-significant 6% in the pre-specified analysis.

In general, unblinded post hoc analysis after futility announcement cannot be considered confirmatory evidence. In addition, the great discrepancy of the results based on analysis methods questions the overall robustness of the HO data. Sensitivity analyses using covariates and subgroups were performed using post hoc methodology but the value of these to strengthen the evidence is questioned. The CHMP considers that there is a high risk that the applicant's current opinion on the most appropriate analysis is data-driven.

Statistical methods and discussion:

The primary and secondary efficacy analyses are based on Principal FAS that includes subjects with baseline and at least one post baseline HO volume measurement. However, the Principal FAS was further focused to include only those subjects who met the ≥50% of regions evaluable (5 out of 9). Although it is normally an acceptable rule to treat a composite score as missing if at least 50% of items have missing values, the primary analysis population becomes limited in this way and not strictly following the ITT principle.

The primary endpoint, annualised change in new HO volume, is modelled using a Bayesian compound Poisson distribution of the number of body regions with new HO and the new HO volume per region where new HO has occurred according to qualitative assessment. The model uses square root transformation of data in order to reduce the influence of outliers. Measured negative volumes of HO over time are represented as having no new HO and the volumes are set to zero in the analysis. The model included covariates sex and age (<18 years; ≥ 18 years old) at time of scan and accounted for potential correlation in measurements from the same subject, which is endorsed as a subgroup of patients crossed over from the NHS to the PVO-1A-301 study. The applicant has justified the choice of this model in the Protocol Amendment 1 based on increased variability in the change from baseline in new HO observed in the updated NHS data, and substantive power decrease for the weighted linear mixed effects model that was initially planned in the original protocol. However, the pre-specified Bayesian analysis did not show statistically significant efficacy of palovarotene on reduction of HO volume. After conducting IA2 and numerous post-hoc analyses, the applicant is of opinion that the primary model is less adequate than the weighted linear mixed effects model without square root transformation and without negative values being zeroed out. The choice of a statistical model is better informed with the data on hand and the applicant's statistical assumptions are not questioned. However, a clinical justification on how data preferably may be handled should also be taken into account, with consideration of the disease itself (i.e. how HO volume is expected to change over time, is it possible that it would decrease?) and also in respect to the known mechanism of action for palovarotene. Also, having outliers in the data may potentially indicate a certain subgroup of patients, which could be explored. It is therefore not entirely clear whether data should or should not be transformed and/or negatives set to zero. Although it may be acceptable to present post-hoc modifications of the primary analysis because of errors in the pre-specified statistical methods or choice of clearly suboptimal statistical models whose assumptions strongly deviate from the empirical data, this does not seem to be the case here. A lack of clinical justification for applicability of data transformations, as well as uncertainties in respect to robustness and clinical relevance of the results yet remain. Formally, the weighted linear mixed effects model can only be considered as post-hoc, as well as most of the sensitivity analyses, because of its timing after availability of data (i.e. disseminations of the results) and its deviations from the pre-specified primary analysis. Also, influence of subjects with unusually high HO volumes has not sufficiently been investigated in the study. Post-hoc analyses are not associated with data transformations (including use of negative values) that were initially clinically justified, and robustness and clinical relevance of the results has not been shown.

It is noted that p-value from Wilcoxon test is presented for majority of endpoints in the CSR, but the test was not planned in the SAP.

It is not acceptable that the choice of the statistical analysis method alone is crucial for determination of study success. Supportive sensitivity analyses are also required to show robustness of the results, together with supportive secondary endpoints and totality of data. The majority of the sensitivity analyses that the applicant performed did not use the pre-specified Bayesian model, but the post-hoc model without square-root transformation and negatives set to zero by region. Also, the wLME was performed without square-root transformation and on observed data (i.e. negatives included).

At the second and third interim analyses, futility was to be declared if the posterior probability of at least a 30% reduction in annualized new HO volume was below 0.05. At IA2, this posterior probability was 0.0488. The study was to be terminated for futility at IA2 but continued shortly after that on the basis of results of a post-hoc analysis. The one-sided significance thresholds of 0.0058, 0.0103, 0.0156, and 0.0190 for the first, second and third interim analyses and the final analysis, respectively, were prespecified and should have been recalculated at the time of each interim analysis based on the estimate of the information fraction. After IA2, type I error control was however not maintained in any subsequent analyses aiming for marketing authorisation, as the thresholds were no longer relevant. The final results are therefore regarded as post-hoc with nominal statistical significance.

Post-hoc analyses as a consequence of futility declaration and loss of type I error control, are to be considered separately from the post-hoc approach to select the appropriate primary analysis method. Overall, previous futility declaration and the application of multiple, modified, data-driven analyses lead to a loss of control of the global risk for false positive conclusions (type I error control).

Study PVO-1A-301 is submitted in the MAA as a single pivotal study. The design is open label, single arm, with the external control (NHS study). The study design poses a limitation to demonstrate a reliable efficacy estimates while, at the same time, intended to be a single confirmatory study, it is expected to provide convincing evidence of efficacy and safety with no doubts in respect to consistency and clinical relevance of the effect, internal and external validity of the study or data quality, in line with the EMA guideline Points to Consider on application with 1. Meta-analyses; 2. One pivotal study. The observed efficacy results cannot be viewed as statistically compelling.

Also, the primary endpoint is a novel composite endpoint that covers 9 body regions. To aid interpretation of the results, and in line with general recommendations for the composite endpoints, the individual components, i.e. annualised change in new HO volume in each body region, should be analysed by means of the primary analysis; this has not been reported. The level of the annualised change that is clinically relevant is not established and, considering the argumentation on the choice of the primary analysis, the endpoint seems not sufficiently explored in previous studies. On further request, the applicant confirmed that minimal clinically important differences have not been established for patients with FOP, and that clinical importance seems to be dependent on the body region so that, for example, a small volume of HO across a joint has a greater impact on mobility than a larger volume of HO which does not cross a joint.

In summary, statistical significance and clinical relevance of palovarotene was not demonstrated. Multiple methodological issues were identified that compromise the interpretability and robustness of the study results. The efficacy results claimed in the MAA are considered post-hoc due to timing of the analysis (i.e. after declaration of futility) and due to post-hoc approach to select statistical methods. The type I error control was not maintained. There are limitations with use and interpretation of the primary endpoint for which assumptions were revised post-hoc (i.e. square-root transformation and inclusion of negative changes). Post-hoc nature of the methodology, although preferred, and differing results of the performed analyses does not provide sufficient confidence to conclude statistical significance of the efficacy results.

Interpretation of effects

Several post-hoc analyses were conducted to explore the influence of different choices that were made for analysis on the results, including the method of analysis (Bayesian compound Poisson model, frequentist weighted linear mixed effects model), data transformation (square root transformed, non-square root transformed), and handling of negatives in the analysis (using as observed, setting to 0 by region, setting to 0 by patient). These choices were shown to have a major impact on the results of the analysis and the conclusions that can be drawn. It needs also to be considered that the results of the different analyses cannot be directly compared. Different effect measures are used and using different data transformations implies that treatment effects are expressed on different scales and have to be interpreted in different ways. The Bayesian analyses expressing the treatment effect as a relative increase are generally not comparable with the frequentist analyses expressing the treatment effect as an absolute increase. This hampers seriously the interpretation of the analyses.

External comparison

It is acknowledged that the use of an external cohort as comparator was considered acceptable at the time of the CHMP scientific advice procedure in 2017, assuming a dramatic effect of the drug, HO volume to be an objective measure that is assessed in a blinded manner, feasibility concerns of a placebo-controlled trial and that the disease course of FOP was considered highly predictable and the velocity of HO to be relatively stable within a range of a few years. However, the use of a natural history control group involves several well-recognised challenges such that it is unclear whether causal conclusions can be made from the analysis. It can be added that, although the actual size of the treatment effect (if any) is currently difficult to deduce from the provided analyses, it is surely substantially smaller than the 'dramatic effect' with up to 97% reduction found in retrospective analyses that were presented during the scientific advice. The set of covariates included in the statistical analysis to adjust for baseline confounding was very limited, which was explained by limited knowledge about prognostic factors. However, limited knowledge about prognostic factors does not exclude selection bias. In particular, when patients are recruited in different centres or are recruited during different calendar time periods, there is potential for selection bias or differences in background treatment and outcome assessment.

In addition, without randomisation of parallel groups, it cannot be excluded that differences in subject characteristics, methods of outcome assessment, background standards of care or other factors may bias the comparison of outcomes between groups. For example, there were differences at baseline HO between cohorts that could indicate more active disease in the NHS, there were differences in flare-up reporting and WBCT scan frequency. Most importantly, the study was interrupted early and submitted analyses of efficacy were carried out with much less amount of data than originally planned, making the available HO data more unreliable especially regarding longer term disease course. It should also be noted that the open-label single arm study design hampers the possibility to make robust conclusions on patient reported outcomes.

2.5.7. Conclusions on the clinical efficacy

The predefined primary analysis and secondary endpoints failed to show efficacy in the main single arm pivotal study PVO-1A-301 compared to the natural history cohort PVO-1A-001. Robustness and clinical relevance of the presented results have not been shown as the study was interrupted for futility and comparison with an external control increases the uncertainty due to potential biases. Unblinded post-hoc analysis of the primary endpoint of radiological data after futility announcement is not considered confirmatory efficacy evidence. In addition, efficacy data from other clinical studies and available long-term results could also not support efficacy.

The applicant's current conclusion of the data, that palovarotene both prevents/minimises new HO overall, and minimises the proportion of subjects who experience large annualised new HO volumes cannot be agreed on. The clinical program has several severe deficiencies and efficacy of palovarotene in treatment of FOP has not been shown.

2.5.8. Clinical safety

The safety database consists of data from 164 palovarotene treated subjects with FOP. As support, safety data has been provided from studies in healthy volunteers (HV), subjects with chronic obstructive pulmonary disease (COPD), and paediatric subjects with multiple osteochondromas (MO). Due to the differences between the studies included in the safety data base, the applicant has pooled data in five pools; the HV-FAS, the MO-FAS, the COPD-FAS, the FOP-FAS and one pool for the FOP population with at least one episode of flare treatment (FOP-F-FAS) (Table 32). Please note that the FOP-FAS fully covers the FOP-F-FAS.

Table 32 Analysis sets

Analysis Set	Study Phase(s)	Studies Included	Population Description	No. Enrolled (PVO Treated)	PVO Daily Dose[1]	Maximum Exposure[2]
FOP-FAS, all subjects	2, 3	PVO-1A-001 (NHS) PVO-1A-201 PVO-1A-202/ Parts A, B, C PVO-1A-203 PVO-1A-301 (MOVE Trial)	All subjects enrolled or dosed in FOP clinical studies (including the NHS)	219 (164)	2.5 to 20 mg	199 weeks
FOP-FAS, target[3]	2, 3			187 (139)	2.5 to 20 mg	199 weeks
FOP-F-FAS, all subjects	2, 3		All subjects with at least one flare-up in the NHS or at least one PVO- or placebo-treated flare-up while on-study in a FOP interventional study	177 (125)	2.5 to 20 mg	199 weeks
FOP-F-FAS target[3]	2, 3			151 (106)	2.5 to 20 mg	199 weeks
MO-FAS	2	PVO-2A-201	All subjects receiving at least one dose of PVO or placebo in Study PVO-2A-20	193 (131)	2.5 and 5.0 mg	85 weeks
HV-FAS	1	RB16327 RB16328 NP17040 NP17041B NP17055 NP17056 NP17584 NP17726 NP21025 PVO-1A-101 PVO-1A-102 PVO-1A-103	All healthy volunteers treated with at least one dose of palovarotene or placebo	335[4] (424)	0.02 to 50 mg	4 weeks (29 days)
COPD-FAS	1, 2	NP17124 NA17098 NB18332 NA17589 NB19751	All subjects with COPD treated with at least one dose of PVO or placebo	950 (611)	0.2 and 5.0 mg	24 months

[1]Daily doses were weight adjusted for skeletally immature subjects.

[2]Maximum duration of dosing as of cut-off date of 28 February 2020.
[3]Target refers to the target population of females ≥8 years of age and males ≥10 years of age.
[4]Number of unique subjects. A total of 516 non-unique subjects were in the HV-FAS.
COPD=chronic obstructive pulmonary disease; F=flare-up; FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; HV=healthy volunteers; MO=multiple osteochondromas; NHS=natural history study; PVO=palovarotene

Age and gender for all pools are given in Table 33.

Table 33 Summary of Integrated Analysis Sets for the FOP-FAS, FOP-F-FAS, HV-FAS, MO-FAS and COPD-FAS (truncated and amended by CHMP)

	Sex		Age Group, years				Unique		
	Male	Female	≥8/10	<8/10	≥8/10 to <18	≥18	PVO Total	Subject Total	Total
FOP-FAS, N	111	108	187	41	97	91	164	–	219
FOP-F-FAS, N	93	84	151	32	76	75	125	–	177
HV-FAS, N	241	94	0	0	0	335	424	335	516
MO-FAS, N	117	76	59	134	59	0	131		193
COPD-FAS	651	299	0	0	0	950	611	950	978

[1]PVO-1A-202/Parts A, B and C includes all subjects treated and not treated with palovarotene. Part B and Part C are the same as Study PVO-1A-204 in France.
[2]Twenty subjects in PVO-1A-202/Part A were untreated but not necessarily treatment naive as they may have previously received flare-up treatment in Study PVO-1A-201.
For HV-FAS and COPD-FAS the PVO Total column refers to the total number of subjects who received at least 1 dose of palovarotene (the subject counts are not of unique subjects) and the Unique Subject Total column includes the count of unique subjects (because subjects participated in multiple studies, it is not the sum of the counts)
COPD=chronic obstructive pulmonary disease; F=flare-up; FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; HV=healthy volunteers; PVO=palovarotene.

For all safety assessments, the FOP-FAS and FOP-F-FAS were stratified by age at study entry. The age group allocation was static, with age allocation for adverse events (AEs) calculated by age at first study entry. Thus, AEs for a subject with FOP would remain in the same age group for all analyses.

Two events led to a prolonged treatment interruption period in Studies 202/Part C and 301; during the partial clinical hold issued by the FDA December 2019 for subjects under 14 years due to the identification of the risk of PPC and following the outcome of the Study 301 second interim analysis that crossed the threshold for futility, which resulted in the per-protocol treatment discontinuation of subjects ≥14 years of age on 24 January 2020. In the Safety Update document, the Applicant has defined two new analysis sets. The FOP-NBAS included all subjects in Studies 202/Part C or 301 who had and received at least one dose of palovarotene after the interruption and the FOP-F-NBAS included subjects in the FOP-NBAS who had at least one palovarotene-treated flare-up after reiteration.

2.5.8.1. Patient exposure

Patient exposure in the FOP-FAS age at first entry ≥8/10 Years is summarised in Table 34 and by flare-up in Table 35.

Table 34 Exposure to Palovarotene by Subject, Original Baseline, Age at First Entry ⩾8/10 Years (FOP-FAS)

		28 February 2020 Cutoff			30 July 2021 Cutoff		
	Parameter	Chronic PVO 5 mg (N=130)	Flare-up PVO 20/10 mg (N=100)	PVO Total (N=139)	Chronic PVO 5 mg (N=131)	Flare-up PVO 20/10 mg (N=105)	PVO Total (N=139)
Duration of dosing, weeks[a]	Mean (SD)	72.6 (39.8)	33.2 (23.9)	94.1 (46.1)	78.9 (50.4)	35.1 (25.8)	102.4 (59.4)
	Median	68.6	27.4	82.4	71.3	28.1	82.6
	Min, max	1, 174	0, 134	4, 199	1, 225	0, 134	4, 242
Total exposure, weeks in study[b]	Mean (SD)	111.9 (42.7)	108.5 (40.3)	192.4 (101.5)	164.1 (61.1)	159.8 (58.0)	285.1 (140.6)
	Median	96.5	94.2	175.4	165.7	164.4	316.3
	Min, max	7, 194	34, 194	7, 457	5, 268	34, 268	5, 605
Distribution of months in study, n (%)	>0 to 3 months	1 (0.8)	0	5 (3.6)	2 (1.5)	0	6 (4.3)
	>3 to 6 months	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
	>6 to 9 months	2 (1.5)	2 (2.0)	0	2 (1.5)	2 (1.9)	0
	>9 to 12 months	1 (0.8)	1 (1.0)	1 (0.7)	1 (0.8)	1 (1.0)	1 (0.7)
	>12 to 18 months	11 (8.5)	9 (9.0)	7 (5.0)	7 (5.3)	8 (7.6)	4 (2.9)
	>18 to 24 months	65 (50.0)	55 (55.0)	19 (13.7)	13 (9.9)	11 (10.5)	2 (1.4)
	>24 to 30 months	14 (10.8)	12 (12.0)	2 (1.4)	5 (3.8)	6 (5.7)	2 (1.4)
	>30 months	35 (26.9)	21 (21.0)	104 (74.8)	100 (76.3)	77 (73.3)	123 (88.5)
PVO total dose, mg	Mean (SD)	2370.6 (1458.2)	2832.8 (2201.1)	4348.0 (2652.3)	2940.2 (1883.9)	3192.7 (2696.7)	5275.6 (3329.7)
	Median	2040.0	2182.5	4010.0	2601.0	2240.0	4750.0
	Min, max	30, 6090	40, 11530	133, 13645	30, 7865	40, 15730	133, 16155

a Duration of dosing (weeks) = (last dose date – first dose date + 1)/7 – days without dosing.
b 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.
FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; max=maximum; min=minimum; PVO=palovarotene; SD=standard deviation.

Table 35 Exposure to Study Drug by Flare-up, Original Baseline, Age at First Entry ⩾8/10 Years (FOP-F-FAS)

Variable	Parameter	28 February 2020 Cutoff Flare-up PVO 20/10 mg (M=217)	30 July 2021 Cutoff Flare-up PVO 20/10 mg (M=260)
Duration of flare-up cycle dosing, weeks[a]	m	216	259
	Mean (SD)	15.4 (11.3)	14.99 (11.3)
	Median	12.0	12.0
	Min, max	0.1, 90.4	0.1, 90.4
Duration of flare-up cycle dosing by weeks, m (%)	≤ 2 weeks	6 (2.8)	8 (3.1)
	> 2 to 4 weeks	6 (2.8)	7 (2.7)
	> 4 to 6 weeks	6 (2.8)	12 (4.6)
	> 6 to 8 weeks	8 (3.7)	11 (4.2)
	> 8 to 10 weeks	5 (2.3)	7 (2.7)
	> 10 to 12 weeks	105 (48.6)	124 (47.9)
	> 12 to 24 weeks	56 (25.9)	60 (23.2)
	> 24 to 48 weeks	18 (8.3)	23 (8.9)
	> 48 to 72 weeks	4 (1.9)	4 (1.5)
	> 72 weeks	2 (0.9)	3 (1.2)
Exposure to high flare-up dose, weeks	m	216	258
	Mean (SD)	6.4 (7.5)	6.4 (7.4)
	Median	4.0	4.0
	Min, max	0.1, 61.1	0.1, 66.0
Total dose, mg	m	215	260
	Mean (SD)	1312.2 (1153.2)	1291.1 (1141.6)
	Median	1120.0	1112.5
	Min, max	6.0, 9930.0	20.0, 9930.0

2.5.8.2. Adverse events

FOP-FAS (all subjects enrolled or dosed in FOP clinical studies (including the NHS))

Treatment-emergent AEs (TEAEs) were AEs that developed or worsened after administration of the first dose of study drug to 7 days after the last dose of study drug.

An overview of AEs in the FOP-FAS ≥8/10 years per 30 July 2021 (20/10 mg only) is given in Table 36.

Table 36 Overview of Adverse Events, Original Baseline, Age at First Entry ⩾8/10 Years (FOP-FAS)

	28 February 2020 Cutoff			30 July 2021 Cutoff		
Characteristics	Chronic 5 mg (N=130)	Flare-up 20/10 mg (N=100)	PVO Total (N=139)	Chronic 5 mg (N=131)	Flare-up 20/10 mg (N=105)	PVO Total (N=139)
Any TEAE[a]	126 (96.9)	95 (95.0)	139 (100)	127 (96.9)	99 (94.3)	139 (100)
Treatment-related TEAEs[b]	121 (93.1)	93 (93.0)	137 (98.6)	122 (93.1)	97 (92.4)	137 (98.6)
Severity of TEAEs						
Mild	53 (40.8)	29 (29.0)	34 (24.5)	46 (35.1)	26 (24.8)	27 (19.4)
Moderate	53 (40.8)	48 (48.0)	75 (54.0)	59 (45.0)	53 (50.5)	79 (56.8)
Severe	20 (15.4)	18 (18.0)	30 (21.6)	22 (16.8)	20 (19.0)	33 (23.7)
Treatment-emergent SAEs	21 (16.2)	20 (20.0)	37 (26.6)	31 (23.7)	24 (22.9)	50 (36.0)
Treatment-related SAEs[b]	8 (6.2)	11 (11.0)	19 (13.7)	8 (6.1)	13 (12.4)	21 (15.1)
TEAEs leading to dose modification	10 (7.7)	41 (41.0)	46 (33.1)	10 (7.6)	45 (42.9)	50 (36.0)
TEAEs leading to dose interruption	18 (13.8)	19 (19.0)	33 (23.7)	22 (16.8)	20 (19.0)	37 (26.6)
TEAEs leading to study drug discontinuation	5 (3.8)	5 (5.0)	10 (7.2)	6 (4.6)	5 (4.8)	11 (7.9)
TEAEs leading to study discontinuation	3 (2.3)	1 (1.0)	4 (2.9)	3 (2.3)	1 (1.0)	4 (2.9)
Deaths	0	0	0	0	0	0
Any post-treatment AE[c]	14 (10.8)	10 (10.0)	44 (31.7)	19 (14.5)	7 (6.7)	46 (33.1)
Treatment-related AEs[b]	3 (2.3)	5 (5.0)	17 (12.2)	6 (4.6)	5 (4.8)	20 (14.4)
Severe post-treatment AEs	1 (0.8)	2 (2.0)	4 (2.9)	2 (1.5)	4 (3.8)	7 (5.0)
Post-treatment SAEs	1 (0.8)	3 (3.0)	7 (5.0)	4 (3.1)	4 (3.8)	11 (7.9)
Treatment-related SAEs[b]	1 (0.8)	1 (1.0)	3 (2.2)	2 (1.5)	1 (1.0)	4 (2.9)
Post-treatment deaths	0	0	0	0	0	0

Of note, 43% of all subjects in the subjects during the 20/10 mg regimen flare-up treatment were subjected to dose modifications, mainly dose reductions, due to TEAEs (see also *Treatment related TEAE in relation to dose).*

The most common TEAE by SOC (≥5% of the subjects in the PVO group) per 30 July 2021 are presented in Table 37.

Table 37 Treatment-Emergent Adverse Events by Primary System Organ Class and Preferred Term (⩾ 5% Subjects in Total PVO) (Age at First Entry: ⩾8/10 Years) (FOP-FAS) (PVO Treatment Period: Original Baseline Through Data Cutoff 30 July 2021)

System Organ Class Preferred Term	PVO Total (N=139)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	137 (98.6)
Dry skin	112 (80.6)
Alopecia	59 (42.4)
Pruritus	59 (42.4)
Erythema	48 (34.5)
Rash	46 (33.1)
Pruritus generalised	43 (30.9)
Skin exfoliation	43 (30.9)
Drug eruption	25 (18.0)
Eczema	23 (16.5)
Skin irritation	15 (10.8)
Ingrowing nail	13 (9.4)

System Organ Class Preferred Term	PVO Total (N=139)
Skin reaction	11 (7.9)
Blister	10 (7.2)
Decubitus ulcer	10 (7.2)
Onychoclasis	10 (7.2)
Skin disorder	10 (7.2)
Acne	9 (6.5)
Dermatitis	9 (6.5)
Rash maculo-papular	9 (6.5)
Dandruff	7 (5.0)
Rash generalised	7 (5.0)
Skin fissures	7 (5.0)
Swelling face	7 (5.0)
GASTROINTESTINAL DISORDERS	120 (86.3)
Lip dry	79 (56.8)
Nausea	34 (24.5)
Vomiting	33 (23.7)
Chapped lips	25 (18.0)
Abdominal pain	24 (17.3)
Diarrhoea	21 (15.1)
Dry mouth	18 (12.9)
Cheilitis	15 (10.8)
Constipation	13 (9.4)
Gastrooesophageal reflux disease	11 (7.9)
Abdominal pain upper	10 (7.2)
Toothache	10 (7.2)
INFECTIONS AND INFESTATIONS	115 (82.7)
Upper respiratory tract infection	37 (26.6)
Nasopharyngitis	33 (23.7)
Paronychia	22 (15.8)
Ear infection	16 (11.5)
Influenza	12 (8.6)
Pharyngitis	12 (8.6)
Urinary tract infection	12 (8.6)
Gastroenteritis	11 (7.9)
Onychomycosis	9 (6.5)
Otitis externa	9 (6.5)
Bronchitis	7 (5.0)
Cellulitis	7 (5.0)
Pneumonia	7 (5.0)
Skin infection	7 (5.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	112 (80.6)
Arthralgia	68 (48.9)
Pain in extremity	58 (41.7)
Musculoskeletal pain	31 (22.3)
Back pain	29 (20.9)
Joint swelling	29 (20.9)
Neck pain	23 (16.5)
Myalgia	19 (13.7)
Musculoskeletal chest pain	17 (12.2)
Joint range of motion decreased	15 (10.8)
Pain in jaw	14 (10.1)
Joint stiffness	10 (7.2)
Epiphyses premature fusion	9 (6.5)
Muscle spasms	9 (6.5)
Musculoskeletal discomfort	9 (6.5)
Groin pain	8 (5.8)
Musculoskeletal stiffness	8 (5.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	94 (67.6)
Skin abrasion	33 (23.7)
Fall	21 (15.1)
Contusion	20 (14.4)
Extraskeletal ossification	9 (6.5)
Skin laceration	9 (6.5)
Sunburn	9 (6.5)
Limb injury	8 (5.8)

System Organ Class Preferred Term	PVO Total (N=139)
Arthropod bite	7 (5.0)
Post-traumatic pain	7 (5.0)
Scratch	7 (5.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	67 (48.2)
Peripheral swelling	23 (16.5)
Pyrexia	21 (15.1)
Fatigue	16 (11.5)
Swelling	15 (10.8)
Oedema peripheral	11 (7.9)
Pain	8 (5.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	66 (47.5)
Cough	24 (17.3)
Epistaxis	21 (15.1)
Oropharyngeal pain	18 (12.9)
Dyspnoea	10 (7.2)
Nasal congestion	8 (5.8)
Nasal dryness	8 (5.8)
Rhinorrhoea	8 (5.8)
NERVOUS SYSTEM DISORDERS	62 (44.6)
Headache	40 (28.8)
Dizziness	15 (10.8)
Migraine	10 (7.2)
Paraesthesia	9 (6.5)
Hypoaesthesia	7 (5.0)
EYE DISORDERS	49 (35.3)
Dry eye	37 (26.6)
Ocular hyperaemia	10 (7.2)
INVESTIGATIONS	47 (33.8)
Lipase increased	11 (7.9)
Blood alkaline phosphatase increased	9 (6.5)
Alanine aminotransferase increased	8 (5.8)
Urine analysis abnormal	7 (5.0)
PSYCHIATRIC DISORDERS	43 (30.9)
Depressed mood	12 (8.6)
Anxiety	11 (7.9)
Irritability	11 (7.9)
Insomnia	9 (6.5)
METABOLISM AND NUTRITION DISORDERS	40 (28.8)
Decreased appetite	17 (12.2)
EAR AND LABYRINTH DISORDERS	37 (26.6)
Ear pain	10 (7.2)
Hypoacusis	10 (7.2)
RENAL AND URINARY DISORDERS	31 (22.3)
Haematuria	11 (7.9)
Pollakiuria	9 (6.5)
Proteinuria	9 (6.5)
Nephrolithiasis	7 (5.0)
CARDIAC DISORDERS	17 (12.2)
Tachycardia	11 (7.9)
Vascular disorders	16 (11.5)
Flushing	7 (5.0)
IMMUNE SYSTEM DISORDERS	11 (7.9)
Seasonal allergy	7 (5.0)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PVO = palovarotene; TEAE = treatment- emergent adverse event
Data are presented as number (%). Data Cutoff: 30 July 2021; MedDRA version 22.0. TEAEs are AEs with first dose date of study drug ≤ AE start date ≤last dose date of study drug +7 days (or after enrolment for the PVO-1A-202A subjects who were not dosed due to the absence of a flare-up) for All AEs (Non-Serious and Serious AEs)
Data Source: Module 5.3.5.3, ISS, Table 14.22.8.7.2

All 139 palovarotene treated subjects in the intended target population≥8/10 years reported at least one TEAE. The most commonly reported System Organ Class (SOC) for TEAEs were *Skin and*

Subcutaneous Tissue Disorders (98.6% of the subjects)*, Gastrointestinal disorders* (86.3%), *Infections and infestations* (82.7%) and *Musculoskeletal and Connective Tissue Disorders* (80.6%)*.*

Treatment related TEAE in relation to the dose

The percentage of subjects reporting a dose reduction in Study 301 was dose dependent (20 mg: 45%; 10 mg: 12%; and 5 mg: 3%). In this context, it should also be taken into consideration that the duration of treatment was longer in the chronic phase compared to flare-up treatment, further emphasising the difference in dose reductions between the higher and lower doses.

In addition, upon request, the applicant performed a review of TEAEs in the high- and low-dose periods of the "flare-up" regimens in Study PVO-1A-301. TEAEs were more commonly reported during High-dose flare-up versus Low-dose flare-up treatment (86% versus 44%, respectively). The most common SOC was Skin and subcutaneous tissue disorders, reported by 76% of the subjects during the High-dose flare-up treatment versus 15% during Low-dose flare-up treatment. Furthermore, the applicant provided a summary of the actual mean dose administered during different treatment phases in the pivotal study (Table 38).

Table 38 Summary of Mean Actual Dose by Dose Category in Subjects Who Received High-Dose Flare-Up Treatment in Study PVO-1A-301 and Study PVO-1A-202 Part C (Safety Set)

		PVO-1A-301 (N=99)	**PVO-1A-202 Part C (N=46)**
Dose Category	**Statistics**	**High-Dose Flare-Up [a]**	**High-Dose Flare-Up [a]**
Mean Chronic Dose (mg)	n	74	30
	Mean	3.69	3.86
	SD	1.168	1.023
	Median	3.50	4.00
	Q1, Q3	2.75, 5.00	3.08, 4.90
Mean High Dose (mg)	n	74	33
	Mean	14.68	12.99
	SD	4.170	4.917
	Median	14.33	15.00
	Q1, Q3	11.67, 20.00	9.55, 16.67
Mean Low Dose (mg)	n	71	31
	Mean	7.95	7.88
	SD	2.624	2.643
	Median	8.17	8.89
	Q1, Q3	6.00, 10.00	5.14, 10.00

Treatment related TEAE were reported in 93 % of the subjects during 5 mg chronic treatment (122 events in 131 subjects) vs 92% (97 events in 105 subjects) during 20/10 mg flare-up treatment; however, subjects during the 20/10 mg flare-up treatment period had a higher incidence of TEAEs leading to dose modifications, drug interruptions, and treatment related SAEs indicating a dose effect on AE reporting. This was further substantiated by additional analyses performed by the applicant to control for the potential confounder constituted by study design, recording the reported AE on the current treatment regardless of if the subjects previously been treated with a higher dose, e.g., when returning to 5 mg chronic treatment after receiving a higher dose during a flare-up episode. Such analyses indicated a notably higher (≥10% difference) incidence of *pruritus/generalized pruritus, erythema, skin exfoliation, arthralgia, joint swelling, skin abrasion, condition aggravated,* and *dry eye* in the 20/10 mg flare-up palovarotene group than in the censored chronic palovarotene group.
The mean exposure to the chronic 5 mg treatment was 79 weeks compared to 32 weeks exposure to the 20/10 mg flare-up treatment. Upon request, the applicant has provided a summary of reported

TEAE normalised for exposure. There was a higher rate of TEAE in the flare-up 20/10 mg group (1,379 per 100 patient years at risk) compared with the chronic 5 mg group (692). A similar pattern was seen with serious AEs.

In general, the most common TEAEs in male and female subjects in the FOP-FAS ≥8/10 years palovarotene group did not differ by SOC. However, some *Skin and Subcutaneous Tissue Disorders* and *Musculoskeletal and Connective Tissue Disorders* TEAEs were more prevalent in female than male subjects including *alopecia* (females, 58.0%; males, 25.7%), *rash* (females, 37.7%; males, 25.7%), *skin exfoliation* (females, 39.1%; males, 22.9%), *arthralgia* (females, 50.7%; males, 37.1%), and *pain in extremity* (females, 43.5%; males, 31.4%).
It is considered particular notable that almost six in ten female subjects in the FOP-FAS reported alopecia, which could be experienced as difficult to tolerate. The applicant has clarified that despite the high incidence of alopecia in female subjects, no events led to discontinuation.

There were some notable specific differences across age groups in the FOP-FAS. In the ≥18 years palovarotene group, *tachycardia* was reported in 11.3% of subjects. In comparison, the incidence of tachycardia in paediatric subjects was lower, reported in 3.9% of subjects in the ≥8/10 to <18 years palovarotene group, and in no subjects in the <8/10 years palovarotene or placebo/untreated groups. In addition, in the palovarotene group, *nausea* was over twice as common in adults (35.5%) than in paediatric subjects (<8/10 years, 0; ≥8/10 to <18 years, 14.3%). Conversely, drug eruption in the palovarotene group was more common in paediatric subjects (<8/10 years, 24.0%; ≥8/10 to <18 years, 21.1%) than in adults (9.7%). *Premature physeal closure (PPC)* occurred in a lower proportion of subjects in the ≥8/10 to <18 years palovarotene group compared with the <8/10 group, reflecting the susceptibility of skeletally immature paediatric subjects to this AE.

Condition aggravated was the MedDRA PT used to capture flare-ups reported during the study that did not meet the protocol-specified criteria for flare-up treatment in PVO-1A-201 and PVO-1A-202/Part A. In Study PVO-1A-201, the incidence of *Condition aggravated* AEs in the palovarotene 10/5 mg group (62%) was about twice that of the placebo group (30%). Additional analyses were performed to determine whether palovarotene flare-up treatment may have caused subsequent additional flare-ups. To normalise for different follow-up times, flare-up based analyses of the number and proportion of *condition aggravated* AEs reported during the 12-week flare-up treatment and assessment periods were performed (Table 39).

Table 39 Flare-ups (AE or TC) Occurring Within 12 Weeks of a Treated or Imaged Flare-up, Age at First Entry ≥8/10 Years (FOP-F-FAS)

Treatment Group	Study	M	m (%)
Age at First Entry ≥8/10 Years			
Untreated	Study PVO-1A-001 (NHS)	41	10 (24.4)
Placebo	PVO-1A-201	10	3 (30.0)
PVO 5/2.5 mg	PVO-1A-201	7	1 (14.3)
PVO 10/5 mg	PVO-1A-201 & PVO-1A 202/Part A	49	18 (36.7)
PVO 20/10 mg	PVO-1A-202/Part B	54	18 (33.3)
All Subjects			
Untreated	Study PVO-1A-001 (NHS)	53	12 (22.6)
Placebo	PVO-1A-201	10	3 (30.0)
PVO 5/2.5 mg	PVO-1A-201	9	2 (22.2)
PVO 10/5 mg	PVO-1A-201 & PVO-1A 202/Part A	52	19 (36.5)
PVO 20/10 mg	PVO-1A-202/Part B	66	24 (36.4)

AE=flare-ups reported as adverse events with preferred term of condition aggravated; FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; ISS=Integrated Summary of Safety; M=number of flare-ups; NHS=natural history study (PVO-1A-001); PVO=palovarotene; TC=flare-ups reported via telephone contact. Source: Module 5.3.5.3, ISS, Table 14.1.7 and Table 14.9.7.

The FOP-F-FAS includes all subjects with at least one flare-up (from teleconferencing and imaged flare-ups) from Study PVO-1A-001 (NHS) and from treated flare-ups in the interventional studies (Table 13, ISS).

Percentages are based on number of flare-ups (M).

The rate of flare-ups within 12 weeks of a flare-up was comparable in the placebo treatment group (30% of all flare-ups), the PVO 10/5 mg treatment group (37%) and the PVO 20/10 mg treatment group (33%) of the ≥8/10 Years FOP-F-FAS.

HV-FAS (all healthy volunteers treated with at least one dose of palovarotene or placebo)

Data in the HV-FAS are heterogenous as a large dose span (0.02-50 mg), as well as both single-dose and multiple doses were represented. Exposure was short (mean 7 days). Safety in the HV-FAS is considered to contribute little to the safety profile of palovarotene.

MO-FAS (all subjects receiving at least one dose of palovarotene ore placebo in study PVO-2A-20)

Even though the doses in the MO-FAS is low, the MO-FAS contains placebo-controlled safety data from an ongoing double-blind study in paediatric subjects. The majority of the subjects were younger, ≤8/10 year; however, the study included 59 subjects (placebo: N=20; PVO 2.5 or 5 mg: N=39) aged >8/10 years.

An overview of TEAEs and post-treatment AEs in MO-FAS subjects is presented in Table 40.

Table 40 Summary of Adverse Events, All Subjects (MO-FAS)

Characteristics	Placebo (N = 62)	PVO 2.5 mg (N = 66)	PVO 5.0 mg (N = 65)	PVO Total (N = 131)
Any TEAE	41 (66.1)	56 (84.8)	56 (86.2)	112 (85.5)
Treatment-related TEAE	29 (46.8)	49 (74.2)	54 (83.1)	103 (78.6)
Severity of TEAEs	30 (48.4)	41 (62.1)	39 (60.0)	80 (61.1)
Mild	11 (17.7)	14 (21.2)	14 (21.5)	28 (21.4)
Moderate	0	1 (1.5)	3 (4.6)	4 (3.1)
Severe	30 (48.4)	41 (62.1)	39 (60.0)	80 (61.1)
Treatment-emergent SAEs	0	2 (3.0)	3 (4.6)	5 (3.8)
Treatment-related SAEs	0	0	2 (3.1)	2 (1.5)
TEAE leading to death	0	0	0	0
TEAE leading to withdrawal from study	0	0	0	0
TEAE leading to discontinuation of study drug	0	2 (3.0)	0	2 (1.5)
Deaths	0	0	0	0
Any post-treatment AEs	13 (21.0)	7 (10.6)	11 (16.9)	18 (13.7)
Post-treatment SAEs	2 (3.2)	0	2 (3.1)	2 (1.5)

The MO-FAS includes all subjects receiving at least one dose of palovarotene or placebo in Study PVO-2A-201.

AE=adverse event; FAS=full analysis set; MO=multiple osteochondromas; PVO=palovarotene; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

The spectrum of TEAEs were consistent with the data from the FOP-FAS. TEAEs from the SOC *Skin and Subcutaneous Tissue Disorders* (PVO 69%; placebo 35%) and *Gastrointestinal Disorders* (PVO 41%; placebo 25%) were more commonly reported in the PVO versus the placebo treatment arm.

COPD-FAS (all subjects with COPD treated with at least one dose of palovarotene or placebo)

The COPD-FAS is of interest as it contains placebo-controlled safety data from a double-blind study. However, the population in the COPD-FAS is not comparable to the target population, as the COPD

study recruited subjects with smoking-related, moderate-to-severe COPD with emphysema receiving concurrent optimal COPD drug therapy. Thereby, the mean age was considerably higher in the COPD-FAS (63.7 years) versus the ≥8/10 Year FOP-FAS (19.1 years). Furthermore, the COPD-FAS represents a population with major comorbidity and a high risk of e.g., cardiovascular events. The Report date of the COPD-study was November 2011.

Table 41 Overview of Adverse Events (COPD-FAS)

		PVO Dose Group					
Variable, n (%)	Placebo (N=367)	0.2 mg (N=38)	0.5 mg (N=10)	1.0 mg (N=57)	2.5 mg (N=24)	5.0 mg (N=482)	PVO Total (N=611)
Any TEAE[1]	297 (80.9)	13 (34.2)	4 (40.0)	34 (59.6)	20 (83.3)	449 (93.2)	520 (85.1)
Treatment-related TEAEs[2]	148 (40.3)	6 (15.8)	0	21 (36.8)	17 (70.8)	347 (72.0)	391 (64.0)
Severe TEAEs	69 (18.8)	0	0	8 (14.0)	3 (12.5)	127 (26.3)	138 (22.6)
TEAEs leading to study drug/study discontinuation	35 (9.5)	0	0	4 (7.0)	2 (8.3)	81 (16.8)	87 (14.2)
Serious TEAEs	54 (14.7)	0	0	3 (5.3)	1 (4.2)	108 (22.4)	112 (18.3)
Deaths	2 (0.5)	0	0	1 (1.8)	0	5 (1.0)	6 (1.0)
Any post-treatment AE[3]	69 (18.8)	5 (13.2)	0	8 (14.0)	6 (25.0)	82 (17.0)	101 (16.5)
Severe post-treatment AEs	12 (3.3)	1 (2.6)	0	0	3 (12.5)	14 (2.9)	18 (2.9)
Post-treatment SAEs	14 (3.8)	1 (2.6)	0	0	2 (8.3)	18 (3.7)	21 (3.4)
Post-treatment deaths	6 (1.6)	0	0	0	0	8 (1.7)	8 (1.3)

[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.
The COPD-FAS included all subjects with COPD treated with at least one dose of palovarotene or placebo in the COPD clinical studies.
Subjects may appear multiple times within and across dose group column(s), as they may have participated in multiple studies/periods.
AE=adverse event; COPD=chronic obstructive pulmonary disease; FAS=full analysis set; TEAE=treatment-emergent adverse event; PVO=palovarotene; SAE=serious adverse event.

The most common AE in the study was *Chronic obstructive respiratory disease* (PVO 31%, Placebo 40%). Apart from this, the spectrum of TEAEs were largely consistent with the data from the FOP-FAS with the second most common AEs reported in the PVO arm being *dermatitis* (PVO 28%, Placebo 15%), *Cheilitis* (PVO 22%, Placebo 8%), *Dry skin* (PVO 18%, Placebo 9%), *Upper respiratory tract infection* (PVO 13%, Placebo 14%), *Conjunctivitis* (PVO 12%, Placebo 7%), and *Pruritus* (PVO 11%, Placebo 1%).

2.5.8.3. Serious adverse event/deaths/other significant events

Deaths

No deaths were reported during palovarotene treatment or for 30 days post-treatment in the FOP-FAS the MO-FAS or HV-FAS.

A subject in the NHS died of a cardiac arrest. This subject never received treatment with palovarotene.

In Study PVO-1A-301 after the 28 February 2020 data cut-off, a subject with a history of restrictive lung disease died 2.5 months after discontinuing palovarotene treatment. A post-mortem examination revealed the cause of death to be due to restrictive lung disease due to complications of FOP.

In the COPD-FAS, 9 fatal events were reported, 3 in the placebo arm and 6 in the PVO arm, representing 2% of each population. Most deaths were from cardiovascular or respiratory events and were considered related to the subjects' age/underlying disease. It is however noted that one event of "Completed suicide" was reported with PVO treatment. According to the narrative, a subject with multiple morbidity committed suicide less than 3 weeks after the start of treatment. The subject had no known history of depression. The death was deemed as unrelated to treatment by Investigator. Notwithstanding, this is of interest, as depression and suicidality have been reported in patients treated with systemic retinoids. This is further discussed below.

Serious adverse events (SAE)

FOP-FAS

Through the safety update data cut-off date, 36.0% of subjects in the ≥8/10 years palovarotene group had at least one treatment-emergent SAE. The most common included epiphyses premature fusion (6.5%), corona virus infection (2.9%), pneumonia (2.9%), condition aggravated (2.2%), exposure to communicable disease (2.2%), cellulitis (2.2%) arthralgia (2.2%), extremity pain (2.2%); and back pain, abdominal pain, impacted teeth, peripheral swelling, pain, syncope, and respiratory distress, each in 1.4% of subjects.

Treatment emergent SAEs as per 30 July 2021 are summarised in Table 42.

Table 42 Treatment-emergent SAEs, Original Baseline, Age at First Entry ≥8/10 Years (FOP-FAS)

	28 February 2020 Cutoff			30 July 2021 Cutoff		
System Organ Class Preferred Term, n (%)	Chronic 5 mg (N=130)	Flare-up 20/10 mg (N=100)	PVO Total (N=139)	Chronic 5 mg (N=131)	Flare-up 20/10 mg (N=105)	PVO Total (N=139)
At least one treatment-emergent SAE	21 (16.2)	20 (20.0)	37 (26.6)	31 (23.7)	24 (22.9)	50 (36.0)
Musculoskeletal and connective tissue disorders	8 (6.2)	9 (9.0)	16 (11.5)	9 (6.9)	11 (10.5)	19 (13.7)
Epiphyses premature fusion	5 (3.8)	2 (2.0)	7 (5.0)	5 (3.8)	4 (3.8)	9 (6.5)
Arthralgia	1 (0.8)	2 (2.0)	3 (2.2)	1 (0.8)	3 (2.9)	3 (2.2)
Pain in extremity	0	2 (2.0)	2 (1.4)	1 (0.8)	2 (1.9)	3 (2.2)
Back pain	0	1 (1.0)	1 (0.7)	1 (0.8)	1 (1.0)	2 (1.4)
Aneurysmal bone cyst	0	0	0	1 (0.8)	0	1 (0.7)
Epiphyseal disorder	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Mobility decreased	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Muscle tightness	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Neck pain	0	0	0	0	0	1 (0.7)
Gastrointestinal disorders	6 (4.6)	3 (3.0)	9 (6.5)	6 (4.6)	3 (2.9)	9 (6.5)
Abdominal pain	1 (0.8)	1 (1.0)	2 (1.4)	1 (0.8)	1 (1.0)	2 (1.4)
Tooth impacted	1 (0.8)	1 (1.0)	2 (1.4)	1 (0.8)	1 (1.0)	2 (1.4)
Diarrhoea	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Dysphagia	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Incarcerated inguinal hernia	0	0	0	1 (0.8)	0	1 (0.7)
Mallory-Weiss syndrome	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Oesophageal stenosis	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Small intestinal obstruction	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Tooth disorder	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Vomiting	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Gastritis	0	0	0	0	0	0

Infections and infestations	3 (2.3)	6 (6.0)	8 (5.8)	7 (5.3)	7 (13.2)	14 (10.1)
Corona virus infection	0	0	0	4 (3.1)	0	4 (2.9)
Pneumonia	1 (0.8)	2 (2.0)	3 (2.2)	1 (0.8)	3 (2.9)	4 (2.9)
Cellulitis	0	2 (2.0)	2 (1.4)	0	3 (2.9)	3 (2.2)
Staphylococcal sepsis	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Appendicitis	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Bacterial sepsis	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Escherichia sepsis	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Gastroenteritis	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Haemophilus infection	0	0	0	0	1 (1.0)	1 (0.7)
Influenza	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Klebsiella bacteraemia	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Mycoplasma infection	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Parainfluenzae virus infection	0	1 (1.0)	1 (0.7)	0	0	0
Urosepsis	0	0	0	0	1 (1.0)	1 (0.7)
Pneumonia bacterial[a]	0	0	0	0	0	0
General disorders and administration site conditions	2 (1.5)	7 (7.0)	8 (5.8)	2 (1.5)	7 (6.7)	9 (6.5)
Condition aggravated	2 (1.5)	4 (4.0)	5 (3.6)	1 (0.8)	3 (2.9)	3 (2.2)
Local swelling	0	2 (2.0)	2 (1.4)	0	0	0
Peripheral swelling	0	0	0	0	2 (1.9)	2 (1.4)
Oedema peripheral	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Vessel puncture site pain	0	0	0	0	0	1 (0.7)
Pain	0	0	0	1 (0.8)	1 (1.0)	2 (1.4)
Nervous system disorders	1 (0.8)	4 (4.0)	5 (3.6)	1 (0.8)	4 (3.8)	5 (3.6)
Syncope	1 (0.8)	1 (1.0)	2 (1.4)	1 (0.8)	1 (1.0)	2 (1.4)
Epilepsy	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Generalised tonic-clonic seizure	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Myoclonus	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Seizure	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Encephalopathy	0	0	0	0	0	0
Injury, poisoning and procedural complications	2 (1.5)	3 (3.0)	4 (2.9)	6 (4.6)	4 (3.8)	9 (6.5)
Ankle fracture	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Extraskeletal ossification [b]	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Femur fracture	1 (0.8)	1 (1.0)	1 (0.7)	1 (0.8)	1 (1.0)	1 (0.7)
Fracture	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Humerus fracture	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Post-traumatic pain	0	0	1 (0.7)	0	0	1 (0.7)
Radius fracture	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Post-procedural haematoma	0	0	0	1 (0.8)	0	1 (0.7)
Skull fracture	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Subdural haemorrhage	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Exposure to communicable disease	0	0	0	3 (2.3)	0	3 (2.2)
Traumatic fracture	0	0	0	0	1 (1.0)	1 (0.7)
Fall	0	0	0	0	0	0
Head injury	0	0	0	0	0	0
Hip fracture	0	0	0	0	0	0
Skin Laceration [c]	0	0	0	0	0	0

Respiratory, thoracic and mediastinal disorders	3 (2.3)	1 (1.0)	4 (2.9)	3 (2.3)	1 (1.0)	4 (2.9)
Respiratory distress	1 (0.8)	1 (1.0)	2 (1.4)	1 (0.8)	1 (1.0)	2 (1.4)
Asthma	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Dyspnoea	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Hypoxia	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Asthmatic crisis	0	0	0	0	0	0
Pneumonitis	0	0	0	0	0	0
Respiratory failure	0	0	0	0	0	0
Renal and urinary disorders	0	2 (2.0)	2 (1.4)	0	3 (2.9)	3 (2.2)
Haematuria	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Renal failure	0	0	0	0	1 (1.0)	1 (0.7)
Urinary retention	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Blood and lymphatic system disorders	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Anaemia	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Endocrine disorders	0	1 (1.0)	1 (0.7)	0	0	0
Adrenal insufficiency	0	1 (1.0)	1 (0.7)	0	0	0
Metabolism and nutrition disorders	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Malnutrition	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Uterine leiomyoma	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Psychiatric disorders	0	0	1 (0.7)	0	0	1 (0.7)
Drug dependence	0	0	1 (0.7)	0	0	1 (0.7)
Skin and subcutaneous tissue disorders	0	0	0	0	0	0
Decubitus ulcer[c]	0	0	0	0	0	0
Vascular disorders	0	0	0	1 (0.8)	0	1 (0.7)
Lymphoedema	0	0	0	1 (0.8)	0	1 (0.7)

a Occurred during the off-treatment period (outside of the chronic and flare-up treatment periods).
b PT of 'extraskeletal ossification' was coded under the SOC of *Musculoskeletal and connective tissue disorders* in the initial ISS as per MedDRA version 21.0, and to the SOC of *Injury, poisoning and procedural complications* as per MedDRA version 22.0 at the safety data cutoff; the difference in coding is due to change in the MedDRA version.
c Occurred in a placebo/untreated subject from Studies PVO-1A-201 and PVO-1A-202/Part A.
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.
FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; ISS=integrated summary of safety; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term;

PVO=palovarotene; SAE=serious adverse event; SOC=system organ class.

MO-FAS

Six treatment emergent SAEs were reported in the MO-FAS, all with palovarotene treatment: radius fracture, ulna fracture, pneumonia, blood loss anaemia, appendicitis, and status epilepticus. One subject in the placebo group was reported with post-treatment PPC. No other PPC events were reported.

COPD-FAS

Treatment emergent SAEs occurred in 18% of subjects in the palovarotene group and in 15% of subjects in the placebo group in the COPD-FAS.

The most frequently reported SAEs occurred primarily in the SOC of *Infections and infestations (pneumonia, gastroenteritis, infective exacerbation of chronic obstructive airway disease, and lower respiratory tract infection)*, *Respiratory, thoracic and mediastinal disorders (COPD, pulmonary mass, and respiratory failure)*, and *Cardiac disorders (acute myocardial infarction and atrial fibrillation)*. The incidence of the most common SAE of *pneumonia* was similar across the palovarotene (2.8%) and placebo (2.7%) groups. All other SAEs had an incidence under 1.0%, were spread among a variety of SOCs.
The PTs *Prostatic cancer* and *Aortic aneurysm* were exclusively reported in the PVO arm. Both PTs were reported in 4/329 (1.2%) of the subjects in the PVO 5 mg arm versus nil in the placebo arm (N=159). None of the events were deemed as treatment related by the Investigator.

Post-treatment SAEs occurred in 21 subjects (3.4%) in the palovarotene group and 14 subjects (3.8%) in the placebo group (dyspnoea, cardiorespiratory arrest, and pneumonia)

Other significant adverse events: Bone safety

Methodology

Systemic retinoids have been associated with a variety of adverse effects on the musculoskeletal system, including PPC, osteoporosis, an increased risk for fracture, and hyperostotic changes or calcification of tendons and ligaments—effects seen only after prolonged use and similar to what has been reported in hypervitaminosis A syndrome.

For this reason, bone safety monitoring programs were implemented across the FOP and MO studies in paediatric subjects (<18 years of age). These programs included linear and knee height assessments, regularly scheduled hand/wrist and knee radiographs, bilateral hand/wrist and knee radiographs and Weight bearing computed tomography (WBCT) scans, including measurement of tibial and femoral length. WBCT scans were also assessed for in all subjects for avascular necrosis (AVN) of the femoral head bilaterally.

During the Phase 2 studies, the review of the hand/wrist and knee radiographs were initially performed by a single reader using standardised procedures. When the PVO-1A-301 Phase 3 study was initiated, a more detailed review process was developed to enhance the protection of subject safety, especially the safety of children. Adaptations to bone safety monitoring continued over time as the study progressed. To ensure the methodology was consistent across the Phase 2 and 3 studies, all bone safety images obtained in the Phase 2 studies and NHS were reread using the same procedures and systems as Study PVO-1A-301.

Linear Height and Growth Velocity

Z-score measurements represent the deviation from the median height for age.

Monitoring linear growth is challenging in the FOP population due to frequent spinal abnormalities and the apparent loss of height due to worsening scoliosis/kyphosis. Despite these limitations, linear height generally increased over time in most paediatric subjects in the palovarotene groups of the Phase 2 and 3 studies and in untreated subjects from the NHS. In subjects treated with palovarotene in Study PVO-1A-301, as well as in untreated subjects, there was a notable trend of declining height z-scores in adolescent subjects, and an apparent loss of linear height likely due to spinal deformities and/or measurement errors. Additionally, compared with untreated (NHS) subjects, linear height z-scores had greater variability and an apparent decrease in younger paediatric subjects in the palovarotene group of Study PVO-1A-301.
When linear height was analysed by growth velocity (GV), there was a greater proportion of palovarotene-treated subjects of all paediatric age categories who had GV at Month 12 of <4 cm/year versus age-matched untreated subjects. For example, in the age group ≥8/10 to <14 years, 61% of the subjects in the palovarotene arm had a GV <4 cm/year versus 41% in the untreated (NHS) subjects.

The applicant has also provided growth velocity categories for some specific locations, i.e., knee height, femur length and tibial length.

Taken together, the data may suggest a negative impact on growth in the two lower age cohorts in the FOP-FAS; however, there are some confounding factors hampering the assessment. There is some data missing, especially in the assessment of growth velocity in specific locations in the NHS, the NHS study could not be considered a true comparator group for the FOP-FAS and there are reports of negative growth of e.g., knee height, indicating measurement error. This is understandable given that radiography and other measurements require keeping a specific position for some time, which could be

difficult both for young children and for subjects with pain and/or limited mobility. Results for linear height, knee height, and femur and tibia lengths demonstrate that the greatest effect of palovarotene was seen in overall linear height and femur length.

In the MO-FAS a similar trend was seen in the 5.0 mg cohort; however, the number of missing data at Month 12 and especially at Month 18 is very large.

Premature physeal closure (PPC)

Premature epiphyseal closure is a labelled side effect of 13-*cis*-RA, related to dose, age at exposure, and treatment duration with more pronounced affects in young individuals exposed to higher doses. According to the PVO-1A-301 CSR, when any epiphyseal closure was identified, the Investigator performed a comprehensive evaluation of the subject and x-ray(s) to determine whether the closure was likely to be premature. This included a review of all available clinical data (e.g., linear growth, age, pubertal status, concomitant medication) and previous x-rays findings (e.g., partial closure at baseline) in consultation with a local radiologist and/or paediatric endocrinologist, as necessary.

The first report of PPC (index case) was initially identified on the Month 6 protocol-specified radiographs of a subject (on enrolment) in Study PVO-1A-301. The index case was reviewed by the data monitoring committee (DMC) at an ad hoc meeting in January 2019.

A second case of PPC was identified in May 2019 in a subject enrolled in Study PVO-1A-301. This second case of PPC led to further review and discussion by the DMC, with the outcome of shifting the potential risk of PPC to an identified risk. In July 2019, the DMC also recommended that the second subject stop treatment and that the study ICF be updated to further characterise the risk of PPC and potential for disproportionate growth.

In September 2019, two additional cases of PPC were identified. A follow-up meeting was held with the DMC on 13 September 2019 to discuss the information requested for subjects ≤10 years of age. The DMC recommended that the frequency of bone safety radiograph monitoring (hand/wrist and knee) be increased from every 6 months to every 3 months for subjects who had not reached 100% closure of the growth plates (as assessed by the central reading facility) and who were receiving flare-up dosing. Upon further review and follow up, 4 additional cases were assessed by Investigators as PPC and captured as SAEs.

When combined with the 4 prior expedited reported cases, a total of 8 reports of PPC across Phase 2 and 3 FOP studies were identified. A safety notification informing the FDA of this information was filed to the agency on 17 October 2019 along with the ICFs with the updates required by the DMC. Following the information provided in the safety notification submitted to the FDA on describing an identified risk of PPC, and a follow-up submission with subsequent safety updates including protocol amendments for Phase 2 and 3 protocols on 19 November 2019, a partial clinical hold was issued by the FDA on 4 December 2019 for subjects under 14 years of age for all FOP and MO studies and implemented in all participating countries. The partial clinical hold still remains in place.

All PPC events were classified as SAEs by the sponsor under the preferred term of epiphyses premature fusion. As of July 2021, PPC was reported for 26 subjects from 4 to 13 years in the FOP-FAS, consisting of 22 subjects with treatment emergent events and 4 subjects with post-treatment events. Six subjects with PPC had partial closure of at least at one physis at baseline, with subsequent progression of closure or identification of additional anatomical locations.

The chronological age at onset of the first recognition of PPC ranged from 5.2 to 13.7 years. PPC was identified in 24 of 102 subjects (24%) <18 years of age, including a subject with PPC reported after the 28 February 2020 data cut-off. PPC was more common in younger (<8/10 years: 14 of 25

subjects, 56%) compared with older (≥8/10 to <18 years: 9 of 77 subjects, 12%; ≥8/10 to <14 years: 9 of 39 subjects, 23%) subjects.

PPC occurred during both the chronic and flare-up treatment periods. As of the data cut-off of 28 February 2020, 5 subjects with PPC received only chronic dosing.

In the MO program as of the data cut-off date, no cases of PPC were identified in treated subjects. All post-baseline physeal closures were assessed as physiologic.

Analysis of the total exposure to palovarotene did not show a higher exposure in subjects with versus without PPC (Table 43) (28 February 2021).

Table 43 Palovarotene Exposure (Through First PPC Finding or Data Cut-off) by PPC Status in the Phase 2 and PVO-1A-301 Studies, Age at First Palovarotene Dose <18 Years (FOP-FAS)

Parameter	Age at First Dose	Statistic	With PPC (N=23)	Without PPC (N=78)
Total AUC (PVO 20, 10, 5 mg)	<8/10 y	N'	9	6
ng•h/mL × days of dosing[1]		Mean (SD)	168234.2 (134711.9)	204841.7 (157605.2)
		Median	152004.0	162654.5
		Min, max	40223.7, 458108.1	78699.2, 502157.6
	≥8/10 to <14 y	N'	8	27
		Mean (SD)	161348.4 (150447.6)	173726.8 (126055.5)
		Median	145727.2	146604.3
		Min, max	3901.2, 396012.3	3165.4, 585614.4
	≥14 to <18 y	N'	0	29
		Mean (SD)	–	228236.1 (132798.7)
		Median	–	211120.1
		Min, max	–	6508.8, 605198.6

[1] Not all subjects had pharmacokinetic data available for analysis.

The FOP-FAS includes all subjects enrolled or dosed in FOP clinical studies.

AUC=area under the curve; FAS=full analysis set; FOP=fibrodysplasia ossificans progressiva; PPC=premature physeal closure; PVO=palovarotene.

The proposed cut-off for palovarotene treatment (⩾8/10 years) was chosen as it corresponds to the age when children on average are expected to have reached approximately 80% of final their height. For a boy, this could mean the difference between 180 cm and 144 cm in final height. A benefit/risk analysis comparing the amount of HO in palovarotene treated versus untreated FOP subjects from different age cohorts with the number of reported PPC events is presented in Table 44.

Table 44 Benefits and Risks Associated With Palovarotene Treatment up to 12 Months

	Treated[b] [A]	**Untreated[b] [B]**	**Difference [A] - [B]**	**P-value[c]**
Benefit: Mean (SD) Change in HO Volume (mg) per Subject [a]				
Age at baseline ≥8 years (female) and ≥10 years (male) (Sought Indication)	8088.58 (25,119.21)	30,141.35 (78,767.12)	-22,052.77	0.065
Age at baseline >12 years	10,495.52 (27,889.06)	31,662.33 (81,147.05)	-21,166.81	0.100
Age at baseline >14 years	12,567.61 (30,967.74)	33,644.51 (84,390.30)	-21,076.90	0.137
Age at baseline >16 years	14,308.14 (30,681.49)	23,830.52 (74,149.03)	-9522.38	0.522
Risk: Number (%) of Subjects With PPC [d,e]				
Age at baseline ≥8 years (female) and ≥10 years (male) (Sought Indication)	8 (14.04%)	-	-	-
Age at baseline >12 years	1 (2.86%)	-	-	-
Age at baseline >14 years	0	-	-	-
Age at baseline >16 years	0	-	-	-

HO=heterotopic ossification; MOVE=Study PVO-1A-301; PPC=premature physeal closure; SD=standard deviation; WBCT=whole body computed tomography

[a] Mean HO volume change was defined as the change from baseline to Month 12 (generously defined as data from a WBCT scan 9 to 15 months after baseline).

[b] Treated subjects were those in the MOVE study, regardless of crossover status. NHS subjects who crossed over into the MOVE study only contributed treated time in the analysis.

[c] For HO change, p-values were estimated using t-tests. For fracture risk, p-values were estimated using Fisher's exact tests when fracture counts were <5 and chi-squared tests when fracture counts were ≥ 5.

[d] Risk of PPC was calculated using data from baseline to Month 12 (generously defined as data on PPC up to 15 months after baseline).

[e] Only subjects <18 years old were considered at risk of PPC because older subjects' growth plates are likely to have already closed

The risk of developing PPC for a subject ≥8/10 but ≤12 years old at baseline was 14% compared to 3% in subjects >12 but ≤14 years old at baseline.

Avascular necrosis (AVN)

To date, there are no reports of AVN of the femur head in the FOP-FAS. It is not completely clear from the study report, but there seem to have been a report of aseptic necrosis, which is used as an alternative verbatim for AVN, of the right hip in a subject in the COPD-FAS, but no further information could be retrieved, i.e. not even whether this was reported in the placebo or PVO population. The Applicant did not propose any measures concerning AVN in the SmPC or RMP. This is supported at this time point

Osteonecrosis (MO-FAS only)

Osteonecrosis was not reported as an AE in any subject in the MO-FAS. Signs of early osteonecrosis could be seen at baseline in some subjects. No measures in the SmPC or RMP concerning osteonecrosis was proposed by the Applicant. This is supported at this time point

Bone Mineral Density (BMD) and bone markers

Case reports of osteoporosis and fracture are reported in patients receiving systemic retinoids. At high doses of palovarotene, juvenile rats exhibited decreases in bone size and some juvenile and adult rats had sternebral fractures at high doses of palovarotene.

Because of challenges related to limitations on the ability to interpret standard assessments of BMD secondary to the substantial heterotopic ossification throughout the skeleton in most subjects with FOP, BMD was not assessed in the FOP clinical program. The bone turnover marker CTX was assessed in both the FOP studies over 12 weeks of treatment and in COPD studies over 1 to 2 years of treatment. From these, there were no indications of high bone turnover. Although CTX was studied in the palovarotene program, this individual clinical laboratory value is not sufficient to determine changes in bone mineral density to assess for risk of osteoporosis.

Preliminary assessments in the MO-FAS showed a trend of lower bone mineral content accrual and BMD loss in the palovarotene group that was both dose- and time-dependent. Of note, at baseline, subjects in the MO-FAS had lower BMD compared with their non-affected peers. Since the clinical concern of low bone density is increased fracture rate, the incidence of bone fracture AEs was similar between treated and untreated subjects in both the MO and FOP studies and were generally associated with traumatic events such as falls. Additionally, no subjects had a vertebral compression fracture. however, in the MO-FAS, a total of 65 subjects received palovarotene 5.0 mg daily for a mean of 226 days. Therefore, any potential differences in fracture data due to a loss in BMD may not be detectable.

Chronic, recurrent use of corticosteroids and issues with malnutrition due to jaw ankylosis and immobility may all contribute to development of decreased BMD and osteoporosis in FOP subjects. Notwithstanding, based on the findings in the MO-FAS, indicating a loss of bone mineral density in the palovarotene group that was both dose- and time-dependent, the non-clinical data and case reports of osteoporosis and fracture reported in patients receiving systemic retinoids, the Applicant was asked to discuss whether the risk of osteoporosis needs to be reflected in the SmPC, particularly as palovarotene treatment is not time limited
In response, the Applicant has presented a signal evaluation report (Bone Safety Report) based on a signal that palovarotene may have a potential negative impact on BMC accrual in paediatric subjects and portend a higher fracture risk in both adult and paediatric subjects. The objective of the signal evaluation report was to assess the possible causal relationship between palovarotene treatment in Study 301 (MOVE) compared with standard of care only (i.e., palovarotene untreated) in Study 001 (NHS) and selected bone safety outcomes in subjects with FOP.
An assessment of vertebral structural integrity using vertebral biomechanical computed tomography (BCT) using the VirtuOst software, and vertebral fracture assessment (VFA) applied to whole body computed tomography (WBCT) scans obtained in the FOP studies were analysed. In total, data from 84 treated subjects from Study 301 and 95 untreated subjects from the NHS study, all ≥8/10 years old, were included in the analyses. No validation for the methods, baseline data or discussion of the clinical relevance of the results were provided. Nonetheless, the BCT data indicate a negative impact of palovarotene treatment on bone strength and mineralisation and VFA indicated a threefold higher risk of new-onset radiological vertebral fractures in palovarotene treated versus untreated FOP subjects.

The potential effects on fracture healing are currently not determined.

Adverse Events by Organ System or Syndrome

Mucocutaneous events

Mucocutaneous events were the most common treatment related TEAEs reported in clinical studies with palovarotene. The incidence of TEAEs under *Skin and subcutaneous tissue disorders* in the FOP ≥8/10 years palovarotene group was 98%. The most common TEAEs observed in over 30% of subjects, which were more common in the ≥8/10 years palovarotene group compared with placebo/untreated subjects, included dry skin (78%), dry lips (56%), alopecia (42%), pruritus (40%), erythema (34%), rash (32%), and generalised pruritus and skin exfoliation (each 31%). TEAEs were generally mild to moderate in severity.
No erythema multiforme, bullous dermatitis, or severe skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or acute generalised exanthematous pustulosis were identified.

Mucocutaneous events were the most common reason for dose reductions, which occurred more frequently during flare-up treatment, suggesting an effect of dose with the higher dosage flare-up treatment (palovarotene 20/10 mg).

Photosensitivity reactions are associated with the use of retinoids. Although palovarotene was negative for phototoxicity when tested *in vitro*, precautionary measures for phototoxicity are still recommended.

Exposure to sun or artificial ultraviolet light might aggravate these TEAEs and should be avoided. Protection from sunlight, when it cannot be avoided (use of sunscreens, protective clothing, and use of sunglasses), is recommended in general.

Musculoskeletal events

The most common musculoskeletal TEAEs across palovarotene groups for all analysis sets was arthralgia. Musculoskeletal TEAEs identified by the SMQ had a similar incidence across the palovarotene and placebo groups across analysis sets. Skeletal effects such as PPC in the FOP-FAS and decreased BMD in the MO-FAS were exceptions.

In total, 27 fractures were reported in 19 subjects in the FOP-FAS (Not specified/heterotopic [4], Foot [3], Humerus [3], Facial bone [3], femur [3], Radius [3], Ankle [2], Skull [2], Hip [1], Spinal/heterotopic [1], Scapula [1], Upper limb/heterotopic [1]). The vast majority of fractures in the FOP-FAS (25/27) were assessed as not related, whereas two fractures (one ankle fracture and one heterotopic spinal fracture) were assessed as possibly related by Investigator.

Teratogenicity, Pregnancy Outcomes, and Fertility

Teratogenicity is an important identified risk in the palovarotene clinical program and a well-known class effect of systemic retinoids. In addition to the foetal risk, adverse pregnancy outcomes, including spontaneous abortions, elective terminations, stillbirths, and extra-uterine pregnancies have been associated with systemic retinoid therapy. Although there were no pregnancies in the palovarotene development program, findings in toxicology studies demonstrate characteristic patterns of foetal malformations typical of retinoids (e.g., cleft palate, misshapen skull bones, short/long bones).

Literature on systemic retinoids state the amount of drug transferred in semen would result in negligible increases in plasma concentrations in a female partner suggesting there is little, if any risk of embryogenesis. A Phase 1 study (PVO-1A-104) characterized the PK of palovarotene in plasma at steady state and palovarotene concentrations in semen after 5 days of 20 mg dosing. Based on these findings, the palovarotene exposure in a female partner and subsequently to an embryo/foetus would be more than 100-fold lower than peak plasma exposure in pregnant rats at the no observed adverse effect level (NOAEL) for effects on foetal development and more than 4 orders of magnitude lower than the plasma exposure in the treated male subjects.

Psychiatric Disorders and Suicidality

Depression, aggravated depression, anxiety, mood alterations, and suicidal thoughts and behaviours have been reported in patients treated with systemic retinoids. Individuals with a personal history of psychiatric illness may be more susceptible.

Approximately, 9.4% of subjects in the ≥8/10 years palovarotene group had a history of depression. There was also a high percentage of untreated subjects in the NHS with a history of depression (24.2%). This may be related to FOP being a chronic, debilitating condition and hampers the causal assessment of new episodes of depression and suicidal ideation during palovarotene treatment.

In total, "suicidal ideation" was reported in 6 subjects (4%) of the palovarotene treated population in the FOP-FAS; however, there was no treatment-related increase in suicide ideation or suicidal behaviour observed in the FOP-FAS as assessed by the C-SSRS (Columbia-Suicide Severity Rating Scale).

Psychiatric Disorder TEAEs in the FOP-FAS are summarised Table 45.

Table 45 Psychiatric Disorder TEAEs, Age at First Entry ≥8/10 Years (FOP-FAS)

	28 February 2020 Cutoff			30 July 2021 Cutoff		
Preferred Term	Chronic 5 mg (N=130)	Flare-up 20/10 mg (N=100)	PVO Total (N=139)	Chronic 5 mg (N=131)	Flare-up 20/10 mg (N=105)	PVO Total (N=139)
Any TEAE	10 (7.7)	15 (15.0)	23 (16.5)	14 (10.7)	15 (14.3)	25 (18.0)
Depressed mood	7 (5.4)	5 (5.0)	12 (8.6)	7 (5.3)	5 (4.8)	12 (8.6)
Suicidal ideation	2 (1.5)	3 (3.0)	5 (3.6)	3 (2.3)	3 (2.9)	6 (4.3)
Depression	0	3 (3.0)	3 (2.2)	3 (2.3)	3 (2.9)	6 (4.3)
Mood altered	1 (0.8)	1 (1.0)	2 (1.4)	1 (0.8)	1 (1.0)	2 (1.4)
Mood swings	0	1 (1.0)	2 (1.4)	0	1 (1.0)	2 (1.4)
Memory impairment	0	2 (2.0)	2 (1.4)	0	2 (1.9)	2 (1.4)
Drug dependence	0	0	1 (0.7)	0	0	1 (0.7)
Intentional self-injury	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Disturbance in attention	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)

Furthermore, as discussed above, one event of "Completed suicide" was reported with PVO treatment in the COPD-FAS. The subject with massive comorbidity but no known history of depression, committed suicide less than 3 weeks after start of treatment.

Hepatobiliary and Pancreatic Effects

TEAEs captured in the hepatotoxicity search strategy in the palovarotene groups across analysis sets are summarised in Table 46.

Table 46 Hepatotoxicity TEAEs, Age at First Entry ≥8/10 Years (FOP-FAS) (28 February 2020)

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	3 (15.0)	8 (6.2)	1 (14.3)	4 (16.0)	10 (10.0)	17 (12.2)
Blood alkaline phosphatase increased	2 (10.0)	4 (3.1)	0	0	6 (6.0)	9 (6.5)
Alanine aminotransferase increased	0	2 (1.5)	0	0	5 (5.0)	6 (4.3)
Gamma-glutamyltransferase increased	0	1 (0.8)	1 (14.3)	0	5 (5.0)	6 (4.3)
Aspartate aminotransferase increased	0	0	0	0	4 (4.0)	4 (2.9)
Blood bilirubin increased	1 (5.0)	1 (0.8)	0	2 (8.0)	1 (1.0)	3 (2.2)
International normalised ratio increased	0	1 (0.8)	0	1 (4.0)	0	2 (1.4)
Urobilinogen urine increased	0	0	0	1 (4.0)	1 (1.0)	2 (1.4)
Hepatic steatosis	0	1 (0.8)	0	0	0	1 (0.7)
Hyperbilirubinaemia	0	0	0	0	1 (1.0)	1 (0.7)

Hepatotoxicity TEAEs were captured from broad SMQs for drug-related hepatic disorders (severe events only) and liver-related investigations signs and symptoms.
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.
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; SMQ=standardized MedDRA query; TEAE=treatment-emergent adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PVO=palovarotene.

Hepatic enzyme elevations were reported in 3-4.5% of the subjects in the FOP-FAS. Retinoids have been implicated in causing mild-to-moderate elevations in routine liver tests. Some retinoids (acitretin, etretinate, retinal acetate) have been associated with a clinically apparent acute liver injury which typically arises during the first 3 months of therapy, has many features of hypersensitivity and can be severe and even fatal.

Inflammatory Gastrointestinal Events

Inflammatory gastrointestinal events have been reported with systemic retinoids, for example isotretinoin.

In the FOP-FAS, inflammatory gastrointestinal TEAEs identified 3 of 139 subjects (2.2%) in the ≥8/10 years palovarotene group and 1 of 20 placebo/untreated subjects (5.0%) with gastritis. All events in the palovarotene group occurred during the chronic treatment period. No subjects had TEAEs of inflammatory bowel disease such as ulcerative colitis. One event each of "Colitis ischaemic" and "Colitis ulcerative" were reported in the COPD-population.

Lipid Metabolism Disorders

In the FOP-FAS, the HLGT search identified 8 subjects (5.8%) in the ≥8/10 years palovarotene group with lipid metabolism TEAEs including hypercholesterolemia and hypertriglyceridemia. No such TEAE was reported in the placebo/untreated subjects (N=20).

Changes in lipid metabolism has been associated with systemic retinoids, the data seem to indicate an increased risk of triglyceride elevations with palovarotene treatment, and there also seems to be a dose effect.

Allergic Reactions

In the FOP-FAS, 11.5% of subjects in the ≥8/10 years palovarotene group and no placebo/untreated subjects were identified with allergic reaction TEAEs, such as facial swelling and cutaneous hypersensitivity (e.g., urticaria). One subject (1.9%) had urticaria during the off-treatment period.

Overall, the incidence was not markedly higher in the palovarotene 20/10 mg flare-up treatment period (8.0%) compared with the chronic treatment period (5.4%).

At this time point, no significant hypersensitivity reactions such as anaphylaxis or systemic allergic reactions were identified. No case of retinoic acid syndrome (RAS) which is a potentially life-threatening complication, described mainly and most frequently in subjects with promyelocytic leukaemia treated with all-trans retinoic acid (ATRA) has been reported.

Central Nervous System Disorders

There has been reports of epilepsy/seizures in all three safety pools (FOP-FAS, MO-FAS and COPD-FAS).

In the FOP-FAS, three subjects (2.2%) in the ≥8/10 years palovarotene group were reported with SAEs with PTs representing epilepsy/seizures.
One subject reported with two events of tonic-clonic seizures, both during "flare-up"-treatment. The first event was reported as associated to head injury on Day 422. According to the narrative, the subject tripped, fell, hurt his head, and had generalised seizures. On day 494, also during flare-up treatment, the subject seems to have had a second episode of generalised seizures without any previous trauma, and prophylactic medication seems to have been started. It is difficult to assess causality in this case. If the second episode had not been reported, the subject's seizures would have been attributable to head injury. Now, it could be hypothesised that the epileptic seizure was actually the primary event also in the first episode. Therefore, a causal association to palovarotene in flare-up dosing is possible.
The second subject was reported with an epileptic seizure at Day 230 during flare-up-dosing. During the next weeks, the subject had additional seizures and was diagnosed with presumed idiopathic epilepsy. In this case, a causal association to palovarotene in flare-up dosing could also be possible.
The third subject in the FOP-FAS was reported with propriospinal myoclonus seizures, which were reported in this subject also prior to dosing.
No events occurred in placebo/untreated subjects or the <8/10 age group.

In the MO-FAS, one subject was reported with status epilepticus during treatment with palovarotene. The subject had a history of febrile seizures. No information was given on the subject's body temperature at the occasion, but CRP was only slightly elevated. It is agreed with the investigator that a causal association is possible.

Finally, in the COPD-FAS, two events of seizures were reported in the 5 mg palovarotene treatment arm. In one case, the seizures were associated with stroke. In the other case, there were no known precipitating factor for seizures. A causal association could be possible.

In summary, in the three safety pools four subjects were reported with generalised seizures during palovarotene treatment where a causal association may be possible. However, no firm conclusions could be drawn. Convulsions are labelled as a very rare ADR for Isotretinoin. Seizures is considered as an adverse drug reaction of palovarotene with a frequency common.

No TEAEs of benign intracranial hypertension or pseudotumor cerebri were reported in the FOP-FAS or MO-FAS. Such events have been reported for Isotretinoin and a wording is included in section 4.4 of the SmPC. The FOP-FAS and MO-FAS are still rather limited.

Hearing Impairment

Hearing impairment is labelled with the frequency very rare in the SmPC of isotretinoin and could therefore be suspected a class effect. However, hearing impairment is also a common feature of FOP itself.

There was a high percentage of untreated subjects in the NHS with a history of deafness (43%), with an additional 5% of subjects having hearing loss over 3 years of observation. In the FOP-FAS ≥8/10 years palovarotene group, 22 subjects (16%) had a medical history of Ear and Labyrinth Disorders, the most common of which were deafness in (7.2%), bilateral deafness (3.6%), and conductive deafness (2.9%).

In the FOP-FAS, 12% of subjects in the ≥8/10 years palovarotene group had TEAEs related to hearing impairment. There were no events in placebo/untreated subjects. The incidence was similar during chronic treatment (6.9%) and palovarotene 20/10 mg flare-up treatment (8.0%), suggesting no effect of dose.

There was no relevant difference in incidence of hearing loss between palovarotene treated subjects and placebo treated subjects in the MO-FAS or COPD-FAS. Furthermore, there are reports in the literature indicating a positive effect on certain forms of hearing impairment. Furthermore, there are reports in the literature indicating a positive effect on certain forms of hearing impairment. The Applicant has proposed not to label hearing impairment in the SmPC of palovarotene. This is accepted, given the confounding factors. It is however considered that it should be mentioned in section 4.4 that hearing impairment is reported for other systemic retinoids.

Eye Disorders

In the FOP-FAS, 49 subjects (35%) in the ≥8/10 years palovarotene group and placebo/untreated subjects (10%) had TEAEs under *Eye Disorders*. The incidence was higher during the palovarotene 20/10 mg flare-up treatment period (32%) compared with the chronic treatment period (18%). The most common events in the palovarotene group were dry eye (26%) and ocular hyperaemia (6.5%). No events of dry eye or ocular hyperaemia were reported in placebo/untreated subjects. Similar results are reported from the MO- and COPD populations. Dry eye (frequency very common) and ocular hyperaemia (frequency common) are therefore considered adverse drug reactions of palovarotene and listed in section 4.8 of the proposed SmPC.

Night blindness (nyctalopia) has been identified as a potentially dangerous effect associated with systemic retinoids and has been reported in at least one subject on palovarotene treatment. This is reflected in section 4.7 in the proposed SmPC for palovarotene and section 4.4, as. this risk is potentially dangerous in everyday life for a FOP patient and not only associated with driving and using machines. Night blindness may increase the risk of minor trauma which in turn may trigger a flare-up in FOP patients. A recommendation on regular ophthalmological screening is also included in section 4.4 of the SmPC.

Carcinogenicity

The applicant has not provided any non-clinical carcinogenicity studies and no data are available yet. The lack of these studies is acceptable based on unmet medical need and the nature of the product. However, such studies would be considered necessary as post-approval measures (non-clinical section) if a positive Benefit Risk on the product could be concluded.

Carcinogenicity TEAEs were obtained from a search for preferred terms under the SOC of *Neoplasms benign, malignant and unspecified (incl. cysts and polyps)*.

The search retrieved 15 events in 9 subjects in the ≥8/10 Years FOP-FAS, all during palovarotene treatment Table 47.

Table 47 Carcinogenic Adverse Events Identified Under the System Organ Class of Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps) (FOP-FAS)

	Chronic PVO 5 mg	Flare-up PVO 20/10 mg	PVO Total
TEAEs (Age at First Entry ≥8/10)[a]			
N	130	100	139
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (3.1)	4 (4.0)	9 (6.5)
Pyogenic granuloma	1 (0.8)	2 (2.0)	3 (2.2)
Uterine leiomyoma	1 (0.8)	1 (1.0)	2 (1.4)
Acrochordon	0	0	1 (0.7)
Chondromatosis	1 (0.8)	0	1 (0.7)
Fibrous histiocytoma	0	1 (1.0)	1 (0.7)
Skin papilloma	1 (0.8)	0	1 (0.7)
TEAEs (All Subjects)			
N	155	119	164
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (2.6)	4 (3.4)	9 (5.5)
Pyogenic granuloma	1 (0.6)	2 (1.7)	3 (1.8)
Uterine leiomyoma	1 (0.6)	1 (0.8)	2 (1.2)
Acrochordon	0	0	1 (0.6)
Chondromatosis	1 (0.6)	0	1 (0.6)
Fibrous histiocytoma	0	1 (0.8)	1 (0.6)
Skin papilloma	1 (0.6)	0	1 (0.6)
Post-Treatment AE (Age at First Entry: ≥8/10)			
N	130	100	139
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.8)	0	1 (0.7)
Neuroendocrine tumour	1 (0.8)	0	1 (0.7)
Post-Treatment AE (All Subjects)			
N	155	119	164
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.6)	0	1 (0.6)
Neuroendocrine tumour	1 (0.6)	0	1 (0.6)

In the MO-FAS, one subject each in the treatment arm and the placebo arm reported a carcinogenicity AE. The data from the COPD-FAS are not comparable in this context, as that study included subjects with severe COPD. Such a population has generally a history of heavy smoking, which is associated to malignancies. Accordingly, 43 neoplasms were reported in the COPD-FAS, 14 in the placebo arm (14/367; 4%) and 29 in the palovarotene arm (29/611; 5%). The number of malignant neoplasms were similar in both treatment arms.
In the FOP-FAS, all reported TEAEs under the SOC of neoplasm (n=9) except one (Neuroendocrine tumour with unknown malignancy status) were benign. The most commonly reported event in the palovarotene group was pyogenic granuloma (periungual) in 2.2% of subjects.

Hormonal Effects

Diabetes mellitus was labelled with the frequency "Very rare" in the SmPC of Isotretinoin. For palovarotene, hyperglycaemia TEAEs were reported in 3 subjects (2.2%) in the palovarotene arm vs 1 (5%) in the placebo/untreated cohort.

Both hypo- and hyperthyroidism have been reported in palovarotene treated subjects (2.9% and 2.1%, respectively). No systematic laboratory investigations were planned to screen the effect of palovarotene with respect to hormonal effects. However, interaction with nuclear receptor RXR is also described in the literature for retinoids (Graeppi-Dulac et al, 2014). It may negatively regulate the expression of the TSHb gene and, at a lesser degree, of TSH and TRH genes leading to central hypothyroidism. Since this effect is observed in nearly 100% of the patients treated with high dose

retinoids (e.g. Bexarotene) and need routine concomitant L-T4 treatment, the impact of palovarotene on the thyroid axis may need further attention. Upon request, The Applicant hypothesises that the difference in central hypothyroidism between bexarotene and palovarotene may be due to differences in mechanism of action. The applicant committed to follow thyroid-associated AEs post-marketing, but not to reflect the risk of thyroid-associated AEs in the SmPC for the time being. This could be acceptable provided that the benefit risk on the product can be concluded positive.

The SMQ for hypothyroidism in the MO-FAS identified 2 subjects (1.5%) with increased TSH in the palovarotene group compared with no subjects in the placebo treated group. No subjects in the MO-FAS had TEAEs of diabetes mellitus or hyperglycaemia.

Immunosuppression

The search largely identified TEAEs associated with infections such as pharyngitis which was the most common event identified in 7.2% of subjects in the ≥8/10 years palovarotene group. Other than a decreased lymphocyte count in one subject, the search did not identify TEAEs indicative of pervasive immunosuppression in the palovarotene group.

In the MO-FAS, apart from infections, TEAEs of immunosuppression in the palovarotene group were rare, identified only in single subjects (0.8%), and included lymphocyte count decreased, neutrophil count decreased, and white blood cell decreased. No serious infections were reported.

Respiratory Effects

Individuals with FOP develop progressive limitations in chest expansion from ankylosis of the costovertebral joints, ossification chest wall muscles and progressive spinal kyphoscoliosis and thoracic lordosis resulting in restrictive lung disease, with reduced vital capacity. Thus, patients are subject to atelectasis, retained secretions, hypoxemia, hypercarbia and pneumonia due to the inability expand their lungs. Respiratory insufficiency commonly causes complications such as pneumonia and right-sided heart failure, leading to cardiorespiratory failure and a markedly shortened survival.

Because of the known respiratory complications associated with FOP, which were supported by the medical histories of treated and untreated (NHS) subjects, respiratory TEAEs in FOP-FAS were anticipated.

In the FOP-FAS, the most common respiratory TEAEs reported in ≥10% of subjects in the ≥8/10years palovarotene group included upper respiratory tract infection (23.7%; placebo/untreated: 5.0%), nasopharyngitis (22.3%; placebo/untreated: 0), cough (16.5%; placebo/untreated: 10.0%), epistaxis (14.4%; placebo/untreated: 0), and oropharyngeal pain (11.5%; placebo/untreated: 0). Severe respiratory TEAEs were rare.

2.5.8.4. Laboratory findings

Clinical chemistry

The majority of new-onset potentially clinically significant (PCS) values for clinical chemistry across all treatment in the ≥8/10 years population of the FOS-FAS concern elevated lipase (2 subjects in the placebo/untreated group vs 10 subjects in the palovarotene group). The PCS lipase elevations were asymptomatic, transient, and generally recovered within 8 weeks while remaining on palovarotene.

Haematology

In the ≥8/10 years palovarotene group of the FOP-FAS, new-onset PCS high values were reported for leukocytes in 3 of 128 subjects (2.3%; placebo/untreated: 0 of 73 subjects) and platelets in 1 subject (0.8%; placebo/untreated: 0). New-onset PCS low values were reported for haemoglobin in 2 subjects

(1.6%; placebo: 0), haematocrit in 1 subject (0.8 %; placebo: 1 subject, 1.4%), and platelets in 1 subject (0.8%; placebo/untreated: 0).

In the MO-FAS, no subject in the palovarotene group had new-onset PCS haemoglobin abnormalities. PCS low haematocrits occurred in 3 of 127 subjects (2.4%) in the palovarotene group. New-onset PCS high values in the palovarotene group was reported for platelets and white blood cells, each in 1 subject (0.8%). In the placebo group, only new-onset PCS high white blood cells were reported (2 of 60 subjects, 3.3%).

Vital signs

Blood pressure and heart rate

In the ≥8/10 years group of the FOP-FAS, the incidence of new-onset PCS high and low systolic and diastolic blood pressure was higher relative to placebo/untreated subjects, especially in female subjects. However, this was not seen in the MO-FAS with the randomised placebo arm. There were thus no consistent findings in blood pressure between palovarotene and placebo over the FOP-FAS and the MO-FAS.

In the FOP-FAS, there was a higher proportion of subjects reporting PCS low heart rate palovarotene treated versus placebo/untreated subjects. This finding was consistent in both chronic and flare-up treatment periods (34% vs 10% for palovarotene and placebo/untreated, respectively, in chronic treatment, and 46% vs 13% in flare-up treatment), and in the MO-FAS (21% vs 10%). The lower proportion of PCS low heart rate in the MO-FAS versus the FOP-FAS may reflect the shorter mean exposure in the MO-FAS vs the FOP-FAS (227 vs 508 days, respectively). Of note, in the FOP-FAS, the incidence of new-onset PCS low heart rate in subjects of other races was higher than white subjects (50% vs 28%). This is consistent with the finding of a higher reporting of prolonged PR duration in other races during flare-up treatment.

No dose dependency was seen in the FOP-FAS flare-up treatment nor in the MO-FAS. In the COPD-FAS, no difference between the placebo and palovarotene groups was seen.

ECG and cardiac safety

A thorough QT-study in 32 healthy volunteers aged 18-55 years (PVO-1A-103) evaluated the effect of therapeutic and supratherapeutic doses (up to 50 mg) of palovarotene on QTcF (Fridericia's QT correction). In summary, palovarotene at the studied doses had no clinically relevant effects on studied ECG parameters.

No PCS increase in QTcF or QTcB (Fridericia's and Bazett's QT correction, respectively), defined as QTcB/F prolongation ≥60 ms from baseline and/or QTcB/F >500 ms was reported in the FOP-FAS, neither during chronic nor flare-up treatment.

In FOP, PCS QRS prolongation was the most common new-onset PCS ECG abnormality, identified in 28% of palovarotene subjects during the chronic and in 32% during flare-up treatment periods. Of note, new-onset PCS QRS prolongation was also reported in 22% of the placebo/untreated subjects in the FOP-FAS. It should also be noted that QRS prolongation was very common also before palovarotene treatment. At baseline of the chronic treatment period, PCS prolongation of median QRS intervals was identified in over 30% of the subjects in both the palovarotene group and placebo/untreated subjects. Taken together, with the high number of reports both at baseline and in the placebo/untreated subjects, the association between palovarotene and QRS-prolongation is considered weak.

From the SMQ for torsade de pointes/QT prolongation as of the data cut-off date of 28 February 2020, there were no pro-arrhythmic TEAEs such as torsade de pointes, ventricular tachycardia, ventricular

fibrillation, or flutter, and no sudden death observed across the FOP-FAS, MO-FAS, and COPD-FAS. Events were identified in the COPD-FAS as anticipated with the underlying disease in COPD; however, they occurred primarily during in the post-treatment period. One subject (0.2%) in the COPD-FAS an on treatment ventricular arrhythmia.

TEAEs of syncope occurred in palovarotene groups for all analysis sets. Syncope was identified in 4 of subjects (2.9%) in the ≥8/10 years palovarotene group (3 subjects during the chronic treatment period and in 1 subject during the 20/10 mg treatment period) in the FOP-FAS and none in the placebo/untreated subjects. Two events of syncope were considered serious. Both SAEs were assessed by the Investigator as unrelated to palovarotene. In the MO-FAS, syncope was reported in 1 subject (0.8%) in the palovarotene group (2.5 mg), assessed as possibly related to palovarotene. No action was taken with the study drug in relation to these events and cardiac work-up at the hospital was negative.

An association to torsade de pointes/QT prolongation has not been shown to any of the serious episode of syncope in the FOP-FAS or MO-FAS.

2.5.8.5. Safety in special populations

Intrinsic factors

The safety profile for palovarotene in subjects with FOP was consistent across sex and race/ethnicity; and was also consistent across adult (≥18years) and paediatric (≥8/10 to <18years) age subgroups except for premature physeal closure (PPC), which was (as expected) more common in younger (<8/10 years, 56%) than older (≥8/10 to <18years, 12%) paediatric subjects. Some mucocutaneous effects such as decubitus ulcers had a higher incidence in adult subjects, which was consistent with disease burden, increasing disability, and prolonged exposure to corticosteroids.

In the FOP-FAS, the oldest subject was 61 years at enrolment and the MO-FAS was a paediatric study. The COPD-FAS, with a mean age of 67 years, differs from the target population in both mean age and morbidity and results from this study are not fully applicable to the intended target population. The summary table on adverse events in different age spans is therefore not considered meaningful.

Use in Pregnancy and Lactation

Pregnant and breastfeeding females were excluded from all palovarotene clinical studies. Systemic retinoids are contraindicated in Pregnant and breastfeeding females due to the risk of retinoic acid embryopathy. For further details, please see section *AE by organ system or syndrome*.

2.5.8.6. Immunological events

The most common allergic reaction TEAEs using the Angioedema SMQ across analysis groups were facial swelling and cutaneous hypersensitivity (e.g., urticaria). No significant hypersensitivity reactions such as anaphylaxis or systemic allergic reactions were identified. No allergic reaction TEAEs were severe, serious, or led to study drug discontinuation. Moreover, in the COPD-FAS and MO-FAS, the incidence of allergic reaction TEAEs in palovarotene-treated subjects did not differ from those identified in the placebo group. Considering the provided information, the risk for allergic reactions seems to be low.

2.5.8.7. Safety related to drug-drug interactions and other interactions

Palovarotene belongs to the same pharmacological class as vitamin A. Therefore, concomitant administration of vitamin A and/or other oral retinoids with palovarotene must be avoided because of the risk of hypervitaminosis A.

Pseudotumor cerebri, headache, pancreatitis and hypertriglyceridemia occur with systemic retinoids when co-administered with tetracycline derivatives. Pseudotumor cerebri consists of an elevated intracranial hypertension accompanied by nausea, vomiting, papilledema, vision disturbance and may be aggravated by combined therapy with tetracycline derivatives. Increased risk for photosensitivity may occur with tetracycline class medications.

Concomitant use of a strong CYP3A4 inhibitor such as azole antifungals (e.g., ketoconazole, itraconazole), macrolide antibiotics (e.g., clarithromycin, telithromycin), and nefazodone should be avoided with palovarotene.

Concomitant use of a strong CYP3A4 inducer such as carbamazepine, phenytoin, rifampin, rifabutin or St John's wort extract should be avoided with palovarotene.

The presented drug-drug interactions were reflected in the proposed SmPC.

2.5.8.8. Discontinuation due to adverse events

TEAEs leading to dose modifications (i.e., dose reductions) were reported in 50 of 139 subjects (36.0%) in the ≥8/10 years palovarotene group, including 10 of 131 subjects (7.6%) during chronic treatment and 45 of 105 subjects (42.9%) during 20/10 mg flare-up treatment. The most common TEAEs leading to dose modification (≥5% of subject in the palovarotene group) were mucocutaneous in the SOC of Skin and subcutaneous disorders.

TEAEs leading to interruption of study drug dosing occurred in 27% of subjects in the ≥8/10years palovarotene group.

TEAEs leading to permanent study discontinuation in the ≥8/10 years population are summarised in Table 48 and TEAEs leading to permanent study drug discontinuation in Table 49.

Table 48 TEAEs Leading to Permanent Study Discontinuation, Age at First Entry ≥8/10 Years (FOP-FAS)

	28 February 2020 Cutoff			30 July 2021 Cutoff		
Preferred Term, n (%)	Chronic 5 mg (N=130)	Flare-up 20/10 mg (N=100)	PVO Total (N=139)	Chronic 5 mg (N=131)	Flare-up 20/10 mg (N=105)	PVO Total (N=139)
Any TEAE	3 (2.3)	1 (1.0)	4 (2.9)	3 (2.3)	1 (1.0)	4 (2.9)
Cellulitis	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Epiphyses premature fusion	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Intentional self-injury	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Dry skin	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)

Table 49 TEAEs Leading to Discontinuation of Study Drug, Age at First Entry ≥8/10 Years (FOP-FAS)

System Organ Class Preferred Term, n (%)	28 February 2020 Cutoff			30 July 2021 Cutoff		
	Chronic 5 mg (N=130)	Flare-up 20/10 mg (N=100)	PVO Total (N=139)	Chronic 5 mg (N=131)	Flare-up 20/10 mg (N=105)	PVO Total (N=139)
Any TEAE	5 (3.8)	5 (5.0)	10 (7.2)	6 (4.6)	5 (4.8)	11 (7.9)
Infections and infestations	1 (0.8)	3 (3.0)	4 (2.9)	1 (0.8)	3 (2.9)	4 (2.9)
Cellulitis	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Furuncle	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Localised infection	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Parainfluenzae virus infection	0	1 (1.0)	1 (0.7)	0	0	0
Haemophilus infection	0	0	0	0	1 (1.0)	1 (0.7)
Musculoskeletal and connective tissue disorders	1 (0.8)	1 (1.0)	2 (1.4)	1 (0.8)	1 (1.0)	2 (1.4)
Epiphyses premature fusion	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Mobility decreased	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Skin and subcutaneous tissue disorders	1 (0.8)	1 (1.0)	2 (1.4)	1 (0.8)	1 (1.0)	2 (1.4)
Dry skin	1 (0.8)	1 (1.0)	2 (1.4)	1 (0.8)	1 (1.0)	2 (1.4)
Erythema	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Ingrowing nail[a]	0	0	0	0	0	0
Investigations	0	0	0	1 (0.8)	0	1 (0.7)
Amylase increased	0	0	0	1 (0.8)	0	1 (0.7)
Lipase increased	0	0	0	1 (0.8)	0	1 (0.7)
Metabolism and nutrition disorders	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Malnutrition	0	1 (1.0)	1 (0.7)	0	1 (1.0)	1 (0.7)
Nervous system disorders	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Myoclonus	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Psychiatric disorders	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)
Intentional self-injury	1 (0.8)	0	1 (0.7)	1 (0.8)	0	1 (0.7)

2.5.8.9. Post marketing experience

Not applicable.

2.5.9. Discussion on clinical safety

Palovarotene is a RARγ agonist. Systemic retinoids have a broad spectrum of class effects: mucocutaneous effects, skeletal effects, and ocular system abnormalities such as persistent dry eye, teratogenicity, and poor pregnancy outcomes. In general, the safety profile of palovarotene was consistent with other systemic retinoids, for example isotretinoin, which is reflected in the proposed label. At the doses and systemic exposures used in the FOP studies to prevent HO, palovarotene inhibits significantly chondrogenesis in growth plates and has dose-related effects on bone size or mass and/or changes in bone shape. Long-term use of other systemic retinoids in humans is known to be associated with a variety of effects on the musculoskeletal system, including PPC, osteoporosis, an increased risk for fracture and avascular necrosis of femoral head as well as hyperostotic changes or

calcification of tendons and ligaments effects. Similarities to hypervitaminosis A syndrome are obvious and are due to the chemical relationship between retinoids and vitamin A.

Safety database

The safety of palovarotene has been examined in 164 subjects with FOP receiving at least one dose of the drug and including 139 subjects ⩾8/10 years. 95% of the subjects in the ⩾8/10 years group were on study for at least 12 months. Supportive studies have enrolled over 1,200 subjects and include one noninterventional NHS of FOP, one study in paediatric participants with MO, 5 studies in participants with COPD, and 12 studies in healthy volunteers.

The integrated analysis sets were central for evaluating the safety profile of palovarotene, comprising safety data from healthy volunteers (HV-FAS), subjects with FOP from Phase 2 and 3 studies and from a noninterventional Study PVO-1A-001 (FOP-FAS), subjects with MO from a single Phase 2 study (MO-FAS), and subjects with smoking-related, moderate-to-severe COPD from Phase 1 and 2 studies (COPD-FAS). The FOP-FAS population is considered most important and relevant for this application. Safety data from the COPD-FAS is also interesting and supportive, since it includes a larger placebo comparison for the chronic treatment dose of 5 mg up to 24 months than available from the very small number of untreated/placebo subjects FOP-FAS. Some support is also provided by the MO-FAS, which provides limited placebo-controlled data in children treated with 2.5 or 5 mg palovarotene for a mean duration of 32 weeks.

Comparisons within and across analysis sets had noteworthy caveats. In the FOP analysis sets, the placebo group was small (N=10) and had a comparatively brief mean duration of follow-up compared with the ⩾8/10 years palovarotene group (~12 weeks vs ~192 weeks). Therefore, the most appropriate comparator group would be the untreated subjects (n=20) from Study PVO-1A-001. However, in Study PVO-1A-001, only events associated with study procedures were recorded as AEs, making the AE comparison with palovarotene-treated subjects uninformative. Comparisons to the COPD-FAS were compromised by large differences in the demography of the study populations. The mean age was considerably higher in the COPD-FAS (63.7 years) versus FOP-FAS (19.1 years). Furthermore, the COPD-FAS represents a population with major comorbidity. The FOP was also unique with respect to palovarotene exposure, as palovarotene 20/10 mg flare-up treatment, which aside from single supramaximal doses administered to healthy volunteers for the TQT study, was the highest daily dosage administered to subjects in any study. This issue is further complicated by censoring, since comparisons of the incidence TEAE across the chronic and flare-up treatment periods are confounded by the possible allocation and carryover of TEAEs that may be associated with the higher palovarotene doses during flare-up treatment.

Exposure

As of 30 July 2021 cut-off, 88%% of the subjects in the ≥8/10 years group were on study for at least 72 months. The mean exposure to the 20/10 mg flare-up treatment was 35.1 weeks compared to 78.9 weeks to the chronic 5 mg dosing. In the 10 placebo treated subjects in study PVO-1A-201, mean exposure time was 6 weeks. This has to be taken into consideration comparing the number of adverse events in the different dosing groups.

For comparison, the mean duration of palovarotene dosing in the ≥8/10 years palovarotene group of the FOP-FAS was 102.4 weeks (approximately 720 days), versus a mean palovarotene treatment duration of 226 days in the MO-FAS and 397 days in the COPD-FAS. In the MO-FAS and the COPD-FAS, the highest dose was 5 mg.

As of 28 February 2020 cut-off, the mean duration of flare-up treatment progressively increased from 5.9 weeks for palovarotene 5/2.5 mg, to 11.0 weeks for 10/5 mg, to 33.2 weeks for the 20/10 mg flare-up regimen. The corresponding mean total doses during flare-up treatment were 123 mg and 482

mg for the 5/2.5 mg and 10/5 mg flare-up treatments, respectively. The mean total dose for the 20/10 mg flare-up treatment was 2,833 mg. The applicant explained that these differences were due to the adaptive design of the studies and how the treatment regimens evolved. This might be correct in principle; however, it may also reflect the ineffective outcome of the proposed lower chronic dose.

Considering that treatment in flare-up seems most important and treatment duration was needed for longer times and probably will be repeated frequently during lifetime, it might be questioned whether exposure in the population is sufficient to assess reliably the safety profile of palovarotene in the target population. In addition, exposure in the presented population was highly heterogeneous due to the adaptive design and the frequent changes in dose (chronic versus flare, dose reductions and treatment interruptions), which increases the concern. Considering the substantial need of dose reductions, due to TEAEs, it seems unlikely that the current safety information fully reflects the risks for the patients treated with the intended posology. Moreover, the cumulative doses administered in the patients are likely to be multiple higher than currently evaluable and long-term safety remains not adequately assessable, as often for products used for the treatment of orphan diseases.

Adverse events

The most common adverse events were from the SOC skin disorders, reported in 99% of the palovarotene treated subjects in the ⩾8/10 Years FOP-FAS. The most reported TEAES of any SOC were dry skin, dry lips, arthralgia, alopecia, pruritus, pain in extremity, erythema, rash, pruritus generalised, and skin exfoliation. Of note, skin exfoliation was generally peeling skin.

Several skin disorder TEAEs (pruritus, erythema, skin exfoliation, and drug eruption) were seen ⩾50% more frequently with flare-up 20/10 mg treatment than with chronic treatment. The duration of treatment was markedly longer for the "5 mg chronic" versus the "20/10 mg flare-up" dose (~79 weeks vs ~35 weeks) and even shorter in the placebo/not-treated arm. Upon request, the applicant provided a summary of reported TEAE normalised for exposure. There was a higher rate of TEAE in the flare-up 20/10 mg group (1379 events per 100 patient years at risk) compared with the chronic 5 mg group (692 events per 100 patient years). A similar pattern was seen with SAEs. This indicates that the dose effect on AEs is underestimated.

Upon request, the applicant summarised discontinuations, dose interruptions and reduction of dose during chronic (5 mg) treatment, and flare-up (20/10 mg) treatment. The percentage of subjects reporting a dose reduction in Study 301 was dose dependent (20 mg: 45%; 10 mg: 12%; and 5 mg: 3%), indicating that there may be a tolerability issue with the highest dose. In this context, it should also be taken into consideration that the duration of treatment was longer in the chronic phase compared to flare-up treatment. Notwithstanding, at least 25% of the subjects actually received 20 mg during High-dose flare-up (median dose 14.3 mg [Q1, Q3 11.7, 20.0]), indicating that even though there in fact seems to be tolerability issues with the highest dose, at least a fraction of the patients tolerated the dose.

Long-term safety remains not adequately assessable. The applicant has proposed to follow this issue in the planned PASS (Voluntary Registry Study [CLIN-60120-453]). This could be acceptable provided that the benefit risk of the product is considered positive.

Serious adverse events, death and other significant adverse events

Fifty (50) palovarotene treated subjects in the FOP-FAS ⩾8/10 Years cohort experienced treatment-emergent SAEs. Most frequently reported SAE PT was PPC in 9 palovarotene subjects (6.5%) in the ⩾ 8/10 Years FOP-FAS. Other SAEs reported for more than one subject were corona infection, pneumonia (4 subjects each), arthralgia, pain in extremity, cellulitis, condition aggravated (3 subjects each), back pain, abdominal pain, tooth impacted, peripheral swelling, pain, syncope, and respiratory distress (2 subjects each). All other PTs were reported in single instances, and some were reported in the same

subject.

No SAE of condition aggravated was reported in placebo/untreated. The applicant has presented additional analyses to determine whether palovarotene flare-up treatment may have caused subsequent additional flare ups; indicating that an increased risk of additional flare-ups after flare-up treatment does not seem probable.

Eleven subjects (8%) in the ⩾8/10 Years cohort reported TEAEs leading to permanent study drug discontinuation, the only event reported by more than one subject was dry skin (2 subjects). No subjects in the placebo/untreated group permanently discontinued study treatment.

There were no deaths during treatment in the FOP-FAS or MO-FAS. In the FOP-FAS, one fatal event was reported 2.5 months after discontinuing palovarotene treatment. The cause of death was due to restrictive lung disease from complications of FOP and it is agreed with the applicant that a causal association to palovarotene treatment is unlikely in this case and that alternative explications to the fatal event (disease progression, complications of FOP) are more probable.

Premature physeal closure

Systemic retinoids have been associated with premature closure of the epiphyses (premature physeal closure; PPC). PPC is not considered reversible and may be associated with growth arrest, leg length discrepancy, disproportionate growth (epiphyseal growth plate closure preferentially affecting the lower extremities), angular deformity in affected joints, and gait disturbance.

A partial clinical hold was instituted by the US FDA on 04 December 2019 since the percentage of PPC-SAEs was higher in the <8/10 years palovarotene group and occurred in 48% of the younger population. Consequences were an immediate interruption of dosing in all subjects under the age of 14 years based on the serious identified risk of PPC. All subjects <14 years of age discontinued dosing at that time and remain off-treatment. In this context, it remains questionable that the applicant applies for treatment of subject >8/10 years.

As of 30 July 2021, PPC was reported for 26/102 subjects (26%) <18 years of age in the FOP-FAS, including 22 subjects with treatment emergent events and 4 subjects with post-treatment events. The incidence of PPC varied across FOP-FAS paediatric age categories, from 12% for subjects ⩾8/10 to <18 years, to 23% for ⩾8/10 to <14 years, to 56% for <8/10 years. No PPC events were reported in subjects over the age of 14 years.

PPC in the FOP-FAS appeared as early as Month 6, which is earlier than what is reported in general retinoid class literature and no correlation between the risk of PPC and palovarotene exposure could be shown.

The median onset of HO involvement of axial/cranial body regions is 6 years of age. In FOP, it would therefore be important to intervene as early as possible to preserve physical function. However, due to the risk of PPC, the applicant's proposal is to restrict the indication to patients 8 years of age and older for females and 10 years of age and older for males with FOP, i.e., the ages at which patients on average achieve approximately 80% of their adult height. For a boy, this could mean the difference between 180 cm and 144 cm in final height. To outweigh such a risk, the benefit of the drug needs to be compelling if the risk cannot be mitigated. Notwithstanding, as stated by the applicant, the results suggest that there is no consistent effect of increased exposure to palovarotene that is associated with PPC and that all skeletally immature subjects receiving palovarotene are at risk.

In order to further address this, the applicant has summarised change in HO Volume per subject and the number (%) of subjects with PPC at different ages at baseline in order to numerically illustrate the benefit/risk ratio of palovarotene with regard to PPC. All subjects but one developing PPC were ⩾8/10 but ⩽12 years old at baseline. The remaining subject developing PPC was >12 but ⩽14 years old at

baseline; thus, in this study population, 89% of all events of PPC were reported in subjects with a baseline age of ⩾8/10 but ⩽12 years. The risk of developing PPC for a subject ⩾8/10 but ⩽12 years old at baseline was 14% compared to 3% in subjects >12 but ⩽14 years old at baseline. This difference is not considered negligible.

For clinical benefit, the applicant has provided a comparison on change from baseline between treated and untreated subjects. Of note, for none of the age cohorts (baseline age ⩾8/10 but ⩽12 years, >12 but ⩽14 years, >14 but ⩽16 years, and >16 but ⩽18 years), the difference between the treatment arms was statistically significant, although in all age cohort there was a trend for a lower increase in HO volume in the palovarotene arm. However, in absolute numbers, the difference of the outcome in the age cohorts ⩾8/10 but ⩽12 years and >12 but ⩽14 years was limited. It is therefore questioned that the risk of PPC is overruled by clinical benefit in this age span. Additionally, the clinical efficacy of Sohonos altogether has not been demonstrated (see section 2.5.6. clinical efficacy discussion).

In a renewed discussion as response to the Day 180 LoQ on the risk for PPC in subjects with immature skeleton contra the advantage with early treatment of FOP to avoid irreversible damage, the applicant argues in support of keeping the ⩾8/10 year-limit for palovarotene treatment. The applicant emphasises that most events of PPC did not represent a total physeal closure but a partial, and that some events may in fact represent an early physiological physeal closure. The applicant also informed that before the clinical hold, approximately half of the patients, or their caregivers, chose to continue treatment when they were told about having signs of PPC. Furthermore, the applicant emphasises that the risk for PPC decreases by age and that only one subjects with baseline age >12 years reported an event of PPC.

The applicant has proposed to expand the information on PPC in section 4.4 of the SmPC. The wording is proposed to include monitoring of growth and radiographs every 6 to 12 months during chronic treatment and every 3 months during flare-up treatment, so that subjects who begin to show early signs of physeal closure can pause treatment and re-assess risk benefit with their healthcare provider based on individual determination. A PASS following this issue is also proposed.

The proposed risk minimisation measures are not considered adequate and feasible. The progression rate of PPC needed to establish the frequency of radiological monitoring needed to allow sufficient time to detect early signs of PPC and reassess treatment before physeal closure is complete is not established. Furthermore, it is not established that assessments of early physeal closure could be robustly performed by radiologists at smaller hospitals in order to avoid cumbersome travelling for routine monitoring. Moreover, it is not established that palovarotene induced PPC, when identified at an early stage, is possible to stop or slow down with treatment interruption. Finally, repeated radiology one to four times per year for from the age of 8/10 years up to skeletal maturity is considered to be associated with radiation hazards.

In the pivotal study 301, all subjects <18 years of age with an immature skeleton were to use a weight-based posology. This indicates that a main reason to introduce weight-based dosing in children was the risk of PPC. With the currently proposed age limit (⩾8/10 years) not accepted due to the risk for PPC, the age-dependent, weight-based approach needed further discussion. Upon request, the applicant has clarified that there is no indication of any specific safety concern except PPC in the paediatric versus the adult subpopulations. Based on this, the applicant has proposed a weight-based dosing for the entire population. This is considered acceptable since there seems to be some tolerability issues with higher doses. Furthermore, it is anticipated that there are adult subjects with a low body weight in whom the exposure with the "5/20/10 mg-dosing" may be unnecessary high. However, some subjects with a body weight <60 kg and over the age of 14 years will receive a lower dose and thus a lower exposure compared to the pivotal study. Therefore, if the benefit risk balance of the product was considered positive, the section 4.2 of the SmPC should be updated with the

information that the "5/20/10 mg-dosing" has been used in subjects <60 kg and mature skeleton in clinical studies and thus, this dose, may be tried in such subjects with unsatisfying effect and good tolerance to the lower dose.

Musculoskeletal events

Arthralgia was the most commonly observed musculoskeletal TEAEs across palovarotene groups. Since FOP subjects are likely to have joint immobility from ankylosis due to HO and multiple bone deformations, this was expected. Moreover, an increased risk of fracture of both normotopic and heterotopic bone due to a greater risk of falls, immobility, and prednisone use may be caused by the disease itself. Normotopic and heterotopic bone fractures were reported from 6.7% of palovarotene treated subjects in the overall FOP-FAS and increased in the ⩾8/10 years palovarotene group up to 9.4%.

Considering that untreated subjects with FOP (NHS) had a high background prevalence of fractures (36%) and the incidence of fractures in the palovarotene group was similar to the incidence of new fractures in untreated NHS subjects (8%) over 3 years of observation, no hazard signal can be identified that clearly indicate an increased risk for the target population with FOP.

The consequences for bone safety during longer, potentially life-long, treatments are not known. Chronic toxicities from long term therapy with other retinoids are known to increase the risk for occurrence of skeletal abnormalities, usually mimicking diffuse idiopathic hyperostosis syndrome (DISH). In contrast to other side effects of retinoids, which are dose dependent and reversible upon withdrawal of the drug, it seems unlikely that bone abnormalities will resolve after discontinuation of the medication, questioning whether the palovarotene efficacy benefits presented for the FOP-population are counteracted by the DISH safety risk. Even though no event of DISH or DISH-like symptoms were reported in the FOP population, this is considered a class effect. In this context, it should be taken into consideration that the studied population is very limited. Furthermore, palovarotene, unlike e.g., Roaccutane, is intended for long-term, even life-long, treatment. Thus, it seems probable that cases could occur with the use of palovarotene.

Based on the findings in the MO-FAS, indicating a loss of bone mineral density in the palovarotene group that was both dose- and time-dependent, non-clinical data and case reports of osteoporosis and fractures reported in patients receiving systemic retinoids, a signal on Bone Safety was raised to assess the possible causal relationship between palovarotene treatment in Study 301 (MOVE) compared with standard of care only (i.e., palovarotene untreated) in Study 001 (NHS) and selected bone safety outcomes in subjects with FOP. No validation for the methods, baseline data or discussion of the clinical relevance of the results were provided. Nonetheless, the data indicate a negative impact of palovarotene treatment on bone strength and mineralisation, and a threefold higher risk of new-onset radiological vertebral fractures in palovarotene treated versus untreated FOP subjects. Fractures, including radiological spinal fractures are considered adverse drug reactions of palovarotene with a frequency very common.

In the context of bone related SAEs, adult subjects in the palovarotene group had five treatment emergent SAEs under Injury, poisoning, and procedural complications related to fractures (ankle, femur, humerus, skull, and fracture of heterotopic ossification) reported in one subject each. The outcome of fracture healing is not reported. The impact of palovarotene on fracture healing remains unknown. Palovarotene's mechanism of action and concomitant longer exposure with corticosteroids, which seems inevitable needed during flare episodes, are likely to have an impact on fracture healing. There is currently no evidence in the palovarotene studies to suggest an impact on fracture healing with palovarotene treatment, however, palovarotene's mechanism of action is compatible with a negative impact on fracture healing. Therefore, fractures and impaired fracture healing are considered important potential risks of palovarotene.

Taken together, significant uncertainties regarding bone safety remain. If the benefit risk balance was considered positive, as risk mitigation measures, the applicant should have extended the warning on "Radiological spinal fractures" in section 4.4 of the SmPC to all aspects of bone safety including DISH/DISH-like symptoms and fractures/impaired fracture healing, and label "Fractures" in section 4.8 with a specification below the table which kinds of fractures have been observed. The Applicant has proposed to include "radiological vertebral fractures" as an important identified risk, and "fractures" and "Diffuse idiopathic hyperostosis syndrome (DISH)" as Important potential risks in the RMP and in the proposed PASS which is accepted. However, it is considered that the wording should read "Fractures and impaired fracture healing" instead of "fractures".

Teratogenicity

Teratogenicity is an important identified risk in the palovarotene clinical program and a well-known class effect of systemic retinoids. Although there were no pregnancies in the palovarotene development program, findings in toxicology studies demonstrate characteristic patterns of foetal malformations typical of retinoids.

Consequently, palovarotene is contraindicated in women who are pregnant or breastfeeding and in females of childbearing potential unless all conditions of the pregnancy prevention are met, or they are not at risk for pregnancy. Furthermore, a "boxed warning" and a pregnancy prevention program is proposed in section 4.4 of the SmPC. This is in line with the SmPC for other systemic retinoids, e.g. isotretinoin, and agreed. Of note, the severe disease burden of FOP results in low reproductive fitness; fewer than 10 multigenerational families are known worldwide.

"Teratogenicity" is listed as an Important identified risk in the proposed RMP. As risk mitigating measures, the applicant proposes an educational material and to collect any reports of use during pregnancy in a planned product registry.

The proposals are fully agreed.

Retinoic acid syndrome

RAS is a potentially life-threatening complication described mainly and most frequently in subjects with promyelocytic leukaemia treated with all-trans retinoic acid (ATRA). Although it is fully acknowledged that no single case is reported in the safety population of palovarotene, it needs to be considered that retinoids are essential in the regulation of a broad range of biological processes and have an impact on the immune system. However, as typical risk factors for RAS in patients with APL, such as elevated white blood cells, or creatinine, are not present in typical patients with FOP, no specific information and warnings in the product information are considered needed. The applicant proposes that RAS/RAS-like events will be monitored in the FOP setting, and risk management activities will be implemented if needed, which is considered adequate.

Mucocutaneous effects

Mucocutaneous effects are an identified risk in the palovarotene program and the most common TEAEs were dry skin, dry lips, alopecia, pruritus, and erythema. Palovarotene may contribute to an increased risk of skin and soft tissue infections, due to a decreased skin barrier from retinoid mucocutaneous effects such as dry and peeling skin. In addition, concomitant systemic corticosteroid use, a standard of care in FOP patients, may lead to fragile skin and make subjects more susceptible to infection and skin breakdown. The applicant proposes guidance with respect to the treatment of mucocutaneous events and to the potential risks of excessive sun exposure in the label, which is considered adequate. It is to be noted that there was a higher incidence of mucocutaneous TEAEs during the palovarotene 20/10 mg flare-up treatment period compared with the chronic treatment period (41% vs 8%, respectively). This suggests an impressive dose dependent effect of palovarotene regarding

mucocutaneous adverse events.

It is considered notable that 58% of the female subjects in the FOP-FAS reported alopecia. Notwithstanding, no events led to discontinuation and therefore the proposed SmPC wording is considered sufficient.

Systemic retinoid class effects

Systemic retinoids have a broad spectrum of class effects, several of these have been reported also for palovarotene, whereas others have not been reported, or reported at a very low number.

The current exposure to palovarotene is not sufficient to rule out a class effects of systemic retinoids. The applicant has amended section 4.4 of the SmPC with a wording on systemic retinoid class effects which are not already labelled for palovarotene, including recommendation on monitoring, to alert prescribers that new onset of such events may be an adverse drug reaction to palovarotene. "Intracranial hypertension or pseudotumor cerebri in the absence of cotreatment with tetracycline", should have also been included as such events have been reported for other systemic retinoids. The applicant has also included increased liver enzymes and elevated triglycerides in the label with adequate recommendation of monitoring.

Psychiatric disorders

Depression, aggravated depression, anxiety, mood alterations, and suicidal thoughts and behaviours have been reported in patients treated with systemic retinoids. Individuals with a personal history of psychiatric illness may be more susceptible.
While no psychiatric disorder TEAEs were reported in the Placebo/untreated subjects, there was a dose dependent increase in such event during palovarotene treatment. There was one event of "Completed suicide" was reported with PVO treatment in the COPD-FAS and one subject in the ≥8/10 years palovarotene FOP-FAS cohort discontinued study treatment due to intentional self-injury. The section 4.4 of the proposed SmPC includes adequate recommendation for monitoring.

Carcinogenicity

Carcinogenicity TEAEs were obtained from a search for preferred terms under the SOC of Neoplasms benign, malignant and unspecified (incl. cysts and polyps). The search retrieved 15 events in the ⩾ 8/10 Years FOP-FAS, all during palovarotene treatment. This may in part be explained by the lower follow up time in the placebo/untreated group. In the FOP-FAS and MO-FAS, all events in this SOC but one (Neuroendocrine tumour with unknown malignancy status) were benign. Pyogenic granuloma (periungual) was the most reported event in the palovarotene group. The applicant argued that this could be associated with paronychia, which is reported in retinoid treatment. The applicant has proposed to label pyogenic granuloma in section 4.8 of the SmPC. This is accepted.

The population in the COPD-FAS differs markedly from the other palovarotene treated population, as COPD is associated with higher age and a history of smoking, both of which increases the risk of malignancies. However, the number of malignant neoplasms were similar in both treatment arms in the COPD-FAS. No indications of an increased risk of carcinogenicity emerged from the palovarotene non-clinical development program. It is agreed with the applicant that despite the difference in reporting between treated and not treated subjects in the FOP-FAS, no firm conclusions can be made based on currently available data.

Laboratory findings

No systematic laboratory investigations were planned to screen the effect of palovarotene with respect to hormonal effects. However, interaction with nuclear receptor RXR is also described in the literature for retinoids (Graeppi-Dulac et al, 2014). This effect is observed in nearly 100% of the patients treated

with high dose retinoids (e.g., bexarotene) prompting routine concomitant L-T4 treatment. The applicant hypothesises that the difference in central hypothyroidism between bexarotene and palovarotene may be due to differences in mechanism of action. This has not been further elaborated. Upon request, the Applicant has summarised events of thyroid dysfunction. Both increasing and decreasing thyroxine levels has been reported and there is no general indication of increased risk for central hypothyroidism, as both low and high TSH has been reported. Thyroid-associated AEs are not labelled or discussed in the SmPC for isotretinoin. Provided that the benefit-risk was positive, the applicant committed to follow thyroid-associated AEs post-marketing, but not to reflect the risk of thyroid-associated AEs in the SmPC for the time being. This would have been acceptable.

In this paediatric population ~11% of the subjects have missing haematology or clinical chemistry assessment which increased to ~32% at 12 months. Although this seems relatively high on the first glance, the limitations may be acceptable considering the difficulties in clinical trials in paediatric orphan populations. The Applicant's view that missing values do not impact the overall safety profile is not fully shared, however, this issue is not further pursued.

There were no apparent safety concerns related to cardiac safety parameters. ECG abnormalities in FOP-FAS were consistent with known cardiac abnormalities in patients with FOP as observed in the untreated subjects from Study PVO 1A 001. However, there was a higher proportion of subjects reporting potentially clinically significant (PCS) low heart rate palovarotene treated versus placebo/untreated subjects in both the FOP-FAS and the MO-FAS. The Applicant has defined PCS changes in heart rate as <55 beats per minute (bpm) and/or decrease of ⩾20 bpm from baseline. With this definition, 43/130 (34%) of the subjects in the chronic treatment period and 49/106 (46%) in the flare-up treatment period in the FOP-FAS were reported with new onset. Among the placebo/untreated subjects, 8/107 (10%) in the chronic period and 5/71 (13%) in the flare-up period reported new onset PCS low heart rate. Of these events, a total of three events represented heart rate <55 bpm. The Applicant proposes that in some cases, a decrease in heart rate may represent a normal maturation in paediatric patients.

Nevertheless, for subjects in the target population (⩾8/10 years and above), eight subjects reached a new onset heart rate <60 bpm, which is given as the lower limit of normal for school children in at least some publications. Even though reports of bradycardia seem to be rare in the pivotal study, decreased heart rate is not uncommon. The applicant was asked to reflect this in section 4.8 of the SmPC.

2.5.10. Conclusions on the clinical safety

Due to the single-arm open-label pivotal study design, it is challenging to assess the safety profile of palovarotene at the intended dosing regimen in the target population. Available data suggests that the AE profile of palovarotene as far as currently evaluable is consistent with other known systemic retinoids consisting mainly of mucocutaneous and musculoskeletal AEs, and negative effects on linear growth and bone maturation in growing children. Teratogenicity and ocular side effects are known important class effects. PPC in growing children has been observed in the FOP clinical program for palovarotene and led to an interruption of the clinical trials by the FDA and the decision that all subjects <14 years of age had discontinued dosing and remain off-treatment. To outweigh such a risk, the benefit of the drug needs to be compelling if the risk cannot be mitigated. The applicant's proposal to restrict the indication to females >8 years and males>10 years of age cannot be supported.

In addition, the risk minimisation measures for PPC in subjects with an immature skeleton proposed by the applicant are not considered adequate and feasible.

2.6. Risk Management Plan

2.6.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns (RMP version 3.1, dated 07 November 2022)

Summary of safety concerns	
Important identified risks	Teratogenicity Premature Physeal Closure including inhibition of long bone growth (in growing children) Radiologically observed vertebral fractures
Important potential risks	Fractures
Missing information	Long term safety

2.6.2. Pharmacovigilance plan

Table Part III.3: On-going and planned additional pharmacovigilance activities (RMP version 3.1, dated 07 November 2022)

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3: Required additional pharmacovigilance activities				
Study Short Name: Voluntary Registry Study (CLIN-60120-453) An International Observational Registry Study to Further Describe Long-term Safety and Effectiveness of Palovarotene in Patients with Fibrodysplasia Ossificans Progressiva (FOP). (Planned)	*Primary Objective:* The objective of this registry study is primarily to collect and assess real-world safety data on paediatric and adult patients with FOP treated with palovarotene and secondly, to describe the effectiveness of this treatment, including its effect on physical function. As part of data collected in this registry, incidence of pregnancies and their outcome will be reported, recorded and analysed. Pregnant women who have previously received and discontinued palovarotene at any time during the	• Teratogenicity • Premature Physeal Closure • Radiologically observed vertebral fractures • Fractures • Long Term Safety	Study start date:	Participant enrolment will start from the date of palovarotene availability in said country and once the investigational site has been activated.
			Study end date (LPO):	Approximately 10 years (from first participant, first visit) with a minimum of 1-year data collected for participants who enrolled within that period
			Target start date of data collection:	November 2022 in Canada
			Interim reports :	Every 2 years
			Planned end of data collection:	November 2033

	pregnancy will be included for safety follow-up. Also, frequency, severity and descriptive details of any fractures, and PPC will be measured along with height velocity and difference between chronological age and bone age for growing children.		Protocol submission due date	Within 6 months of EC decision

2.6.3. Risk minimisation measures

Table V.3 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern (RMP version 3.1, dated 07 November 2022)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Teratogenicity **(Important identified risk)**	Routine risk minimisation measures: • *A black box warning* • *Prescription-only medicine* • *SmPC Section 4.2, 4.3, 4.4 and 4.6* • *Package Leaflet Section 2* Additional risk minimisation measures: • *Educational Programme*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Voluntary Registry Study (CLIN-60120-453)*
Premature Physeal Closure including inhibition of long bone growth (in growing children) **(Important identified risk)**	Routine risk minimisation measures: • *Continued monitoring is recommended every 6-12 months during chronic treatment and every 3 months during flare-up treatment until patients reach skeletal maturity or final adult height* • *Temporary interruption during the evaluation period or permanent discontinuation of treatment should be made based on individual benefit-risk determination* • *Prescription-only medicine* • *SmPC Section 4.2, 4.4, and 4.8* • *Package Leaflet Section 2* Additional risk minimisation measures: • *Educational Programme*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Voluntary Registry Study (CLIN-60120-453)*

Radiologically Observed Vertebral Fractures **(Important identified risk)**	Routine risk minimisation measures: • *Periodic radiological assessment of the spine is recommended.* • *Prescription-only medicine* • SmPC Section 4.4, 4.8, and 5.3 • *Package Leaflet Section 2 and 4* Additional risk minimisation measures: *Educational Programme*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: *Voluntary Registry Study (CLIN-60120-453)*
Fractures **(Important potential risk)**	Routine risk minimisation measures: • *Periodic radiological assessment of the spine is recommended.* • *Prescription-only medicine* • *SmPC Section 4.8 and 5.3* • *Package Leaflet Section 2 and 4* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: *Voluntary Registry Study (CLIN-60120-453)*
Long Term Safety **(Missing Information)**	Routine risk minimisation measures: • *None* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Voluntary Registry Study (CLIN-60120-453)*

2.6.4. Conclusion

The CHMP and PRAC, having considered the data submitted in the application were of the opinion that due to the negative benefit-risk, the risk management plan cannot be agreed at this stage.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

Not applicable

2.8. Product information

In light of the negative opinion, a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

However, in light of the negative opinion, a satisfactory package leaflet cannot be agreed at this stage.

2.8.2. Labelling exemptions

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The Group agreed on an English only blister. However, for markets where a high demand is expected (e.g. DE, FR, IT and ES) the use of multilingual packs should be considered by the applicant. BE would also like to request the applicant to consider having a multilingual pack in the three local languages (DE/FR/NL), if feasible. For the other markets, the use of an outer carton in English only would be acceptable.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.8.3. Additional monitoring

Not applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication for palovarotene therapy is:

"Sohonos is indicated for the treatment for the prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia (myositis) ossificans progressiva (FOP)."

FOP is an ultra-rare, severely disabling disease characterised by painful, recurrent episodes of soft tissue swelling (flare-ups) and abnormal bone formation. Lesions begin in early childhood. There are approximately 800 confirmed cases of FOP globally. The prevalence is estimated at approximately 1.36 per million individuals, with no geographic, ethnic, racial, or sex preference. The result of recurrent extra-skeletal bone formation, HO is cumulative immobility, with patients becoming wheelchair-bound or bedridden by the third decade of life. Life-threatening complications include severe weight loss due to ankylosis of the jaw, and respiratory insufficiency due to ankylosis ossification of thorax and progressive spinal deformity. Thoracic insufficiency commonly causes complications such as pneumonia and right-sided heart failure, leading to markedly shortened survival (Kaplan-Meier median survival is 56 years).

Palovarotene is an orally bioavailable RARγ agonist. RARγ are expressed in chondrogenic cells and chondrocytes where they operate as unliganded transcriptional repressors. The aim of the treatment is to prevent HO formation and improve symptoms.

3.1.2. Available therapies and unmet medical need

Currently, there are no effective medical treatment options to prevent flare-ups, HO, or disease progression in FOP. Surgical resection of heterotopic bone is not recommended as it can exacerbate flare-ups and further HO formation. Current pharmacologic intervention for FOP is limited to palliative management and is not known to be disease modifying. Medications used to treat FOP include high-dose corticosteroids, oral or topical acetaminophen, NSAIDs in combination with a proton pump inhibitor, cyclooxygenase-2 (COX-2) inhibitors, muscle relaxants, opioids, gabapentin, pregabalin, or tricyclic antidepressants.

3.1.3. Main clinical studies

The application is based on a single pivotal clinical study PVO-1A-301 (MOVE).

This is a multicentre, single-arm, open-label, phase 3 study in 107 adult and paediatric subjects with FOP. The results are compared with data collected from a 3-year, longitudinal, non-interventional NHS in 114 subjects with FOP due to the R206H mutation.

A phase 2 open-label extension study PVO-1A-202/204 study enrolled 54 subjects and provides important follow-up data up with palovarotene treatment up to 3 years. The results from this study may also be compared with NHS as similar doses were used and similar endpoints were recorded in this study. An earlier placebo-controlled dose finding study PVO-1A-201 tested two active doses 5/2.5mg and 10/5mg at flare-up.

Based on the serious identified risk of PPC, a partial clinical hold was implemented on subjects <14 years old on 04 December 2019 in ongoing palovarotene program including main study PVO-1A-301 and PVO-1A-202/204. Shortly after, the sponsor paused dosing for all remaining subjects (14 years and older) in the FOP palovarotene program on 24 January 2020 due to futility. After that, the sponsor became unblinded to all study data.

3.2. Favourable effects

Palovarotene's effect on HO was investigated in two *in vivo* studies using a mouse model for the disease. When administered prior to injury, palovarotene reduced or eliminated HO formation and a dose-response relationship was demonstrated.

The first dose finding study PVO-1A-201 did not meet its primary responder endpoint, nearly all participants had "no or minimal new HO" at week 6. Sparse data from 9 participants by week 12 indicated, however, that palovarotene could have an effect on new HO volume.

The primary endpoint in studies PVO-1A-301 (main study) and PVO-1A-202/204 Part C was radiological mean observed annualised new HO volume. The prespecified primary analyses did not shown clinically or statistically significant differences in the mean observed annualised new HO volume (square root transformed data zeroed out by body region) between the phase 3 study PVO-1A-301 and NHS. In this analysis, the observed annualised new HO volume for PVO-1A-301 was 140 mm^3 (mean SEM) or 137 mm^3 (LSmean) in treated patients and 150 mm^3 (mean SEM) or 130 mm^3 (LSmean) in untreated subjects. These numbers correspond to a non-significant difference of approximately 6%, p=0.52.

In this pre-defined analysis, the square root transformation was used to limit the effect of outliers. Only regions with new HO in a qualitative examination were measured quantitatively. Negative quantitative values were to be zeroed as they were likely considered as measurement errors. According to the applicant's current position, however, the wLME analysis without square-root transformation would be the appropriate analysis method of results, including negative values. In this post-hoc analysis presented by the applicant, the LS mean (SEM) of new HO was 9427 mm^3 in study PVO-1A-301 compared to 23.720 mm3 in NHS. This corresponds a reduction of new HO by 60%. The nominal statistical significance of Wilcoxon test was p=0.0003.

Using this "without square-root transformation negatives included" approach, no reduction of annualised new whole-body HO volumes was seen in PVO-1A-202/204 Parts B and C compared to NHS. HO volumes in this study were numerically even higher compared to untreated subjects. The mean annualised new HO was 27.967 mm^3 in Study PVO-1A-202/Part B, 24.290 mm^3 in Part C and 23.720 mm^3 in the NHS.

3.3. Uncertainties and limitations about favourable effects

The population PK analysis performed to support the initially proposed weight-adjusted posology in children below 14 years of age (skeletally immature children) could not demonstrate that the targeted exposure corresponds to an efficacious and safe dosing regimen. The proposed dosing appears to result in a similar exposure in all weight groups but higher fluctuations in the smaller children. Potential clinical relevance of increased fluctuation is not possible to assess, and therapeutic exposure range is unknown.

Due to interruptions due to safety and futility in the pivotal study (PVO-1A-301), final submitted analyses of efficacy were carried out at a different time point and much less amount of data were analysed than originally planned. The single-arm design and primary endpoint were previously

accepted by CHMP as the disease course was considered relatively stable during a couple of years. However, comparative data with the NHS is principally available only at month 12. Short study duration makes single-arm design questionable and interpretation of results unreliable.

There was no difference between the pivotal study (PVO-1A-301) and NHS in the primary endpoint, (i.e. in the prespecified analysis using square root transformed data zeroed out by body region). There were no differences between these two studies in the secondary endpoints either: there was no substantial difference in the number of new body regions with new HO between the palovarotene treated subjects (1.3) and the subjects in the NHS (1.5); the proportion of subjects reporting flare-ups at month 12 was 65 % in the palovarotene treated study and 54 % in the NHS i.e. there was no improvement in number of flare-ups with the treatment with palovarotene; the flare-up rate per month was higher in the palovarotene treated study than in the NHS where subjects were untreated. The exploratory endpoints did also not provide support for palovarotene efficacy.

The fact that the main studies were not placebo-controlled increases the uncertainty of results due to potential biases in external comparisons. There were considerable differences at baseline HO between cohorts that could indicate more active disease in the NHS. In addition, the great discrepancy of the results based on analysis methods seriously questions the overall robustness and reliability of the HO data. It is noted that there was a considerable intra- and interindividual variability in the assessments of new HO indicating these measurements are challenging to perform. The palovarotene clinical program had focus on preventing new HO. Therefore, the whole-body HO was not systematically quantitively measured after baseline. Only regions with qualitatively detectable new HO were measured. It is reasonable to expect these values to be positive. Negative values in these measurements could reflect uncertainties in the method of measuring HO or at best be hypothesis generating, that palovarotene could possibly affect existing HO. To study such a hypothesis further, existing lesions should be systematically followed. Such data does not exist. Assessment of existing lesions (which could generate possible negative values) was not pre-planned and was not performed in systematic, comprehensive, clinically or scientifically sound manner. This is one of the concerns in the post-hoc approach presented by the applicant.

Based on different dosing regimens studied in the phase 2 program, an exploratory analysis was conducted to describe the relationship between palovarotene exposure and the increase in HO volume after flare-up in subjects with FOP. There was no dose response trend across the flare-up doses utilised in the phase 2 program to support that the drug would be effective in FOP and support for the proof of concept in humans. In the analysis of flare-up outcomes comparing phase 2 data with untreated, there was no evidence that palovarotene would reduce clinical symptoms of pain and swelling during flare-up.

During the assessment, new data from the ongoing PVO studies: PVO-1A-301 and Study PVO-1A-202/204 Part C was submitted by the applicant consisting of 45 patients from study PVO-1A-301 and 26 patients from PVO-1A-202/204. The available longer term new efficacy data from these studies did not indicate that PVO treatment would have an effect in decreasing new HO volume. The numbers reported were similar or higher compared to those from the natural history cohort. Furthermore, PVO treatment had no effect on flare-up rates as numbers reported during on-and off treatment periods were similar.

3.4. Unfavourable effects

Systemic retinoids have a broad spectrum of class effects: mucocutaneous effects, skeletal effects, and ocular system abnormalities such as persistent dry eye, teratogenicity, and poor pregnancy outcomes. In general, the safety profile of palovarotene is consistent with other systemic retinoids.

There was a higher rate of TEAE in the flare-up 20/10 mg group (1379 events per 100 patient years at risk) compared with the chronic 5 mg group (692 events per 100 patient years at risk). A similar pattern was seen with SAEs. The percentage of subjects reporting a dose reduction in Study 301 was dose dependent (20 mg: 45%; 10 mg: 12%; and 5 mg: 3%).

Teratogenicity is an important identified risk in the palovarotene clinical program and a well-known class effect of systemic retinoids. Although there were no pregnancies in the palovarotene development program, findings in toxicology studies demonstrate characteristic patterns of foetal malformations typical of retinoids (e.g., cleft palate, misshapen skull bones, short/long bones). At higher dosages, these effects resulted in reduced foetal survival. Similar to other systemic retinoids, palovarotene is assumed to be a potent teratogen and has the potential to adversely affect development of an embryo or foetus if given to a pregnant female patient and lead to adverse pregnancy outcomes. Consequently, palovarotene if authorised would have been an absolute contraindication during pregnancy and for females of childbearing potential unless all of the conditions of the pregnancy prevention are met, or they are not at risk for pregnancy. The applicant had also proposed guidance and warnings in the label as well as additional risk minimisation measures in the form of a pregnancy prevention program.

Premature Physeal Closure (PPC) has been demonstrated to be an important identified risk associated with palovarotene treatment in growing children with FOP. In clinical studies, epiphyses premature fusion was identified as an irreversible serious risk associated with palovarotene treatment and has been reported in children< 14 years. PPC was identified in 26 of 102 subjects (26%) <18 years of age in the FOP-FAS, including 22 subjects with treatment emergent events and 4 subjects with post-treatment events. The incidence of PPC varied across FOP-FAS paediatric age categories, from 12% for subjects ≥8/10 to <18 years, to 23% for ≥8/10 to <14 years, to 56% for <8/10 years. No PPC events were reported in subjects over the age of 14 years. PPC in the FOP-FAS appeared as early as Month 6 in the clinical program, which is earlier than what is reported in the general retinoid class literature. There are no clear characteristics that define or predict who will develop PPC, over what period, or after what duration of palovarotene exposure. Therefore, given the high incidence of PPC over relatively short periods of time, it is assumed that upon initiation of treatment with palovarotene, all growing children are considered at risk for PPC. Moreover, there is the potential for longer-term consequences, including growth arrest, leg length discrepancy, disproportionate growth (epiphyseal growth plate closure preferentially affecting the lower extremities), angular deformity in affected joints, and gait disturbance. Given the relatively short follow-up times to date, these longer-term consequences have not been identified in subjects treated with palovarotene.

Radiologically observed vertebral fracture were identified as an important identified risk associated with palovarotene based on analyses performed on whole body computed tomography (WBCT) data in FOP subjects in the phase 3 (MOVE) study.

Mucocutaneous effects were seen in almost all patients treated with palovarotene during clinical studies and included dry skin, lip dry, pruritis, alopecia, rash, erythema, skin exfoliation, dry eye, drug eruption and skin irritation, in decreasing order of frequency, which may contribute, due to a diminished skin barrier, to an increased risk of skin and soft tissue infections, particularly paronychia and decubitus ulcer.

3.5. Uncertainties and limitations about unfavourable effects

The median onset of HO involvement of axial/cranial body regions is 6 years of age. In FOP, it would therefore be important to intervene as early as possible to preserve physical function. However, due to the risk of PPC, the applicant's proposal is to restrict the indication to patients 8 years of age and older

for females and 10 years of age and older for males with FOP, i.e., the ages at which patients on average achieve approximately 80% of their adult height. For a boy, this could mean the difference between 180 cm and 144 cm in final height. To outweigh such a risk, the benefit of the drug needs to be compelling if the risk cannot be mitigated. Notwithstanding, as stated by the applicant, the results suggest that there is no consistent effect of increased exposure to palovarotene that is associated with PPC and that all skeletally immature subjects receiving palovarotene are at risk. With no method to identify individuals with risk of PPC, which may already be irreversible when suspected, the applicant's proposal to restrict the indication to females >8 years and males>10 years of age cannot be supported. The applicant has proposed to expand the information on PPC in section 4.4 of the SmPC. The wording is proposed to include monitoring of growth and radiographs every 6 to 12 months during chronic treatment and every 3 months during flare-up treatment, so that subjects who begin to show early signs of physeal closure can pause treatment and re-assess risk benefit with their healthcare provider based on individual determination. A PASS following this issue is also proposed. The proposed risk minimisation measures are not considered adequate and feasible. The progression rate of PPC needed to establish the frequency of radiological monitoring needed to allow sufficient time to detect early signs of PPC and reassess treatment before physeal closure is complete is not established. Furthermore, it is not established that assessments of early physeal closure could be robustly performed by radiologists even at smaller hospitals in order to avoid cumbersome travelling for routine monitoring. Moreover, it is not established that palovarotene induced PPC, when identified at an early stage, is possible to stop or slow down with treatment interruption. Finally, repeated radiology one to four times per year for from the age of 8/10 years up to skeletal maturity is considered to be associated with radiation hazards.

Therefore, based on the current available data, palovarotene treatment to patients with immature skeleton is not acceptable.

Chronic toxicities from long-term therapy with other retinoids are known to increase the risk for occurrence of skeletal abnormalities, usually mimicking diffuse idiopathic hyperostosis syndrome (DISH). In contrast to other side effects of retinoids, which are dose dependent and reversible upon withdrawal of the drug, it seems unlikely that bone abnormalities will resolve after discontinuation of the medication. Even though no event of DISH or DISH-like symptoms were reported in the FOP population, this is considered a class effect. To date, the studied palovarotene population is very limited. Furthermore, palovarotene, unlike e.g., isotretinoin, is intended for long-term, even life-long, treatment. Thus, it seems a possibility that cases may occur over such a period of time.

A signal on Bone Safety was raised by the applicant to assess the possible causal relationship between palovarotene treatment in Study 301 compared with standard of care only (i.e., palovarotene untreated) in Study 001 (NHS) and selected bone safety outcomes in subjects with FOP. No validation for the methods, baseline data or discussion of the clinical relevance of the results were provided. Nonetheless, the data indicate a negative impact of palovarotene treatment on bone strength and mineralisation, and a threefold higher risk of new-onset radiological vertebral fractures in palovarotene treated versus untreated FOP subjects. The consequences for bone safety during longer, potentially life-long, treatment are not known.

There is currently no evidence in the palovarotene studies to suggest an impact on fracture healing with palovarotene treatment; however, palovarotene's mechanism of action is compatible with a negative impact on fracture healing. Therefore, the safety concern should be read "Fractures and impaired fracture healing" and listed as an important potential risk of palovarotene.

Interaction with nuclear receptor RXR is also described in the literature for retinoids, which may lead to central hypothyroidism. This effect is observed in nearly 100% of the patients treated with high dose retinoids (e.g., Bexarotene) prompting routine concomitant L-T4 treatment. For palovarotene,

however, both increasing and decreasing thyroxine levels has been reported and there is no general indication of increased risk for central hypothyroidism, as both low and high TSH has been reported.

3.6. Effects Table

*Table 50 Effect Table for the **pivotal study PVO-1A-301 vs NHS cohort** for Sohonos in the treatment of FOP (data cut-off: 28 February 2020).*

Effect	Short Description	Treatment N=97	Control N=101	Uncertainties/ Strength of evidence
Favourable effects				
New HO volume	Mean, mm^3 (SEM)	140,2 (23,6)	149,8 (19,4)	Marginal difference favouring treatment in comparison to untreated historical controls, non-significant
Proportion of subjects with any new HO	at month 12, n (%)	59 (64,1%)	56 (62.2%)	Small uncertain difference favouring control
Number of body regions with new HO	per subject, mean (SD)	1.3 (1.4)	1.5 (1.6)	Small uncertain difference favouring treatment
Proportion of subjects reporting flare-ups	at Month 12, n (%)	64 (64.6%)	60 (54.1%)	Favours control
Flare-up rate through Month 24	per subject-month exposure (95% CI)	0.13 (0.09, 0.17)	0.07 (0.05, 0.08)	Favours control
Unfavourable effects				
Proportion of subjects with PPC in FOP-FAS population	n/N (%)	<18 y: 24/102 (24%) <8/10 y: 14/25 (56%) ≥8/10 to <14 y: 9/39 (23%) >14 y: 0	0	Reported exclusively in palovarotene treated subjects with immature skeleton.
Dry skin	n/N (%)	109/139 (78)	3/20 (15)	≥8/10 Years (FOP-FAS)
Dry lips	n/N (%)	78/139 (56)	1/20 (5)	≥8/10 Years (FOP-FAS)
Pruritus	n/N (%)	56/139 (40)	1/20 (5)	≥8/10 Years (FOP-FAS)
Erythema	n/N (%)	47/139 (34)	0	≥8/10 Years (FOP-FAS)

Abbreviations: HO: heterotopic ossification, PPC: Premature physeal closure, y: years

*Table 51 Effects Table for **trials PVO-1A-202/Parts B and C vs Natural history cohort** for Sohonos in treatment of FOP*

Effect	Short Description	Treatment Part B N=37	Treatment Part C N=32	Control N=101	Uncertainties/ Strength of evidence
Favourable effects					
New whole body HO volume	Mean, mm^3 (SD)	27967 (82436)	24290 (63290)	23720 (48741)	Small uncertain difference favouring control

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the palovarotene clinical programme, results of single arm studies have been compared with external natural history cohort. The uncertainties of results from external comparisons due to potential biases are well known. There were considerable differences at baseline HO between cohorts that could indicate more active disease in the NHS. The active treatment studies were interrupted for futility and data was unblinded. It is clear from the interim data submitted that the main study PVO-1A-301 did not meet its primary predefined radiological endpoint: mean observed annualised new HO volume. The great discrepancy of the results based on analysis methods seriously questions the overall robustness and reliability of the HO data. Descriptive presentations of the radiological data that show a great overlap between treated and non-treated cohorts. There was no substantial difference in secondary endpoints such as the number of new body regions with new HO in treated and untreated cohorts either. Long-term data after clinical hold and data from the other clinical study PVO-1A-202/204 were not supportive for efficacy. Discussion regarding clinical relevance of favourable effects seems therefore redundant.

Therefore, any potential beneficial radiological effects would be expected to be supported by clinical endpoints at least to some extent. However, there was no substantial difference in patients reporting flare-ups or any of the patient reported outcomes Cumulative analogue joint involvement scale (CAJS), FOP-Physical function questionnaire, PROMIS Global health scale or flare-up outcomes pain and swelling. Therefore, any clinically relevant effect of palovarotene in any of the main symptoms of FOP is seriously questioned.

The major safety issues identified with palovarotene treatment is PPC, bone safety and teratogenicity. Teratogenicity can be adequately handled by contraindicating the medicinal product in pregnant women, together with a strong cautionary wording in the label and additional risk minimisation measures in the form of a pregnancy prevention program. Likewise, different aspects of bone safety may be mitigated with adequate wordings in the SmPC and with additional Pharmacovigilance activities. For PPC, on the other hand, all subjects with growing skeleton seem to be at risk. The proposed risk minimisation measures are not considered adequate or feasible (such as monitoring of growth and radiographs every 6 to 12 months during chronic treatment and every 3 months during flare-up treatment and PASS). The progression rate of PPC is not established which prevents calculating the frequency of radiological monitoring needed to allow detecting early signs of PPC and

reassess treatment before physeal closure is complete. Furthermore, it is not established that assessments of early physeal closure could be robustly performed by radiologists at smaller hospitals in order to avoid cumbersome travelling for routine monitoring. It is also not established that palovarotene induced PPC, when identified at an early stage, is possible to stop or slow down with treatment interruption. Repeated radiology one to four times per year for from the age of 8/10 years up to skeletal maturity is considered to be associated with radiation hazards.

The median onset of HO involvement of axial/cranial body regions is 6 years of age. In FOP, it would therefore be important to intervene as early as possible to preserve physical function. However, due to the risk of PPC, the applicant's proposal to restrict the indication to patients 8 years of age and older for females and 10 years of age and older for males with FOP, i.e., the ages at which patients on average achieve approximately 80% of their adult height is not acceptable. For a boy, this could mean the difference between 180 cm and 144 cm in final height. To outweigh such a risk, the benefit of the drug needs to be compelling if the risk cannot be mitigated. Notwithstanding, as stated by the applicant, the results suggest that there is no consistent effect of increased exposure to palovarotene that is associated with PPC and that all skeletally immature subjects receiving palovarotene are at risk.

The dose of 20 mg is higher than previously used in other indications/populations. At least 25% of the subjects actually received 20 mg during High-dose flare-up, indicating that even though there seems to be tolerability issues with the highest dose, at least a fraction of the patients tolerated the dose. To further mitigate the risk of too high exposure, a weight-based dosing for the entire population, not only subjects >18 years of age with immature skeleton, has been proposed.

For other safety issues with palovarotene, including class effects for systemic retinoids, SmPC wordings and additional Pharmacovigilance activities are deemed sufficient, and these issues are not considered to affect the benefit/risk ratio of palovarotene.

3.7.2. Balance of benefits and risks

The applicant's position that palovarotene both prevents/minimises new HO overall cannot be agreed on. The application is based on a post-hoc analysis of primary endpoint radiological data, that is not scientifically or clinically justified.

Efficacy of palovarotene on new HO volume formation, compared to natural history cohort PVO- 1A-001, is not established. The predefined primary analysis failed in the main single arm study PVO-1A-301, efficacy data from the other clinical study PVO-1A-202/204 was not supportive, data from secondary endpoints (flare up rate, patient reported outcomes) did not show efficacy and available longer-term clinical data after clinical hold did not support efficacy. Overall, robustness and clinical relevance of the presented results have not been shown. This is unfortunate as FOP is a devastating disease with a high unmet medical need.

On the other hand, major safety concerns were identified with palovarotene treatment (Premature physeal closure (PPC), risk for hyperostosis from retinoids). It is not considered sufficiently shown that the risk of PPC is overruled by clinical benefit in this age span.

Considering that the efficacy has not sufficiently been demonstrated and the important safety concerns in the claimed indication the benefit risk balance cannot be considered positive.

3.7.3. Additional considerations on the benefit-risk balance

The applicant submitted a letter from key opinion leaders and patient testimonies which have been considered and acknowledged in the assessment.

3.8. Conclusions

The overall benefit/risk balance of Sohonos is negative.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Sohonos 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), the CHMP considers by consensus that the quality, safety and efficacy of the above-mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product. The CHMP considers that:

- There are several outstanding issues on the quality of the active substance pertaining to the redefinition of two starting materials, the justification of the omission of testing for three active substance impurities and the request to include an additional method to identify one of the impurity standards for control of the active substance. Furthermore, appropriate instructions for special storage condition should be added to the product information.

  These concerns were raised with the applicant during the procedure but have not yet been adequately addressed. The CHMP considers that the quality of the medicinal product is currently not acceptable but could be considered acceptable if these outstanding issues were satisfactorily addressed.

- The applicant's conclusion of the data that palovarotene effectively reduces new heterotopic ossifications (HO) cannot be agreed on. The applicant's conclusion is based on a post-hoc analysis of primary endpoint radiological data that is neither scientifically nor clinically justified.

  Effects of palovarotene on new HO volume formation were investigated in the main single-arm study PVO-1A-301 and the results compared to the natural history cohort from study PVO- 1A-001. The predefined primary analysis failed to demonstrate efficacy of palovarotene and there are limitations of the comparison against the natural history cohort in light of baseline differences and primary endpoint assessments. In addition, results on secondary efficacy endpoints (flare up rate, patient reported outcomes), data from the other clinical study PVO-1A-202/204 and available longer-term clinical data after clinical hold did not support efficacy. Overall, robustness and clinical relevance of the presented results have not been shown.

- The results suggest that all skeletally immature subjects receiving palovarotene are at risk for premature physeal closure (PPC), which is a known safety risk for all retinoids. PPC is an irreversible serious risk which may be associated with growth arrest, leg length discrepancy, disproportionate, angular deformity in affected joints, and gait disturbance. PCC was reported with palovarotene treatment in children< 14 years. Therefore, the proposed indication in females> 8 years and males >10 years cannot be supported and risk minimisation measures for PPC in subjects with an immature skeleton are not considered feasible or sufficient.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, following review of the available data in the context of the applicant's claim of new active substance status, the CHMP position at the time of this report is reflected in Appendix 8.1. However, in

light of the negative recommendation, the CHMP is of the opinion that it is not appropriate to conclude on the new active substance status at this time.

5. Re-examination of the CHMP opinion of 26 January 2023

Following the CHMP conclusion that Sohonos was not approvable as the quality, efficacy, and safety of the product were not sufficiently demonstrated, the applicant submitted detailed grounds for the re-examination of the grounds for refusal on 27 March 2023.

Detailed grounds for re-examination submitted by the applicant

The applicant presented their detailed grounds in writing on 27 March 2023 and at an oral explanation on 23 May 2023. A summary of applicant's detailed grounds for re-examination is presented below.

Ground #1

There are several outstanding issues on the quality of the active substance pertaining to the redefinition of two starting materials, the justification of the omission of testing for three active substance impurities and the request to include an additional method to identify one of the impurity standards for control of the active substance. Furthermore, appropriate instructions for special storage condition should be added to the product information.

These concerns were raised with the applicant during the procedure but have not been adequately addressed at the end of the procedure. The CHMP considered that the quality of the medicinal product is therefore not acceptable but could be considered acceptable if these outstanding issues were satisfactorily addressed.

Applicant's ground for re-examination: point 1

The applicant refers to the major concern related to the redefinition of two starting materials which is planned to be addressed through a post-approval commitment, as previously agreed with EMA, in the event that the benefit-risk balance would be considered positive by the CHMP.

A major objection was raised by CHMP as part of the initial assessment regarding two of the proposed starting materials which were considered non-acceptable due to concerns regarding potential regioisomeric impurities. In response to this major objection, the applicant proposed a two-step approach at D120 whereby the concerns with respect to regioisomeric impurities on the batches already manufactured and planned for launch would first be addressed during the ongoing procedure, whereas the redefinition of starting materials would be implemented via a post-approval variation application. Data addressing concerns regarding regioisomeric impurities have been provided at D120 & at D180 and CHMP agreed (15th of September 2022) with the applicant rationale to release current manufactured batches.

To respond to the redefinition of starting material request reiterated in the ground for refusal, the applicant states that the active substance manufacturing process would be updated to include the D120 presented upfront redefinition of the starting materials and would be submitted (with an update of Module 3 Drug substance sections) as part of a post approval commitment in H1 2024. This submission would occur when corresponding active substance batch data would become available and an agreement is reached on the overall benefit/risk balance of palovarotene.

The other outstanding issues on quality of the active substance and the update of the product information to add specific storage condition have been addressed.

The below responses were provided by the Applicant to address the outstanding issues from the original procedure:

MO1. Starting materials

Conclusion of CHMP at the end of the initial procedure:

The acceptability of a post-approval commitment/variation strategy with respect to the redefinition of starting materials still depends on whether the benefit-risk of the Sohonos drug product would be considered positive by CHMP.

Response from Applicant in re-examination procedure:

To respond to the redefinition of starting material request reiterated in the ground for refusal, the applicant confirmed that the active substance manufacturing process is being updated to include the D120 presented upfront redefinition of the starting materials and would be submitted (with an update of Module 3 Drug substance sections) as part of a post approval commitment in H1 2024. This submission would occur when corresponding active drug substance batch data would become available and an agreement is reached on the overall benefit/risk balance of palovarotene.

The outstanding other issues on quality of the active substance and the update of the product information to add specific storage condition have been addressed as follows:

OC1. Testing for three impurities

Conclusion of CHMP at the end of the initial procedure:

The justification of the omission of testing for the three impurities is not considered sufficient. The reasoning presented is not easy to follow, e.g. reference is made to purging data where spiking has been made at an earlier step than the one where the impurities are actually controlled, and it is not clear how the proposed purge factor from stage 1 can be used in the calculation for stage 2. This needs to be explained and justified before it can be concluded that each of the impurities can be controlled to below 30% of the TTC-derived limit in the final drug substance if they are present at their maximum permitted level in the designated intermediate. Hence, unless additional justification and clear explanation of the control strategy is provided, tests with a justified limit at a suitable stage should be introduced.

Response from Applicant in re-examination procedure:

The potential genotoxic impurities which may be present in palovarotene active substance include the three impurities. These impurities originate in Stage 1 of the synthesis of palovarotene and, if formed, will be purged in Stage 1 and Stage 2.

The Applicant has agreed to set routine palovarotene active substance specifications for the three impurities. The updated palovarotene active substance specifications are presented in the responses document, and in the corresponding section 3.2.S.4.1. The proposed specification corresponds to the threshold of Toxicological Concern (TTC), calculated to be 75 ppm based on the maximum daily dose (20 mg) administered during flare-up periods.

The applicant proposes to test 10 consecutive palovarotene batches and, in case these impurities are absent in the batches, proposes to remove their testing from the drug substance specification through a post approval variation.

In addition, sections 3.2.S.4.4 (batch analysis), 3.2.S.4.5 (justification of specifications) and 3.2.S.5 (reference standards or materials) have been updated accordingly.

While already shared in the response document at Day 120, the results on genotoxic impurities for 5 batches (3 commercial validation batches and 2 commercial batches) have been added in section 3.2.S.4.4.

New sections 3.2.S.4.2.11 and 3.2.S.4.3.11 have been added to describe the analytical method to test the three genotoxic impurities and its validation.

OC2. Additional method to identify one of the impurity standards for control of the active substance

Conclusion of CHMP at the end of the initial procedure:

The issue related to the need to include an additional method to identify the impurity standard (for example by MS spectroscopy or other suitable method) remains unresolved.

Response from Applicant in re-examination procedure:

In addition to the proposed methods, an additional identification of this impurity will be implemented. Thus, the impurity will be therefore identified also by its retention time. The proposed updated impurity specifications and results for reference standard are provided in the responses document and in Section 3.2.S.5. Section 3.2.S.5 (reference standards or materials) has been updated accordingly.

OC3. Special storage condition

Conclusion of CHMP at the end of the initial procedure:

The special storage condition "Do not store above 30°C" should be added to the product information.

Response from Applicant in re-examination procedure:

The applicant has agreed to add the special storage condition "Do not store above 30°C", and sections 3.2.P.8.1 and the product information has been updated accordingly.

Ground #2

- The applicant's conclusion of the data that palovarotene effectively reduces new heterotopic ossifications (HO) cannot be agreed on. The applicant's conclusion is based on a post-hoc analysis of primary endpoint radiological data that is neither scientifically nor clinically justified.

  Effects of palovarotene on new HO volume formation were investigated in the main single-arm study PVO-1A-301 and the results compared to the natural history cohort from study PVO- 1A-001. The predefined primary analysis failed to demonstrate efficacy of palovarotene and there are limitations of the comparison against the natural history cohort in light of baseline differences and primary endpoint assessments. In addition, results on secondary efficacy endpoints (flare up rate, patient reported outcomes), data from the other clinical study PVO-1A-202/204 and available longer-term clinical data after clinical hold did not support efficacy. Overall, robustness and clinical relevance of the presented results have not been shown.

Applicant's grounds for re-examination: Point 2

As stated by the CHMP in the Day 180 Letter to the Applicant, it may be acceptable to present post-hoc modifications of the primary analysis because of errors in the pre-specified statistical methods or choice of clearly suboptimal statistical models. In fact, the pre-specified Bayesian analysis was flawed due to the different visit schedules between the NHS and Study 301 in conjunction with the square root transformation manipulation of the data. The analysis performed on the pre-specified analysis taking into account this bias (either by accounting for the visit schedule difference or the square root transformation), as well as each analysis performed using the empirical data including negative HO values consistently supported its efficacy.

3.1.1 Pre-specified Bayesian Model Analysis

3.1.1.1 Prespecified Bayesian Model using Square-Root Transformation Masks Treatment Effect

It is acknowledged that based on the pre-specified primary analysis using a Bayesian model with square-root transformation, Study 301 crossed futility at IA2. However, this was primarily due to differences between WBCT visit schedules in NHS and Study 301 in conjunction with the square-root transformation, which biased the results against palovarotene due to more frequent assessments in Study 301. To illustrate the impact of the WBCT assessment timepoint differences, consider the following 2 examples.

Example 1:

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

- In the NHS, the volume would appear as 8,000 mm^3 over 12 months.
- In Study 301, the volume could be split across two 6-month intervals: 4,000 mm^3 in the first 6-month interval and 4,000 mm^3 in the next 6-month interval.
- Without square-root transformation, the sum of new HO volume is the same in both patients (8,000 mm^3).
- With square-root transformation, the sum of new HO volume in the NHS is $\sqrt{8,000}$=~89 mm^3, while the sum in Study 301 is $\sqrt{4,000}+\sqrt{4,000}$=~63+63=126 mm^3, which is substantially larger than ~89 mm^3.

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

Example 2:

2 patients – 1 patient with twice as much new HO volume increase in the NHS (8,000 mm3) compared to a second patient in Study 301 (4,000 mm^3) in one body region over the first year:

- In the NHS, with square root transformation ($\sqrt{8,000}$), the volume would appear as ~89 mm^3 over 12 months
- In Study 301, with the square root transformation, the volume could be split across two 6-month intervals: 44.7 mm^3 ($\sqrt{2,000}$) in the first 6-month interval and 44.7 mm^3 ($\sqrt{2,000}$) in the next 6-month interval.
- Without square-root transformation, the sum of new HO volume is twice as much in NHS compared to Study 301 (8,000 vs 4,000 mm^3).
- With square-root transformation, the sum of new HO volume in the NHS is $\sqrt{8,000}$=~89 mm^3, while the sum in Study 301 is $\sqrt{2,000}+\sqrt{2,000}$=~45+45=90 mm^3, which is the same.

While the patient in Study 301 actually had a 50% reduction in HO volume, the treatment effect is masked by inappropriately using the square-root transformation.

Table 55 shows the posterior probability of palovarotene efficacy (ie, Pr[γ < 1]) and median posterior γ using the data per each protocol-specified timepoint (every 6 months in Study 301 and every 12 months in NHS) and when the first year of Study 301 new HO volume was collapsed into one 12-month interval to mirror the NHS. It is important to note that the volume of new HO observed for each patient is the same in both analyses – the only change is to the timing of the detection of the new HO

in the first year to match the visit schedule of the NHS, and hence to address the mathematical inaccuracy that is inherent to the pre-specified analytical approach. Collapsing new HO in Study 301 for the first year over a 12-month interval when using the square-root transformation fitted a 16% reduction in new HO volume on the square-root scale (which would translate to approximately 36% reduction on non-square-root scale).

Table 52 Posterior γ Using the Data at Protocol-Specified Timepoints and When New HO Volume was Collapsed Over 12 Month Interval (Principal FAS)

Study 301 New HO Volume		Posterior Pr(γ < 1)	Median Posterior γ (95% Credible Interval)	% reduction on Sq-root scale	% reduction WITHOUT Sq-root
Square-root transformation	Collapsed over 12-month interval	0.9065	0.84 (0.64, 1.09)	16%	~36%
	Protocol-specified timepoints	0.6543	0.95 (0.74, 1.22)	5%	~31%
No square-root transformation	Collapsed over 12-month interval	0.997	0.61 (0.42, 0.87)	-	39%
	Protocol-specified timepoints	0.9935	0.64 (0.45, 0.90)	-	36%

FAS=Full Analysis Set; HO=heterotopic ossification

Similarly, Figure 10 shows the results of the primary efficacy endpoint analysed using the protocol-specified timepoints (every 6 months in Study 301 and every 12 months in NHS) and when the first year of Study 301 new HO volume was collapsed into one 12-month interval (bottom). As expected, collapsing new HO in Study 301 across 12-month intervals when using the square-root increases the probability of any reduction in HO by palovarotene from 65% to 91%.

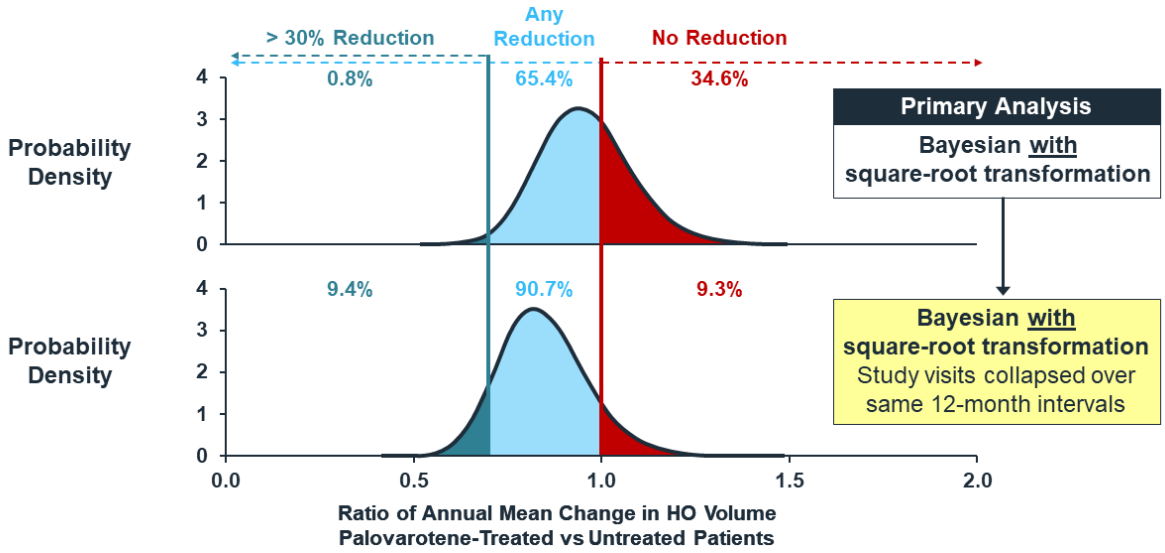


Figure 10 Differences in WBCT Visit Schedules in Study 301 vs NHS Impacts Analysis of HO Reduction

As such, using the pre-specified Bayesian primary efficacy analysis with the square-root transformation while adjusting the dataset to normalise the visit schedule in the first year between Study 301 and the NHS better demonstrates the efficacy of palovarotene in reducing new HO volume.

3.1.1.2 Bayesian Analysis Without Square-Root Transformation

Another way to account for the bias of the visit schedule is to remove the square root transformation in the prespecified Bayesian analysis. Presented below in Figure 12 is the Bayesian Analysis with and without square root transformation. With square-root transformation, at interim analysis 3 (IA3) the

model predicted a 65% probability that palovarotene would reduce annual mean new HO volume compared with no treatment, while without square-root transformation, the model predicted a 99.4% probability that palovarotene would reduce any new HO compared with no treatment.

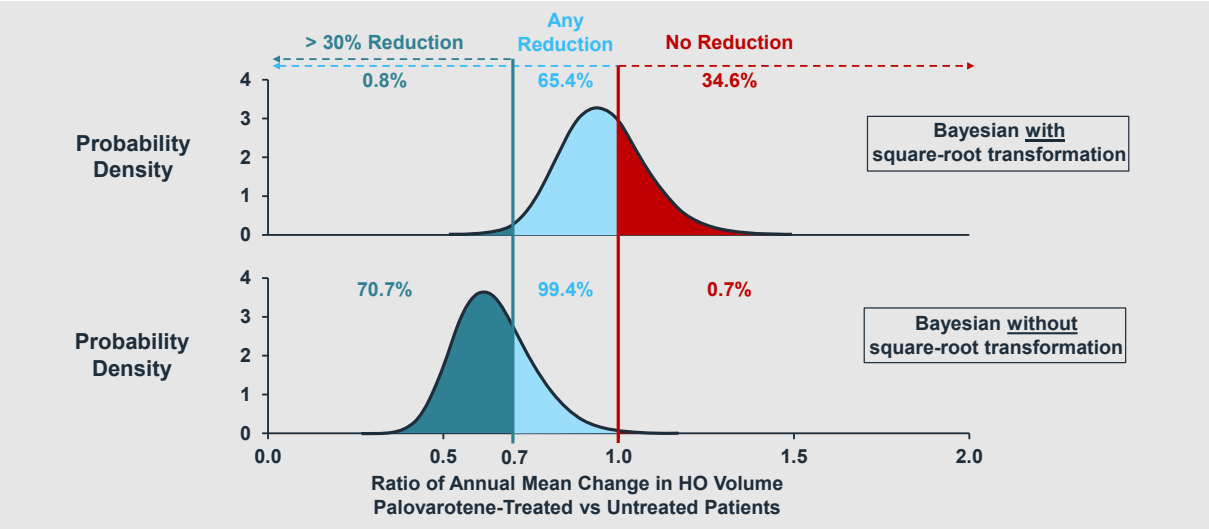


Figure 11 Annualised New HO Volume Using Bayesian Analyses in Study 301 at IA3

3.1.1.3 Patient-Level Analysis of Mean Annualised New HO Volume

Given the variability in disease course among patients with FOP, individual patient level data are important to our understanding of palovarotene's efficacy. Figure 13 shows the mean annualised new HO volume for each individual patient treated with palovarotene in Study 301 and untreated patients from the NHS. While the majority of patients in both groups developed new HO, the overall volume was less in palovarotene-treated patients. Importantly, fewer patients treated with palovarotene had large volume increases in new HO compared with untreated patients.

A similar analysis of only those 39 patients who participated in both the NHS and Study 301 showed consistent results; patients treated with palovarotene had smaller increases in annualised new HO volume, and more patients treated with palovarotene had decreases in annualised new HO volume, compared with when they were untreated as part of the NHS (see Section 3.1.3.3.1).

The empirical data presented here – at a patient level without transformation – do not align with the results of the pre-specified primary analysis using square-root transformation.

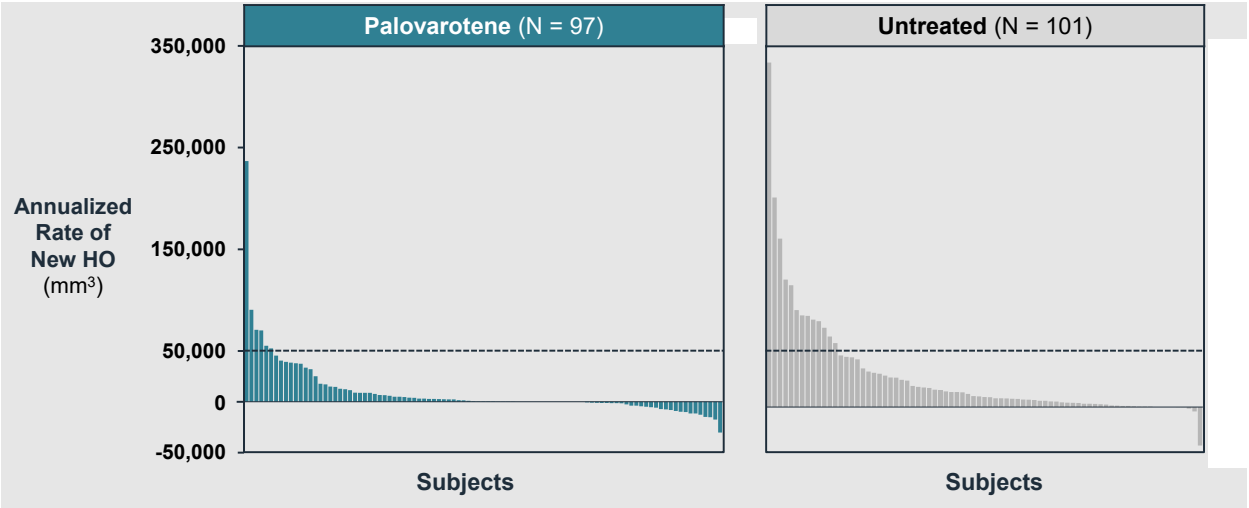


Figure 12 Annualised New HO Volume by Patient in Study 301 vs Untreated Subjects in the NHS (Principal FAS Population)

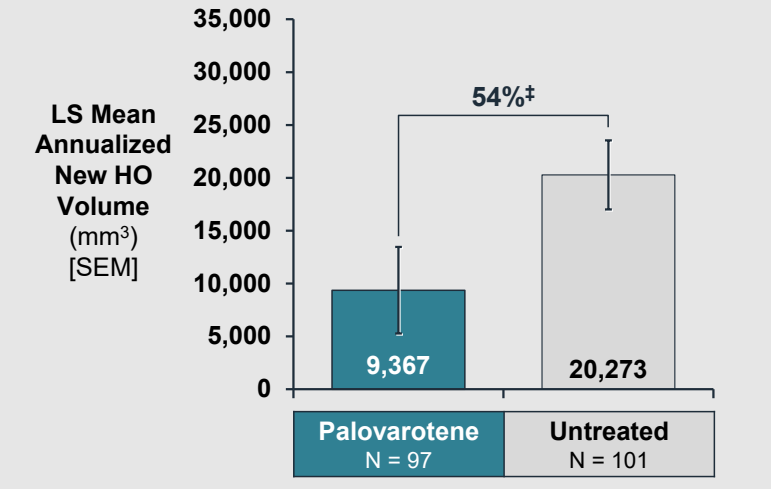
3.1.2 Clinical Data from Sensitivity and Supplementary Analyses Consistently Demonstrate Benefit of Palovarotene and Directly Address Potential Biases

To support the positive results shown above on the corrected primary analysis, additional analyses included in this section show the robustness of the results to outliers, negative values, missing data, imbalances/covariates between the NHS and Study 301, and the choice of analytical approach based on pre-specified and additional, post-hoc, sensitivity and supplementary analyses. All of these analyses show consistently positive results in favour of palovarotene

3.1.2.1 wLME Analysis in FOP-FAS

Below is a summary of the assessment of mean annualised new HO volume at IA3 conducted using a wLME model, including all observed data. Notably, this was the original primary efficacy analysis before the introduction of the Bayesian compound Poisson analysis with square-root transformation as the new primary analysis in Protocol Amendment 1 (Study 301).

The wLME model, adjusting for baseline covariate of baseline total HO volume/baseline age (ie, average yearly HO volume prior to study participation) showed a mean reduction of 54% in the FOP Full Analysis Set (FOP-FAS) when comparing data from palovarotene-treated patients with that from untreated subjects (nominal wLME p=0.0392) (Figure 13).



FAS=full analysis set; HO=heterotopic ossification; IA3=Interim Analysis 3; LS=least squares; SEM=standard error of the mean; ‡ Nominal p-value=0.0392.

Figure 13 Mean Annualised New HO Volume at IA3 (Principal FAS)

3.1.2.2 Analysis with Adjustment for Additional Covariates Including Propensity Score Analysis

In the wLME analysis, the mean observed annualized new HO volume was reduced by 56% (nominal wLME p=0.0314) in palovarotene-treated patients compared with untreated patients. The model uses multiple covariates including baseline total HO volume divided by baseline age, baseline age, sex, baseline months since last flare-up, baseline CAJIS and treatment as covariates. (Note that that this analysis includes annualised HO volume for 4 fewer untreated patients than the original analysis which only used baseline total HO volume divided by baseline age as the covariate, due to missing data for the additional covariates) (Figure 15).

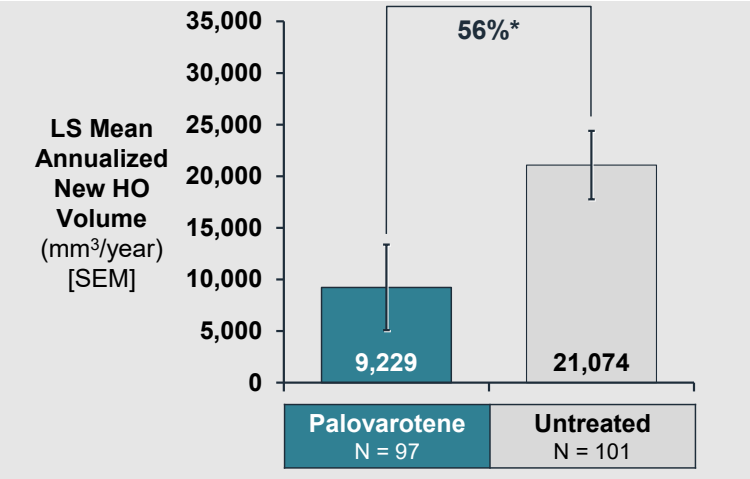


Figure 14 wLME Analysis of Mean Annualised New HO Volume Without Square-Root Transformation and With Additional Covariates Included in Study 301

HO=heterotopic ossification; LS=least squares; SEM=standard error of the mean. * Nominal p-value=0.0314.

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

The results were also similar when this analysis was performed with the same co-variates but replacing "baseline total HO/age" with "baseline total HO" per feedback from the CHMP in the Day 180 assessment report.

Note that propensity scores are also used in the matched pairs analysis of patients who participated in either Study 301 or NHS (Section 3.1.3.3.1), but not in both studies, as well as the propensity weighting analysis. In that analysis, propensity scores are used to create the matched pairs for use with the paired t-test and to assign a weight based on their propensity score value for the weighting analysis.

3.1.2.3 Tipping Point Analysis

Table 56 presents the wLME analysis for annualised new HO volume using a tipping point analysis for missing data through Month 18 in palovarotene-treated patients from Study 301. The data from untreated patients from the NHS are unchanged from the wLME with no square-root transformation and negatives included; no imputation was performed for missing data in this population.

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

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

In the first row in Table 53, the wLME least squares (LS) mean annualised HO volume observed in Study 301 (ie, 9,367 mm^3 or equivalently 20,273 mm^3 [NHS] - 10,906 mm3 [100% of treatment effect retained]), is assumed as the mean annualised HO volume in the intervals for which new HO volume was not available. This mean is used to multiply-impute the new HO volume for the missing WBCT in order to analyse a 'complete' dataset (ie, with the full complement of 297 WBCT timepoints). In the second row in Table 2, 12,639 mm3 (or equivalently 20,273 mm3 [NHS] - 0.7*10906 mm3 [70% of treatment effect retained]), is used in the multiple imputation. In the final row in Table 2, 31,179 mm3 (or equivalently 20,273 mm3 [NHS] + 10906 mm3 [100% of treatment effect retained]), is used in the multiple imputation.

The nominal p-value tips above 0.05 (p=0.0502) at a treatment effect of -100% (ie, the magnitude of the LS mean treatment effect estimate on top of the NHS LS mean annualised HO of 20,273 mm3, or 31,179 mm3), supporting the robustness of results to changes in missing data assumptions, including assumption of missingness not at random. The consistency of these results reflects the completeness of the Study 301 dataset through Month 18.

Table 53 wLME for Annualised New HO Volume (No Square-root Transformation and Negatives Included) in Tipping Point Analysis (Principal Enrolled Population)

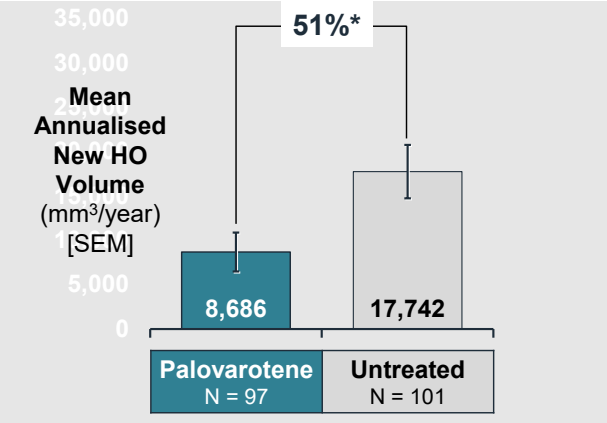
% Observed Treatment Effect Retained	Number of Patients	LS mean (SEM) mm^3 (NHS-301)	LS mean % Reduction (NHS-301/NHS)	Treatment p-value
100%	99	-12577.9 (4615.5)	60.6	0.0064
70%	99	-12054.3 (4614.9)	58.0	0.0090
50%	99	-11705.5 (4615.3)	56.3	0.0112
20%	99	-11182.5 (4617.3)	53.8	0.0155
0%	99	-10833.9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

HO=heterotopic ossification; LS mean=least squares mean; NHS=Natural History Study; SEM=standard error of the mean; wLME=weighted linear mixed effect model

Note: The annualised new HO wLME LS mean estimate and SEM are from a mixed model with dependent variable annualised new HO and independent variables including fixed effects of treatment and baseline total HO/baseline age and a random patient effect. % Reduction is average % reduction across the mixed effect models (10 datasets). The Principal Enrolled Population includes imputed data for 2 patients without post-baseline HO.

3.1.2.4 Assessment of the Impact of Extreme Values for Annualised New HO Volumes

To determine whether extreme values for annualised new HO volumes in Study 301 and the NHS unduly influence the described treatment effect, annualised new HO volume values >100,000 mm3 were set to 100,000 mm3 (4 patients in the NHS and 1 patient in Study 301). The results of this analysis are shown in Figure 15.



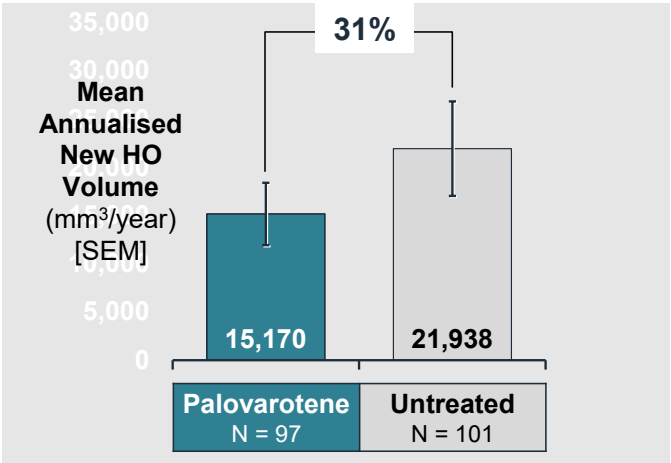
* Nominal p-value=0.0103. Source: Module 5.3.5.1 Report PVO-1A-301 Table 36

Figure 15 wLME Analysis of Mean Annualised New HO Volume with Extreme Values (>100,000 mm3) Truncated

The analysis showed that annualised new HO volume was significantly reduced by 51% in palovarotene-treated patients compared with untreated patients through Month 12 (nominal p=0.0103). Given the understanding that square-root transformation reduces the influence of extreme values, with the similarity of model fit between the Bayesian analysis without square root transformation and with square-root transformation with adjusted visit schedule, these findings support that extreme outliers did not influence the results of these analyse did not influence the results of these analyses.

3.1.2.5 Assessment of the Impact of Negative New HO Volumes in Study 301 and the NHS

While the studies were not designed to characterise this phenomenon and it was not anticipated at the beginning of the trial that HO would decrease over time, more palovarotene-treated patients had negative HO volumes. To determine whether negative new HO volumes in Study 301 and the NHS unduly influence the described treatment effect, negative HO values were imputed as zero, similar to how the pre-specified Bayesian analysis is required to handle the data. In this analysis, palovarotene treatment is associated with a 31% reduction compared with the NHS, which is consistent with the findings from the pre-specified Bayesian analysis (Figure 16).



HO=heterotopic ossification; SEM=standard error of the mean.

Figure 16 wLME Analysis of Mean Annualised New HO Volume without Square Root and with Negative Values Zeroed Out By Body Region

As Study 301 was the first Phase 3 trial to utilise WBCT imaging, there were no prior learnings or observations that could have informed the choice to transform the data. There is now more evidence that there is a lack of clinical justification for applicability of data transformations, which is evidenced not only by demonstration of reductions in the NHS but also in other clinical programmes (Di Rocco et al 2023).

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

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

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

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

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

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

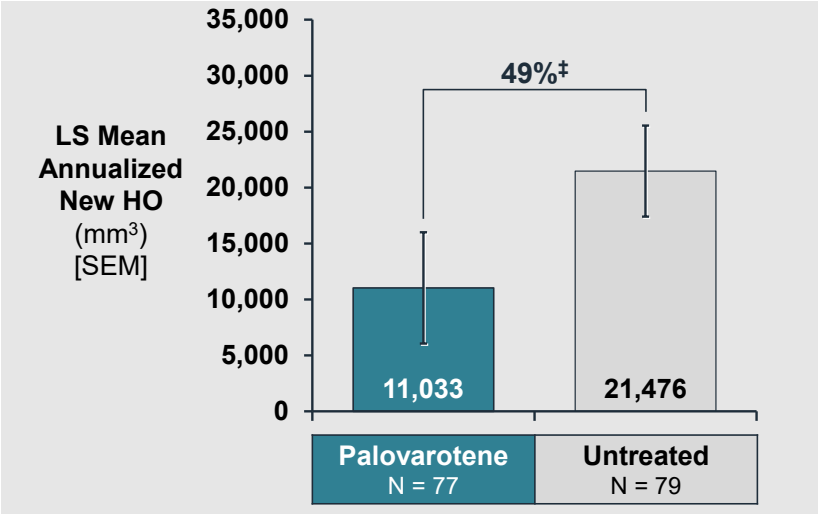
Although it is possible that these negative observations are due to heterotopic bone remodelling as described above, it is acknowledged that they may also be due to measurement variability in patients with negligible changes in HO. It is important to note, however, that the WBCT scans from the NHS and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

As such, inclusion of negatives will not introduce bias. It is therefore appropriate that analyses which can accommodate the data as collected be performed and duly considered in a comprehensive assessment of the efficacy of palovarotene.

3.1.2.6 Analysis in Females ≥8 Years of Age and Males ≥10 Years of Age

Similarly, analysis of the primary endpoint in the target population of females ≥8 years of age and males ≥10 years of age demonstrated efficacy. There was a 56% reduction in the mean annualised new

HO volume in palovarotene-treated subjects (11,419 mm3) as compared with untreated subjects (25,796 mm3). When covariates and follow-up-based weights are considered in the wLME, there was a 49% reduction in the model-fitted mean annualised new HO volume in palovarotene-treated subjects (11,033 mm3) as compared with untreated subjects (21,476 mm^3) (nominal wLME p=0.1124) (Figure 17).



‡Nominal p-value = 0.1124. HO=heterotopic ossification; IA3=Interim Analysis 3; LS=Least Squares; SEM=standard error of the mean.

Figure 17 Mean Annualised New HO Volume at IA3 (Target Population ⩾8/10 Years of Age)

Overall, these results demonstrate that palovarotene reduced the volume of new HO in patients with FOP, both in the FAS and target population. Since HO is the pathognomonic feature of FOP and a major cause of disability accumulation, this HO reduction is expected to change the trajectory of the disease course over the lifetime of patients with FOP.

3.1.3 Adequacy of the NHS as External Control

3.1.3.1 Choice of NHS for Comparison

The NHS provides a unique and valuable dataset that is being utilised to better understand FOP. The 114 patients in the NHS are representative of the worldwide population of individuals with FOP and comprise approximately 14% of known patients with the disease globally (7 study sites representing patients from 24 countries). The analysis of these data provides important information about clinical measures in FOP that describe disease progression over time. Moreover, the flare-ups studied in the NHS expand the understanding of the duration and outcomes of untreated flare-up symptoms.

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

3.1.3.2 Baseline Characteristics in the NHS and Study 301

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

Almost all patients in both groups had experienced a flare-up, with a median of 1 flare-up within the past 12 months prior to study in both groups. The mean number of flare-ups within the past 12 months (1.4 in palovarotene-treated patients and 2.5 in untreated patients) was higher than the median (1.0 in palovarotene-treated patients and 1.0 in untreated patients); however, the skewed distribution allows the median to be more relevant for comparison. The median time since last flare-up was longer in palovarotene patients (10 months) than in untreated patients (6 months).

On average, palovarotene-treated patients were younger by approximately 2.5 years than untreated patients. This age difference is reflected in the lower baseline total WBCT HO volumes and lower CAJIS and FOP-PFQ scores in palovarotene-treated patients compared with untreated patients. This does not mean that the palovarotene group had less severe disease or would be predicted to progress more rapidly over the follow-up period, but rather that, due to their age, they had less time for HO development and consequently less functional impairment. For example, the NHS data suggest that patients with FOP will form approximately 25,000 mm3 of new HO per year; if 62,500 mm3 of total WBCT HO volume is added to the observed baseline volume in palovarotene-treated patients, the "age-adjusted" volume would be approximately 332,000 mm3 – and thus similar to untreated patients. The same calculations can be performed for CAJIS (estimated annual change of 0.5 units) and FOP-PFQ (estimated annual change of 1.3%), giving "age-adjusted" values of 11.3 and 47.6, respectively.

3.1.3.3 Analyses Supporting Use of NHS as External Control

The concerns around potential bias that may arise due to differences in the baseline patient characteristics between Study 301 and the NHS (such as patients in the NHS being relatively older and of worse disease severity) are acknowledged. To address the potential impact of measured confounding factors, multiple sensitivity analyses were conducted using methods that are commonly used for causal inference.

As described in below, these analyses do not change the overall conclusions and consistently demonstrate that palovarotene treatment provides meaningful reductions in the volume of new HO. For these reasons, it can be concluded that there is no evidence supporting the concern that the differences in annualised new HO between treated and untreated patients is driven by any systemic difference in baseline covariates or the use of a non-randomised external control group.

3.1.3.3.1 Patients Who Transitioned from the Natural History Study to Study 301

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

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

Patients were older at Study 301 baseline (mean age 15.3 years) than the NHS baseline (mean age 13.1 years). Consistent with what would be expected for disease progression, patients also had higher total HO volume (259,186 mm3 and 207,890 mm3, respectively) and higher CAJIS and FOP-PFQ scores at Study 301 baseline compared with NHS baseline. The mean and median number of flare-ups within 12 months prior to study enrolment (retrospectively reported) was 3.7 and 1.0 at the NHS baseline, respectively, and 1.1 and 0.5 at Study 301 baseline, respectively.

Based on the wLME analysis in the 39 patients who transitioned from the NHS to Study 301, there was a 52% lower annualised new HO volume during the palovarotene 5 mg chronic/20/10 mg flare-up regimen in Study 301 compared with no treatment in the NHS (nominal wLME p=0.0634).

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

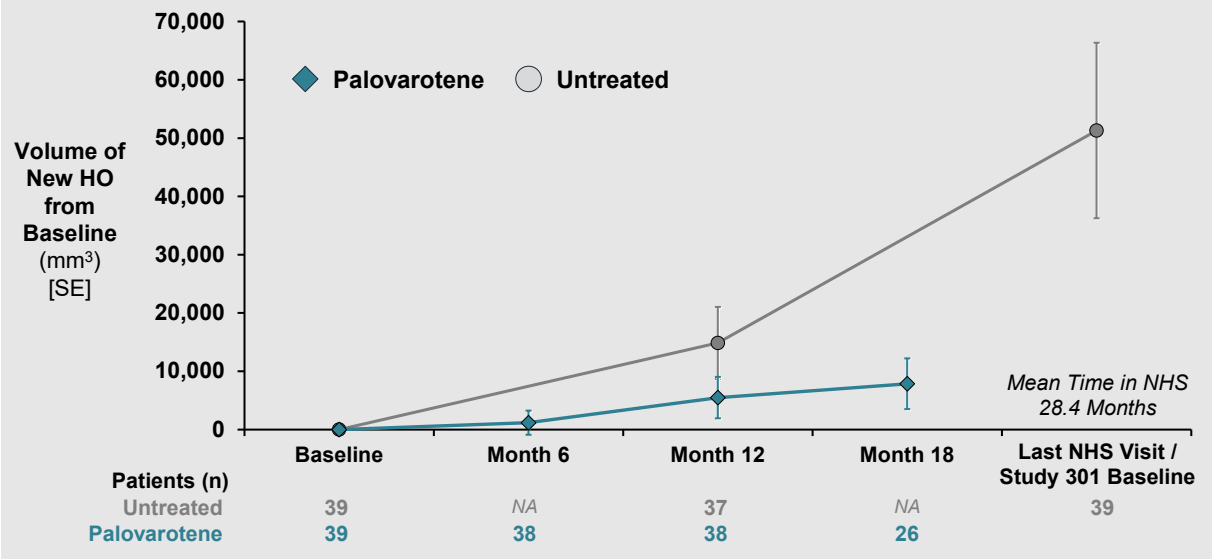


Figure 18 Volume of New HO Over Time in Patients who Transitioned from the NHS to Study 301 (Principal FAS)

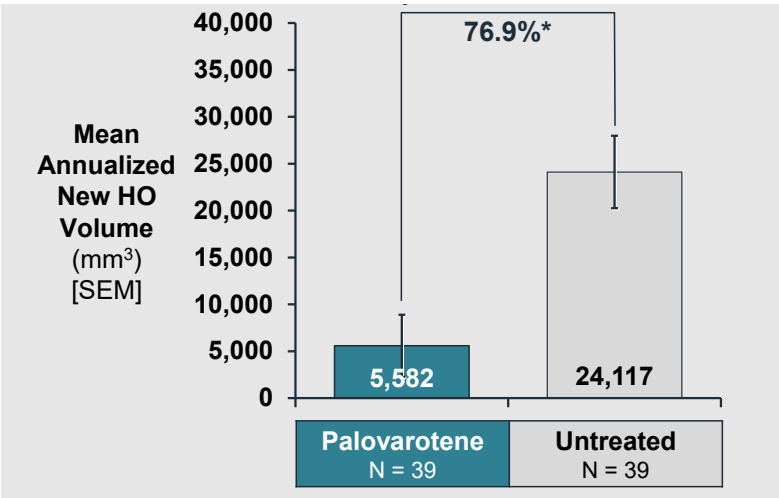
3.1.3.3.2 Matched Pairs Analysis of Patients who Received Palovarotene in Study 301 vs Patients who Participated in the NHS Only

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

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

The matched analysis showed a 77% reduction in annualised new HO volume in Study 301 compared with no treatment in the NHS as shown on Figure 19. In palovarotene-treated subjects, the mean

annualised new HO volume was 5,582 mm^3, compared with 24,117 mm^3 in untreated subjects. The difference between the untreated and palovarotene groups, 18,534 mm^3, was statistically significant (nominal p-value <0.05). This matched pairs analysis provides evidence that efficacy is not an artifact of confounding of differences between subjects in Study 301 and the NHS.



FOP=Fibrodysplasia Ossificans Progressiva; HO=heterotopic ossification; NHS=Natural History Study; SEM=standard error of the mean. ǂ Two sample t-test p-value < 0.05

Figure 19 Matched Analysis of Reduction in Annualised New HO Volume Among Palovarotene-Treated (Study 301) and Untreated (NHS) Patients with FOP

3.1.3.3.3 Propensity Score Weighting Analysis

There was a nominally statistically significant difference in annualised new HO volume among treated and untreated subjects when using both unstabilised and stabilised weights. The mean (± SD) difference in annualised new HO volume between treatment groups was 19,415.50 (± 8,524.66) mm3 after unstabilised weighting (nominal p <0.05), and 19,430.38 (± 8,524.00) mm^3 after stabilised weighting (nominal p < 0.05).

The effect of palovarotene on formation of new HO was consistent in patients who transitioned from the NHS to Study 301 as well as those matched for baseline characteristics who did not transition compared with the overall study population. Together these analyses provide further reassurance that the observed efficacy is not due to confounding by differences between patients and support that the NHS is an adequate control for Study 301.

3.1.4 Discussion on Secondary Efficacy Endpoints

Study 301 pre-specified two secondary efficacy endpoints for evaluation (i.e. proportion of patients with new HO at Month 12 and the flare-up rate per patient-month exposure through Month 24).

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

3.1.4.1 Secondary Endpoint: Proportion of Patients with New HO at Month 12

Although nonclinical results consistently demonstrated dose-dependent decreases of HO with palovarotene across the models and indicated that a human equivalent dose of 20 mg palovarotene should provide maximal inhibition of HO across all injury conditions it is clear that the rigorously

controlled conditions in animal studies versus the extremely complex and heterogenous disease process observed in individuals with FOP account for the fact that a similar proportion of palovarotene-treated and untreated patients had any new HO at 12 months, with similar mean number of body regions with new HO. Month 12 was chosen for this analysis as it is the post-baseline timepoint with the most consistent amount of follow-up data per group. In individuals with FOP, including those enrolled into the palovarotene clinical studies, the cause of the majority of flare-ups is unknown, thus making it impossible to truly know the exact timing of the initiation of the catabolic process seen in flare-ups. In addition, as flare-ups evolve in humans, different locations within the same tissue may be in the catabolic phase and other areas in the anabolic phase, making this situation much more heterogeneous than in the injury-based animal models. As such, flare-up dosing in the clinical trials was targeted immediately after the initiation of the catabolic process versus before this phase in the animal studies. Importantly, in the clinical trials, flare-ups could be located in muscles, tendons, or ligaments anywhere in the body, unlike nonclinical studies where the flare-up was a single, controlled region (except for the Prrx1-R206H model where HO formation is spontaneous). However, when interpreted within the context of the post hoc results for annualised new HO volume, these results suggest that while the percentage of patients forming any amount of new HO is similar between the groups, the mean volume of new HO formed by palovarotene-treated patients when there is new HO is less than the volume formed by untreated patients when there is new HO.

3.1.4.2 Secondary Endpoint: Flare-up Rate Per Patient-month Exposure Through Month 24

The percentage of patients reporting at least 1 flare-up (defined as having at least 1 symptom) was 64.6% in palovarotene-treated patients in Study 301 and 54.1% in untreated patients. The flare-up rates (ie, $\geq$ 1 symptom) per patient-month of exposure were 0.15 (95% CI: 0.13, 0.17) in palovarotene-treated patients and 0.07 (95% CI: 0.06, 0.08) in untreated patients.

Flare-up rates were higher during flare-up treatment compared with chronic treatment in Study 301. The overall flare-up rate (95% CI) of new flare-ups/patient-months exposure was 0.28 (0.23, 0.32) in Study 301 and 0.11 (0.08, 0.14) in the NHS. Both rates remained relatively consistent through 20 weeks. The majority of intercurrent/worsening flare-ups occurred within the first 12 weeks of an index flare-up in both studies. The mean and median time between last dose of systemic corticosteroid and onset of the next new flare-up event within flare-up cycle in Study 301 were 22 days and 9 days, respectively, compared with 27 days and 14 days, respectively, in the NHS. Therefore, the flare-ups observed within the first 4 weeks of the index flare-up were possibly related to rebound of flare-up symptoms following the discontinuation of corticosteroids, particularly in Study 301 given the time from discontinuation of corticosteroids. In a retrospective flare-up survey of 500 participants reported by Pignolo et al (2016): "Forty-three percent (126/293) of participants confirmed a rebound effect after completion of a course of steroids, with 65.1% (82/126) reporting the time to rebound being within 1 to 7 days." Given median time since last systemic glucocorticoid in Study 301 (particularly in the "worsening" category), it is possible that many of these events were secondary to a rebound effect from glucocorticoids.

Additional consideration of the differences observed in intercurrent/worsening flare-up rates between studies include incongruences in the collection of flare-up assessments. The difference in flare-up rates may be due to the more frequent interactions the clinical sites had with the study participants in Study 301 compared with the untreated patients in the NHS. Patients and/or their parents/caregivers in the NHS were asked to telephone the site at the time of any suspected flare-up for the duration of participation in the study. If a flare-up was confirmed by the Investigator, then information about the flare-up was recorded. During the 36-month observation period, up to 1 flare-up per year could be evaluated in-clinic on Days 1 and 84, with Day 48 as a clinic visit or telephone contact. Location of flare-up site was specifically captured during flare-up assessments; however, worsening of an existing flare-up was not. Regular contact was made with patients every 6 months, although no specific

questions were asked regarding occurrence of new-flare-ups during these protocol-specified contact points. Contrary to the objective and standardised assessments related to new HO volume, other assessments and tools that were systematically used in the interventional trials, including patient diaries to document flare-up symptoms, were not used in the NHS.

In Study 301, patients and/or caregivers were also asked to telephone site personnel to report potential flare-up symptoms. However, in contrast to the NHS, if a flare-up was confirmed patients were initially assessed by remote visit at Flare-up Cycle Day 1 and every 4 weeks until the last flare-up in the cycle had resolved and flare-up treatment was completed. Starting with Protocol Amendment 2, all assessments after Week 4 occurred every 8 weeks, and starting with Protocol Amendment 3, assessments occurred every 12 weeks. If a patient experienced an intercurrent/worsening flare-up (defined as a new flare-up location or marked worsening of an original flare-up), or if the Investigator confirmed the presence of a high-risk traumatic event likely to lead to a flare-up, at any time during flare-up-based treatment, the 12-week dosing regimen was restarted. Regular contact was also made with the patients at Baseline, Week 6, and every 3 months (either in-clinic or remotely). Additionally, patients were asked to document daily flare-up symptoms in diaries, which were specifically reviewed to collect existing, worsening, and new flare-up information at every contact.

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

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

3.1.4.3 Exploratory Endpoints: Patient-Reported Outcomes

Physicians and patients completed assessments of functional outcomes using the CAJIS and FOP-PFQ. Overall, the results showed that these assessments were not sensitive enough measures to demonstrate the loss of physical function in untreated patients, even with a 3-year study duration. As such, without a measure sensitive enough to demonstrate change over the timing of a clinical trial, it is not possible for a difference to be shown in a similar time frame.

Cross-sectional analysis of CAJIS score and FOP-PFQ by age from the NHS showed an estimated annual rate of change of 0.49 units (in scale 0–30 units) and 1.3% (in a scale 0%–100%). Given these results, these functional assessments were known to not be sufficiently sensitive to demonstrate disease progression over the timeframe of a clinical trial and therefore were only used as exploratory endpoints. While palovarotene is not expected to improve these measures in the setting of a clinical

trial, data from the NHS support that the reductions in annualised new HO observed with palovarotene treatment should result in preserved function if observed over longer periods of time.

3.1.5 Phase 2 Study Results

The Phase 2 programme was designed to determine whether the convincing animal pharmacology data would translate into efficacy in individuals with FOP. As such, the initial Phase 2 studies evaluated the effect of short-term palovarotene treatment on HO formation following a flare-up. The assessment of total body HO burden by WBCT was introduced into the Phase 2 programme during Study 202 Part B, at the time that the chronic/flare-up dosing was initiated in skeletally mature subjects. However, interpretation of the annualised new HO from Part B is difficult and does not reflect the true palovarotene treatment effect due to key differences in patient enrolment characteristics, dosing regimens, and flare-up definitions compared with Study 301.

The Study 202 Part C population includes all subjects enrolled in Part C who had a Part C baseline (defined as the first WBCT scan in Part C that was not obtained during a flare-up or within 1 month of the end of a flare-up) and at least one post-baseline scan. This population better aligns with the enrolment criteria of Study 301 and the NHS and provides data using the proposed dosing regimen of chronic palovarotene therapy with flare-up dosing; however, there are still limitations in making direct comparisons to the NHS and Study 301. In their grounds for re-examination, the applicant describes the data from both the flare-up only treatment as well the chronic flare-up treatment and provide support for the treatment benefit of palovarotene.

The applicant considers that the flare-up outcome data clearly demonstrate the efficacy of palovarotene in reducing new HO volume at the flare-up body region at Week 12, supporting the annualised new HO volume outcomes observed in Study 301.

Figure 20 summarises the annualised new HO volume up to the MAA data cut-off by flare-up treatment categorisation described below:

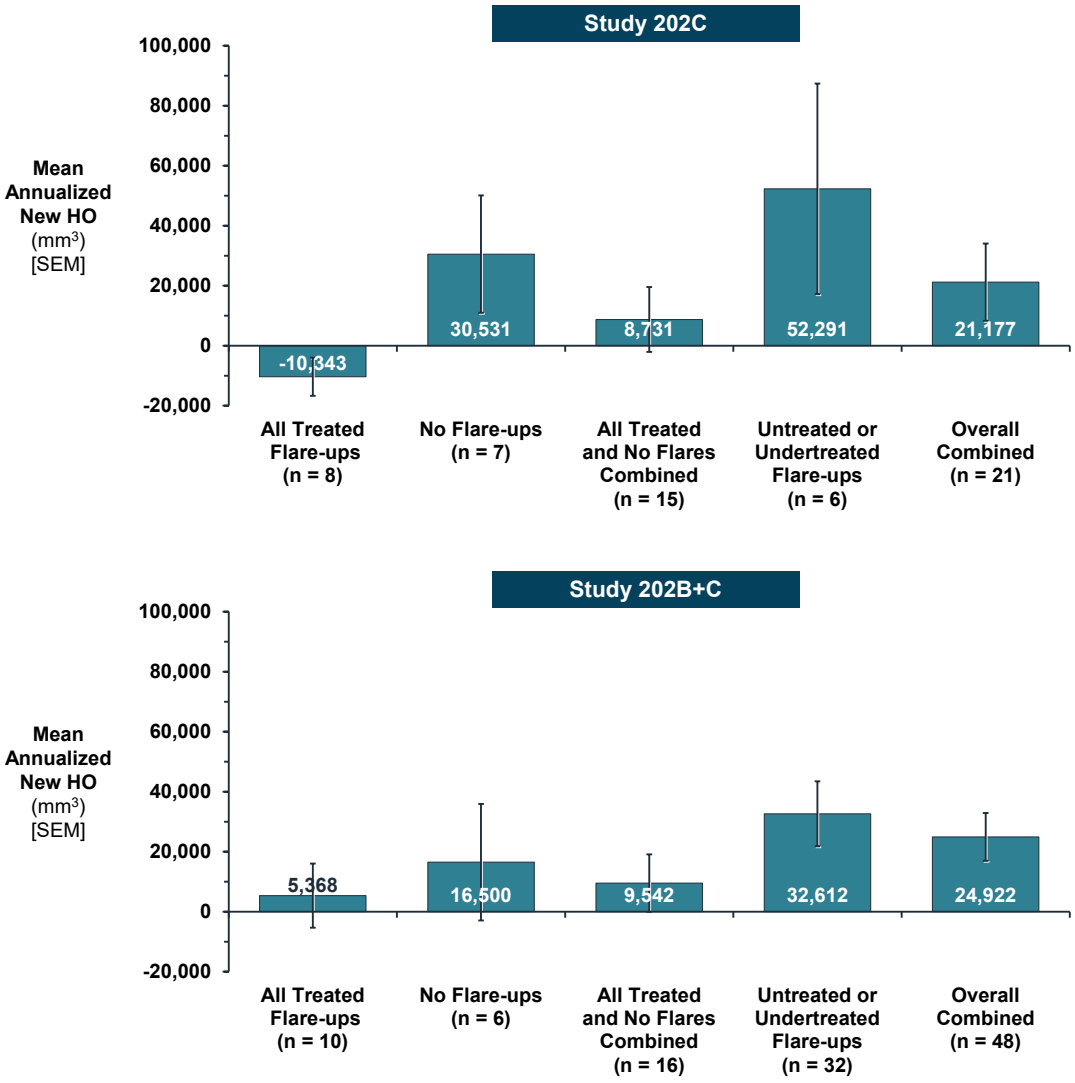


Figure 20 Annualised New HO Volume (mm3) by flare-up treatment categorisation in Study 202C and Study 202B/C (Principal Full Analysis Set - MAA data cut-off)

Based on this analysis, the applicant considers that it is evident that the majority of subjects (67%; 32/48) in Study 202B/C were untreated/undertreated, which likely greatly impacted the volume of annualised new HO formation. As would be expected, compared with subjects with all treated flare-ups, subjects with untreated/undertreated flare-ups had a much greater annualised new HO volume (5,368 mm^3 vs 32,612 mm3). The Study 202B/C and 202C populations that best approximate the Study 301 population is the "All Treated and No Flares Combined" groups. The annualized new HO volume in these groups was similar to that observed in Study 301 (9,542 mm3 in 202B/C and 8,731 mm^3 in 202C vs. 9,427 mm3 in 301), and less than in the NHS (23,656 mm^3).

3.1.6 Supporting Data from Long-term Results

3.1.6.1 Long-term Phase 3 data

Following the completion of the last visit for the last patient in Study 301, analyses using the entire dataset up to Last-Patient-Last-Visit (September 2022) were conducted to evaluate longer-term effect of palovarotene treatment and assess whether efficacy was still maintained

Overall, for the analysis looking at the longer-term data to Last-Patient-Last-Visit, annualised new HO volume was less with palovarotene treatment during Study 301 compared with the NHS. This was

evident in both the pre-pause and post-pause (re-start) time periods. As expected, when dosing was interrupted, data from the entire ITT population (representing both time periods on and off treatment), demonstrated a greater volume of new HO than when data were analysed in subjects who were treated continuously with palovarotene. Despite including the treatment interruption period, annualised volume of new HO was still lower in Study 301 than what was observed in the NHS. Further support is seen in the 16 subjects who contributed data both while on treatment and then subsequently entirely off treatment, which showed an increase in annualised volume of new HO during the off-treatment time period. In totality, the data summarised here are supportive of a palovarotene treatment effect and consistently demonstrate the benefit of reducing new HO formation in patients with FOP.

3.1.6.2 Long-term Phase 2 data

Similar to Study 301, the long-term analysis using the entire dataset up to Last-Patient-Last-Visit (September 2022) in Study 202 was also performed (Note: these analyses were updated to include the most comprehensive dataset by including baseline CAJIS that was most proximal to the WBCT scan even if it was obtained during participation in prior studies).

The analysis for the ITT period from baseline to last visit in Study 202C vs the NHS (using all 5 co-variates listed above) showed a 17% reduction in mean annualised new HO volume in palovarotene-treated subjects (19,555 mm3) compared with untreated subjects in the NHS (23,656 mm3). The wLME analysis showed a 1.2% reduction (nominal p-value=0.9802) (see Appendix 1 Table 16.1.4).

The analysis for the post-restart treatment period, the mean observed annualised new HO volume was 73% lower in palovarotene-treated subjects in Study 202C (6,396 mm3) than untreated subjects in the NHS (23,656 mm3). The wLME analysis showed a 26% reduction in in palovarotene-treated vs untreated subjects (nominal p value=NE). When looking at the post-restart data with negatives zeroed-out, the raw HO annual reduction was 69.5% and the wLME showed a reduction of 29.5% (nominal p-value=NE).

In conclusion, although the ITT treatment period includes time off palovarotene treatment, subjects treated with palovarotene still showed a decrease in annualised new HO volume. Subjects who re-started palovarotene after the pause continued to demonstrate a reduction in new HO volume compared with untreated subjects.

3.1.7 Efficacy Conclusions

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

Study 301 is the largest and first prospective longitudinal study evaluating a potential therapeutic in this ultra-rare disease. Along with the NHS and the Phase 2, the total number of individuals contributing data represents approximately 25% of the world's known population with FOP. The NHS provides a unique and valuable dataset. Recognising the challenges of relying on a natural history comparator, several important characteristics make the NHS an appropriate control group for Study 301 as detailed in Section 3.1.3.

Although for the pivotal Phase 3 trial the futility boundary was crossed at IA2, this was primarily due to differences between WBCT visit schedules in the NHS and Study 301, which, in combination with the application of a square-root transformation to the data, inappropriately biased the results against palovarotene, masking the treatment effect. When accounting for the bias through adjustment of the visit schedules, the pre-specified Bayesian model predicted a 91% probability that palovarotene would reduce mean annualised new HO volume, compared with no treatment. When accounting for the bias by removing the square-root transformation, the model predicted a 99.4% probability that palovarotene would reduce any new HO compared with no treatment. Whilst these analyses are de

facto post-hoc, the only post-hoc aspect is the correction of the mathematical error in the calculation of HO values in each treatment arm. There is no attempt to present a fundamentally different approach to data analysis in order to rescue a study that has failed based on an appropriate primary analysis. Furthermore, every additional analysis performed provides confirmation of the beneficial effects of palovarotene in reducing new HO volume (see Section 3.1.2). The confidence to rely on these post-hoc analyses is derived from their comprehensiveness and the strength of the data, which consistently demonstrate benefit.

In addition, the analysis looking at the longer-term data through to study completion demonstrated that annualised new HO volume was reduced with palovarotene treatment during Study 301 compared with the NHS (see Section 3.1.6.1). Similar to the pre-pause treatment period, the highest reduction was seen when subjects were actively treated after post treatment re-start.

Finally, annualized new HO Phase 2 data provide additional supportive evidence of the efficacy of palovarotene in reducing the volume of new HO in subjects with FOP. When excluding untreated/undertreated flare-ups for both the 202B/C and 202C, reduction in new HO volumes similar to Study 301 were observed. This indicates that the apparent discrepancies between the Phase 2 and Phase 3 WBCT data are due primarily to key differences in how flare-ups were defined and treated.

In conclusion, the totality of data supports the efficacy of palovarotene in patients with FOP. The primary results were demonstrated based on the pivotal Phase 3 Study 301, with supportive data derived from mechanistic evidence of benefit in nonclinical models and findings from Phase 2 Studies 201 and 202. What appears to be critical is the use of increased dosing at the time of every flare-up or trauma. Overall, the multiple statistical methodologies employed to analyse the new HO volume data in Study 301 and the NHS in conjunction with the comparable data from Phase 2 studies are consistent in their conclusion of efficacy. Given that HO is cumulative and irreversible, reducing the trajectory of HO formation would be expected to preserve function over the course of a patient's lifetime. Collectively, results from the nonclinical and large clinical development programme support the efficacy of palovarotene in FOP, particularly in the context of an ultra-rare disease with no available treatment options.

Ground #3

- The results suggest that all skeletally immature subjects receiving palovarotene are at risk for premature physeal closure (PPC), which is a known safety risk for all retinoids. PPC is an irreversible serious risk which may be associated with growth arrest, leg length discrepancy, disproportionate, angular deformity in affected joints, and gait disturbance. PCC was reported with palovarotene treatment in children< 14 years. Therefore, the proposed indication in females> 8 years and males >10 years cannot be supported and risk minimisation measures for PPC in subjects with an immature skeleton are not considered feasible or sufficient.

Applicant's grounds for re-examination: Point 3

To characterise the potential consequences of PPC as indicated by the CHMP (lower limb asymmetry and unsatisfactory short stature) and directly address the concerns, a detailed review of the individual patient narratives was conducted, including radiologic and clinical assessments of growth for all 13 patients diagnosed with PPC in the initially proposed target population. Section 3.2.1 below describes how PPC can be detected and monitored. Given that the potential consequences of PPC have not been shown with the available data, thus cannot be considered as severe as untreated FOP disease progression, it should be left to the individual patients, their caregivers and healthcare providers to decide their treatment path. To further support an indication in paediatric patients, additional expert consultation with a growth expert (e.g., endocrinologist) could be requested prior to and during

palovarotene treatment. Further characterisation of patients with PPC in the target population are provided in Section 3.2.2. Note that age was categorized based on age at enrolment.

3.2.1 Overview of PPC – Detection, Long Term Effects and Mitigation

Throughout the palovarotene clinical development program, 13 patients in the initially proposed target population were diagnosed with PPC. To characterise the magnitude of this risk and directly address the concerns previously outlined by CHMP, Ipsen has conducted a detailed review of the individual patient narratives, including radiologic and clinical assessments of growth for all 13 patients. This assessment includes off-treatment data for 8 patients ranging from 1 to 3 years which provide a robust assessment of growth after treatment discontinuation and the potential long-term consequences of PPC. Individual patient narratives are included in Appendix 3 and the results are summarised below.

Regarding concerns for patient growth, some key aspects to consider are listed below. Of the 13 patients diagnosed with PPC:

- 9 patients diagnosed with PPC continued to grow after diagnosis, 2 patients had already achieved near adult height, one patient showed growth deceleration prior to palovarotene, one patient had moderate scoliosis develop by month 12.
- 6 achieved a height within the normal adult range (≥fifth percentile) by the last follow-up visit (average height z-score at last visit: 0.7)
- 2 did not exhibit any detrimental effects on growth
- subjects had moderate scoliosis that contributed to their height deceleration (2 showed signs of growth deceleration prior to the PPC diagnosis PPC)
- 1 was near adult height at the time of palovarotene initiation
- 7 patients had heights below the fifth percentile for sex-matched adults at end of study (average height z-score at last visit: -1.7)
- 3 patients showed growth deceleration prior to initiating palovarotene
- 6 patients showed growth deceleration after treatment initiation (of these, 4 showed growth deceleration prior to the diagnosis of PPC)
- 1 was near adult height at the time of palovarotene initiation
- 5 had moderate scoliosis and/or severe kyphosis (not related to palovarotene) that contributed to their height deceleration
- 2 had evidence of partial closure of at least one growth plate prior to the diagnosis of PPC
- 1 achieved growth stabilisation following discontinuation of palovarotene
- Note: some patient may be contributing to multiple observations above

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

Regarding leg length assessment and angular deformity, given that dedicated radiographic and computed tomography were not performed to quantify these parameters, accurate measurements were often difficult due to uneven patient positioning. This applies to patients treated with palovarotene as well as those included in the NHS. Of the of the 13 patients diagnosed with PPC:

- No patient demonstrated a distal femoral angle post baseline that would indicate angular deformity up to last assessment.
- A single patient had a potentially clinically significant leg length difference at Month 48 (1.6 cm), however this began 2 years off treatment with no previous timepoints meeting the threshold for leg length discrepancy (>1.5 cm). No adverse event was reported.

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

Consequently, not all patients who develop PPC would be expected to have detrimental effects on final height and leg length discrepancy or angular deformity. The clinical consequences of FOP and HO formation are severe, and thus for every growing patient the potential risks of PPC need to be weighed against the benefits of reducing the volume of new HO formation and potential for preserved mobility. As a precautionary measure, the proposed risk minimisation plan recommends radiologic monitoring of the occurrence of PPC and clinical assessment of growth every 6 to 12 months for patients receiving chronic therapy and every 3 months while patients are being treated for a flare-up. Overall, for patients who had any negative observation of growth, 6 of 11 showed signs of either growth deceleration or growth plate closure prior to the PPC diagnosis and/or prior to palovarotene initiation and 2 of 11 were already at near final height. As such, careful monitoring of growth patterns and x-rays both prior to starting palovarotene and at regular intervals can provide treating clinicians with the information necessary to follow patients and intervene if deemed necessary.

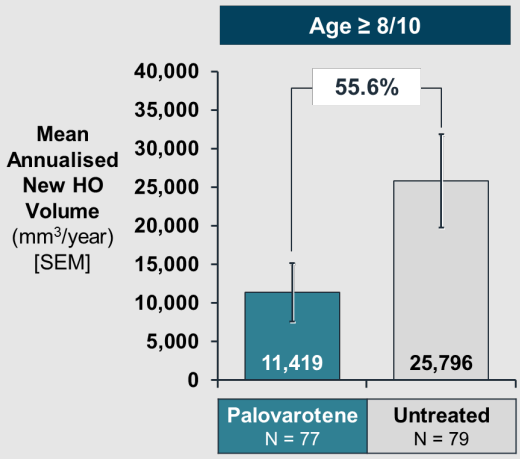
Clinicians who care for these patients, such as paediatricians, are equipped to assess paediatric patients, in the context of PPC occurrence and impact, ensuring appropriate monitoring and informing clinical actions as applicable. The proposed assessments can be done with routine x-rays at any facility with radiologic capabilities and thus are feasible at smaller hospitals. Importantly, the proposed frequency of x-ray monitoring presents a low risk of radiation exposure. The radiation associated with a single PPC assessment is equivalent to about two days of environmental background radiation exposure, or approximately 15 times less than an aeroplane ride.

Lastly, to further mitigate the potential risk, the Applicant has also proposed new language in the Summary of Product Characteristics (SmPC) /Leaflet and Educational Materials recommending that all growing patients have a consultation with an expert in growth (i.e., paediatric endocrinologist) prior to starting palovarotene and ongoing as required.

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

3.2.2 Assessment of PPC Risk in the Context of Benefits for the Target Population of Patients >8/10 Years of Age

Palovarotene has been shown to decrease annualised new HO volume across all paediatric age groups with the largest reductions observed in the youngest patients. In the initially proposed target population, 13 palovarotene-treated patients were diagnosed with PPC. The clinical meaning of PPC is discussed in Section 3.2.1 and individual patient details are displayed in Appendix 3 PPC Patient Profiles. As shown in Figure 21, when looking at the efficacy in this same age category, there was a 56% reduction in annualised new HO formation in palovarotene-treated patients compared to untreated patients in the NHS.



Age at Study Enrollment	Palovarotene n / N	Palovarotene %
Total PPC Events < 18 years	27 / 102	26%
Age < 8/10	14 / 25	56%
Age ≥ 8/10 to < 12/14	12 / 23	52%
Age ≥ 12/14 to < 14	1 / 11	9%
Age ≥ 14	0 / 43	0%

PPC Events in Phase 2 and Phase 3

Figure 21 Benefit-Risk Assessment in Target Population (Patients >8/10 Years of Age)

HO=heterotopic ossification; PPC=premature physeal closure; SEM=standard error of the mean. Note: Post-hoc comparison of raw data as collected in Phase 3.

The initially proposed target population (females ≥8 years of age and males ≥10 years of age) was identified based on the risk of PPC, together with skeletal maturity, and in conjunction with the knowledge that physical impairment can occur in patients with FOP as young as 4 years of age (Pignolo et al 2019). The specific age cut-offs were chosen based on the average ages at which paediatric female and male patients achieve approximately 80% of their adult height (ie, at 8 and 10 years of age, respectively). Because of this, the target population mitigates the potential consequences of PPC in the youngest of patients, while still allowing for treatment to be initiated at the median age of onset of large joint immobility such as the shoulders, hips, and knees, a critical time in disease progression. Appropriate warnings and risk minimisation activities will facilitate personalised treatment discussions among physicians, patients, and parents/caregivers. These discussions would allow patients, their caregivers, and their healthcare providers to consider the potential benefits and risks for each individual patient, allowing intervention at the most appropriate time.

3.2.3 Benefit-Risk in a Narrowed Patient Population of Patients ≥12/14 Years of Age

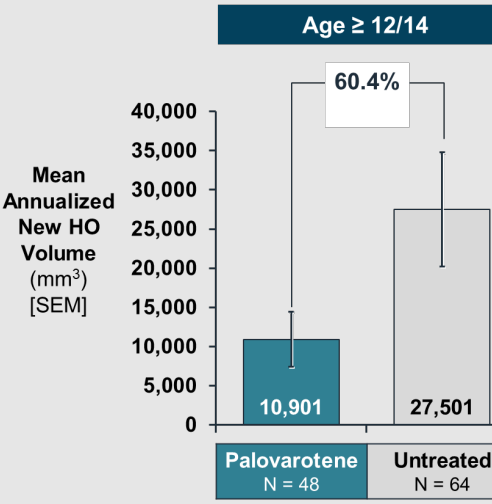
Palovarotene has shown efficacy in all paediatric subgroups, but it is understood that the youngest patients are at the highest risk of developing PPC. As illustrated above, the specific age cut-offs were selected to mitigate the potential consequences of the PPC while allowing for treatment with palovarotene to be initiated before major joint mobility is lost. As outlined in Section 3.2.1, this risk of PPC can be satisfactorily monitored.

However, because growth is a continuum and the risk of PPC decreases as paediatric patients mature, narrowing the patient population to females ≥12 years of age and males ≥14 years of age would nearly eliminate this risk. These specific ages represent the average time when paediatric female and male patients achieve approximately 90% of their adult height and would further mitigate the potential occurrence of PPC.

Throughout the palovarotene clinical development program, in the ≥12/14 patient population, there was one single event of PPC diagnosed. The patient began palovarotene in late puberty having attained menarche one year prior to starting treatment and had negative growth from baseline through end of study, likely indicating near final height with measurement error due to spinal fusion and scoliosis. There were no long-term consequences including no angular deformity or leg length discrepancy; as such the clinical impact of PPC was minimal.

When looking at the efficacy in the ≥12/14 age category at the MAA data cut-off date, palovarotene-treated patients achieved a 60% reduction in annualised new HO volume when compared with the NHS (HO=heterotopic ossification; PPC=premature physeal closure; SEM=standard error of the mean. Note: Post-hoc comparison of raw data as collected in Phase 3.

Figure 22).



Age at Study Enrollment	Palovarotene n / N	Palovarotene %
Total PPC Events < 18 years	27 / 102	26%
Age < 8/10	14 / 25	56%
Age ≥ 8/10 to < 12/14	12 / 23	52%
Age ≥ 12/14 to < 14	1 / 11	9%
Age ≥ 14	0 / 43	0%

PPC Events in Phase 2 and Phase 3

HO=heterotopic ossification; PPC=premature physeal closure; SEM=standard error of the mean. Note: Post-hoc comparison of raw data as collected in Phase 3.

Figure 22 Benefit-Risk Assessment in Target Population (Patients ≥12/14 Years of Age)

A narrowed patient population would effectively mitigate the occurrence of PPC, but still have a clinically meaningful impact on the known progression of FOP and the onset of irreversible disability, in joints such as the elbow, hip, knee and ankle. These are critical joints which allow a patient to continue to walk without the aid of a wheelchair.

Overall, the benefits of palovarotene treatment outweigh the potential risks in the target population of patients with FOP. FOP is a devastating disease with no approved therapies. For the first time, an opportunity exists to offer patients living with this ultra-rare condition a disease modifying therapy that reduces the volume of new HO with the potential to preserve their mobility and function over the course of a lifetime. Because heterotopic bone formation in FOP is cumulative with irreversible consequences, the earlier the intervention the greater the potential to slow disease progression. The target age initially proposed for palovarotene represents a crucial time to slow the cumulative progression of HO formation and preserve a patient's ability to function. However, the Applicant acknowledges CHMP's feedback in the assessment report with regards to the acceptability of this risk in young patients. As such, narrowing the indication to an older population of patients such as those ≥ 12/14 years would further improve the benefit-risk profile by greatly diminishing the population at risk for the occurrence of PPC while still allowing for treatment to be initiated early enough to preserve a patient's mobility and independence.

Report from the ad hoc expert group

Following a request from the applicant at the time of the re-examination, the CHMP convened an Ad Hoc expert Group inviting the experts, including patients/representatives, to provide their views on specific questions based on the CHMP grounds for refusal, taking into account the applicant's response.

Question 1

The heterotopic ossification (HO) measurement procedure was a 2-step process starting with the central imaging laboratory readers performing a qualitative assessment of each body region whether there was any new HO compared to baseline (or the previous scan). If the qualitative assessment suggested new HO in any body region, then the change in total HO volume vs. baseline or the previous scan within this region was determined. If no new HO was found, no further volume measurements were performed and the HO volume change was set to zero in the analysis. Reductions in HO were not expected. The experts are invited to provide their views on the radiological assessment of HO:

a. Are low-dose whole body computed tomography and radiological assessments as performed considered suitable for reliably estimating the change in new HO volume in young children with FOP?

The experts noted the ability of computed tomography (CT) to highlight the high contrast between soft tissue and bone. Measuring HO volume in cubic centimetres was considered acceptable by the experts and the semi-automated nature of HO volume measurement was welcomed. The experts noted however that there may be difficulties to determine the exact border between normal bone and HO when the HO is attached to the skeleton. The experts considered that a radiological assessment method using only X-ray would be less reliable in estimating the change in new HO volume in young children.

The observed and potential inter- and intra-assessor variability in radiological assessments was noted by the experts. Additionally, the ability to detect very small areas of HO development in normal soft tissues and the potential clinical impact of this was mentioned. The finding of negative HO values during the pivotal trial was highlighted as a finding of concern by the experts in the setting of ascertaining the suitability of the proposed assessment method. Adequate clarification on this matter is still outstanding.

The experts and one of the patient representatives noted that in certain tertiary centres, nuclear imaging is the method of choice to assess location and volume of newly formed HO. Specifically, computed tomography plus positron emission tomography (18F-FDG PET/CT) is used, in particular in the setting of clinical trials to accurately measure abnormal bone growth. PET scanning provides more information on disease activity. However, it was acknowledged by the experts that nuclear imaging is not available in all centres or geographical settings and that this would restrict access for certain subjects to a trial in FOP.

The difference in assessment intervals between the treatment arm in the pivotal study and the Natural History Study (NHS) were highlighted as a limitation by all experts. This was considered a major bias likely favouring palovarotene effect. It was also noted that skeletal areas without new HOs were not assessed during the pivotal trial.

In conclusion, due to the discrepancy in the applicant data presented during the AHEG, compared to data presented by the applicant during the MAA procedure it was considered difficult to provide a definitive answer to this question. The proposed method can be considered to be reliable from a clinical perspective to estimate the change in new HO volume in young children with FOP.

b. How well can new HO be visualised and their size estimated with this method? How is the measurement error of this method judged?

The experts commented that detection of small areas of new bone growth using CT scan is possible, even at the level of millimetres of difference. It was however not clear to the experts what would be the minimum size of areas that could be detected by the CT scan examination. The concern of the experts was how these data from the pivotal trial would be analysed and interpreted. In general terms, precision, accuracy and minimum detection value are considered to be very important. However, the measurement error nor standardisation of the assessment guidelines for the pivotal study could be found in the application dossier by the experts. It was noted that reproducibility of the proposed method is key to reliability, but ultra-rare diseases provide challenges due to the limited number of available subjects and there are inherent limitations of NHS.

The limitations due to the discrepancy in assessment timepoints between the pivotal study and the Natural History Study were again highlighted.

The experts questioned why the applicant did not assess total body new HO formation and instead measured HO formation across 9 different body regions individually.

In conclusion, the proposed radiological assessment method may adequately visualise the occurrence and size of new HO in FOP. The issue of inter- and intra-assessor reliability was raised and must be further demonstrated and justified by the applicant. In addition, longer term reliability of the proposed assessment method would need to be further justified.

Question 2

The Applicant argues that the choice of the Bayesian analysis (with square-root transformation) was an error and their conclusion on palovarotene efficacy is now based on a post-hoc analysis of the primary endpoint radiological data. From the provided data, it can be observed that the chosen analysis affects the estimated treatment effect (depending on the analysis model, data transformation and handling of negative values).

a. In the grounds for re-examination, the Applicant provided a "corrected" Bayesian analysis with data from study PVO-1A-301 collapsed over 12 months to better match the visit schedule in the natural history study (NHS). Other analysis aspects (square-root transformation and negative value imputation to zero) remained as specified in the primary analysis. What is the view of experts on the choice of this "corrected" Bayesian analysis?

Generally, the experts mentioned that Bayesian methods are not commonly used in clinical trials analysis. The experts acknowledged that the square root transformation and different visit schedules led to inconsistencies. The "corrected" Bayesian analysis was considered an improvement compared to the square root choice. It addresses the issue of the time points aggregation inconsistency. However, the experts agreed that additional sensitivity analysis would be needed to minimise bias related to e.g. the choice of the prior, age cut-off. Not all experts were convinced that the specified Bayesian compound model would be the 'right' model, especially the binary age cut-off was questioned. One expert mentioned that the applicant had combined two parameters (for the prevention and reduction) which was not an optimal choice.

The experts also noted that no prior sensitivity analyses were performed by the applicant to ensure that the prior they selected would not introduce a bias towards a treatment effect. The experts also expressed concerns that the comparison between baseline to month 6 and month 6 to month 12 in the clinical study compared to the NHS introduces a bias towards a treatment effect (there is less chance to see an HO at 6 months compared to 12 months). Comparison between baseline and 12 months in

the clinical trial would have been more adequate to be able to truly compare with data from the NHS study (i.e. only using timepoints that match between the two studies, i.e. deleting the 6 month data).

Overall, the experts agreed that the applicant's "corrected" Bayesian analysis partly remedied the problem concerning the different time points, but it did not completely solve the problems with the design. A wish was expressed to only use timepoints that matched. However, it was highlighted that this would require re-assessment of all scans in the trial, as all 12-month scans would have to be compared to baseline (and not to month 6). In addition, the experts also noted that a sensitivity analysis was missing to show the robustness of the results.

b. Given the study results of PVO-1A-301, can an effect be considered established in the studied population? The above mentioned "corrected" Bayesian analysis indicates that there is approximately a 90% chance that there is "any reduction" in new HO. The treatment effect was estimated to be a 16% reduction in new HO, with a median posterior gamma (CI) of 0.84 (0.64, 1.09). What is the view of the experts on this result?

Considering both, the issue of the timepoint of the assessments and the lack of sensitivity analyses to define the prior, introduces concerns whether the effect seen is truly attributable to the treatment. This should also be seen in the context of an open label study, without comparator, and the fact that the study was stopped for futility. It was acknowledged that there were issues with the design, unblinding and post-hoc analyses in this study that add further uncertainty to the results. The fact that 39 patients transitioned from the NHS to the clinical study adds to the complexity in analysing the observed results. According to the experts there is not definitive evidence of a reduction because of the methodological limitations.

One expert shared a plot of the prior distribution for gamma, which was based on simulated uniform distributions. The prior distribution for the gamma parameter was skewed, favouring palovarotene. The question was raised whether this choice would overestimate the treatment effect. Usually, a sensitivity analysis on the influence of different priors would be expected but it seems that this had not been done here.

The experts agreed that the effect is rather small compared to the assumed prior effect. The chosen outcome consisted of two parameters. The experts concluded that this combined parameter was biased towards smaller numbers. Therefore, the 16% reduction, when unbiased, could be even lower. This combined outcome parameter measure makes the interpretation of the results very complex.

The absence of an effect on the number of new HO regions was also noted by the experts.

Overall, the experts did not seem convinced that an effect can be considered established in the studied population. It could not be ruled out that the effect is driven by something else other than treatment. In addition, the effect measured is not very large in comparison to what was expected a priori. Moreover, their 16% combined effect measure makes the interpretation of the results very complex. The 90% chance that there is "any reduction" in new HO was considered by the experts overestimated and a sensitivity analysis on the influence of different priors would be needed.

c. Taking into account the limitations and uncertainties of the data and study design, do the experts consider the observed treatment effect to be clinically relevant in the claimed indication, in view of the "corrected" Bayesian analysis results? Subgroups should only be considered after efficacy has been demonstrated. In case the experts consider that there is sufficient certainty on efficacy of palovarotene, the experts are invited to discuss the relevance of the effect in older children, as the potential treatment effect seems to decrease with increasing age.

The experts agreed that any reduction in HO would be considered clinically relevant considering the seriousness of the disease and the irreversible nature of the HO. This view was shared by the patient representatives.

However, the experts noted that it is difficult to determine if there is an effect with palovarotene considering the methodological limitations. One expert asked whether there are also time effects that may not have been captured in the model. Overall, the length of the study may not be long enough to capture a longer-term outcome. Following the patients in Real World setting over extended time periods will be extremely difficult due to their progressive disability that makes it challenging to travel.

From a clinical perspective, given the treatment is efficacious to prevent HO development, the earlier the treatment the better to prevent progression of the disease. Early start would be especially important if the effect decreases with age. However, given that the experts were not convinced that efficacy was proven, they did not conclude on the relevance of the effect in older children as based on the data reviewed the potential treatment effect seems to decrease with increasing age.

d. Negative "new HO" values were observed, generating the hypothesis (after futility declaration and unblinding) that palovarotene could be involved in bone remodelling. Potential explanations for these negative values range from measurement errors to a true pharmacological effect of palovarotene. The experts are invited to discuss whether they consider it likely that the negative new HO values truly represent a treatment effect of palovarotene.

The experts were surprised by the presence of negative values observed since volume was only assessed if the initial assessment indicated new HO. If the initial assessment indicated no new HO, delta-volume was set to 0. The experts could therefore not rule out that the negative effects come from the measurement errors. The explanation of the negative values remained unclear. It is possible that palovarotene has a pharmacological effect and decrease established HO. However, there is no evidence for this in the literature and the experts were not convinced that the negative values could be due to a pharmacological effect as no reduction in new HO was observed. In addition, the experts could not exclude that the presented effect is not due to mismatching time point. A reanalysis with only matching timepoints could be considered suitable.

e. Are there other relevant signs of efficacy in the submitted data that could be considered?

Longitudinal observation and analysis of the patient's growth over time and appearance / change in total volume of HO lesions would be of value compared to the natural history group.

Question 3

The experts are invited to discuss whether the observed safety profile of palovarotene in the population studied, in particular the risk of premature physeal closure (PPC), can be considered manageable and whether any particular measures should be considered to mitigate the risk of PPC.

- **The effectiveness and feasibility of the monitoring proposed by the applicant, i.e., radiological assessments including but not limited to an assessment of skeletal maturity via hand/wrist and knee x-rays, standard growth curves and pubertal staging at baseline and every 6-12 months until patients reach skeletal maturity or final adult height should be discussed.**

The experts highlighted that the X-rays and measurements is not an effective tool to mitigate the risk of PPC (as it is too late when seen on X-rays) but they considered that measurements and X-rays still provide valuable clinical data to assess growth plate and should thus be monitored.

The experts considered bone age a good clinical predictor for how much growth the patient in this population is still expected to experience in his/her lifetime before treatment with palovarotene. By taking into consideration how much a patient is still expected to grow, a more suitable risk assessment for PPC can be performed. There are not sufficient data to assess the risk of PPC and loss of height with palovarotene treatment.

In conclusion, the follow up and the proposed assessments were considered to be feasible and close to the scheduled visits in clinical practice, however, they are not useful to predict the PPC in time as they may be performed relatively late. All remaining growth should therefore be considered at risk when palovarotene is started.

- **If radiological evaluations are considered useful for identifying patients at risk of PPC, what would be their optimal frequency, also taking into account cumulative radiation exposure in this age group (children/adolescents).**

In view with the rare and disabling disease, the experts consider 6 to 12 months frequency acceptable as the radiation exposure is considered low and patients will only require it for a couple of years.

- **If radiological monitoring is not judged appropriate, is there an age or bone age cut-off above which the risk of PPC is considered minimal or acceptable?**

Yes, losing a small amount of height would likely be acceptable to most patients if HO development can be delayed. Palovarotene can induce PPC and growth arrest even in young children. There is still insufficient data on the dose-response effects on PPC and loss of height in individuals with FOP. All remaining growth should therefore be considered at risk when palovarotene is initiated. Establishing a bone age cut-off would therefore make sense as remaining growth correlate better with bone age than chronological age. There are well documented literatures on the correlation between bone age and remaining growth. For example, at a bone age at 12y/o for girls and 14y/o for boys approximately 92% of adult height have been attained. With this example the negative effect of PPC on adult height would be limited to 8% or less. The experts noted that the amount of remaining growth that each child and family is willing to risk would depend on how tall the patient is and on how severely the patient is affected. Alternatively, an even younger bone age could be considered acceptable and the final decision on how much height each child/family is willing to risk is to be agreed between the treating physician, and patients/patient's family following an individual benefit-risk assessment.

Question 4

In case the experts consider that there is sufficient certainty on efficacy of palovarotene, follow up will be necessary to address the long-term efficacy and safety of the product post-approval. What suitable key endpoints and methodological design could be advised for such a study in the post-authorisation setting, also taking into account feasibility?

Provided that efficacy has been demonstrated, the experts agree that a study with annual follow-up would be considered necessary to address the long-term efficacy and safety of palovarotene post-approval. As a method, PET scan use is encouraged besides the X-rays although it was also recognised that such method may be challenging with certain patients (narrow tunnel) and the need for an invasive approach for the i.v. contrast agent application. Radiological assessments are considered suitable to assess growth plate however as mentioned in the previous question, they are not an effective tool to mitigate the risk of PPC.

The experts mentioned that the following endpoints should be measured in such study: quality of life e.g. PROMIS, disease stage (time to end stage, time to event endpoint), jaw limitation, mobility and fatigue assessment, joint/functional assessments. Pain and pain management (chronic and acute pain)

was also mentioned as an important aspect to look at. Experts agreed that blood tests should not be performed in this population to avoid the risk of new HO.

Question 5

Is there anything else the experts would like to provide their views on the data submitted by the applicant to address the grounds for refusal (failed pre-defined primary analysis, post-hoc analysis, limitations of the natural history cohort, results on secondary endpoints and the robustness and clinical relevance of the findings) regarding efficacy and safety of palovarotene in the claimed indication?

The failed pre-defined primary analysis, post-hoc analysis, limitations of the NHS and robustness and clinical relevance of the finding were already discussed by the experts in previous questions. The lack of supportive evidence derived from the secondary endpoints was again noted together with the lack of functional outcomes as compared to the natural history group.
It was highlighted by the experts that longitudinal data analyses and further long-term data for palovarotene in FOP are required, including real world data. It is noted that the applicant proposes a post-approval registry, should the medicinal product be recommended for approval by the CHMP.
Overall, it was felt that many of the issues detailed within Question 5 had been addressed in responses to earlier questions.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the ad hoc expert group.

Ground #1

MO1:

The applicant proposed to redefine the starting material as a post approval commitment in H1 2024 when corresponding active substance batch data will become available. If view of the negative benefit/risk balance, the acceptability of a post-approval commitment/variation strategy concerning the redefinition of starting materials was not concluded.

Conclusion of CHMP at the end of the re-examination procedure:

MO1 remains unresolved and the applicant's proposal to redefine the starting material as a post approval commitment in H1 2024 when corresponding active substance batch data will become available is not agreed in view of the CHMP negative opinion on this application.

OC1. Testing for impurities

The applicant has not provided a justification/explanation for the initially proposed control strategy to omit the testing in the active substance of certain impurities and has instead introduced a routine test in the active substance for these impurities. This proposal resolves this remaining quality OC. The GC method to be used to determine these impurities in palovarotene active substance has been adequately validated, and the proposed acceptance criteria are adequately justified. The proposed updated specifications for palovarotene active substance are acceptable.

Section 3.2.S.4 has been updated accordingly.

Conclusion of CHMP at the end of the re-examination procedure:

Point resolved.

Note:

The proposal to test 10 consecutive palovarotene batches and, in case those impurities being absent in the batches, to remove their testing from the active substance specification through a post approval variation, is not supported. However, as per ICH M7, periodic verification testing could be justified in the future when it could be shown that levels of the mutagenic impurity in the drug substance would be less than 30% of the acceptable limit for at least 6 consecutive pilot scale or 3 consecutive production scale batches. If this condition is not fulfilled, the routine test for those impurities in the active substance specification would have to be kept.

OC2. Additional method to identify one of the impurity standards for control of the active substance

The applicant fully addressed the outstanding issue on the quality of the active substance related to the need of including an additional method to identify the impurity standard for control of the active substance. The impurity will be identified also by its retention time using the HPLC method already in place for assay and purity testing. The Primary Reference Standard Results were provided. The proposed updated impurity specifications are acceptable. Section 3.2.S.5 has been updated accordingly.

Conclusion of CHMP at the end of the re-examination procedure:

Point resolved.

OC3. Special storage condition

The applicant fully addressed the outstanding issue on the quality of the finished product related to the need of adding appropriate instructions for special storage condition to the product information. The Applicant agrees to add the special storage condition "Do not store above 30°C". Section 3.2.P.8.1 and the product information has been updated accordingly.

Conclusion of CHMP at the end of the re-examination procedure:

Point resolved.

Ground #2

The Applicant argues that the totality of data supports the efficacy of palovarotene in patients with FOP, particularly in the context of an ultra-rare disease with no available treatment options. As stated by the CHMP in the Day 180 Letter to the Applicant, it may be acceptable to present post-hoc modifications of the primary analysis because of errors in the pre-specified statistical methods or choice of clearly suboptimal statistical models. However, based on the data provided, the CHMP do not agree with the Applicant that the correction of the error in observation periods results in robust confirmatory evidence on the efficacy or clinically relevant effect of palovarotene, nor that the square root transformation and setting negative values should be viewed as errors.

It should be emphasized that there was no difference in the mean observed annualised new HO volume in the pre-specified Bayesian analysis (square root transformed data zeroed out by body region). This was consistent with the futility conclusions from the interim analysis. In this context, analyses defined after the futility decision and the unblinding of the trial cannot be considered confirmatory evidence, and a data-driven selection of alternative statistical analyses cannot be excluded. Multiple sources of uncertainty remain, type I error is no longer controlled and bias of a relevant magnitude cannot be excluded.

The following observations and uncertainties reduce the robustness of the conclusions:

1. No difference in the percentage of patients with new HO was observed

In study 301, no difference was observed in the percentage of patients with new HO: 64% of patients in the palovarotene group versus 62% of in the control group showed the formation of new HO. This finding was not in line with the hypothesis at study planning. The study was powered based on an expected reduction in the number of regions with new HO by 30% and a reduced volume of new HO conditional on new HO per body region by 50% (overall 65% reduction). Given the rarity of the disease, it may be understood that limited earlier phase studies have been performed, however, the Applicant explains this finding by stating that "*it is clear that the rigorously controlled conditions in animal studies versus the extremely complex and heterogenous disease process observed in individuals with FOP account for the fact that a similar proportion of palovarotene-treated and untreated patients had any new HO at 12 months, with similar mean number of body regions with new HO*". To our opinion, this statement highlights that this finding is unexpected and can also not be fully explained in hindsight. The same complexity and heterogeneity also apply to the amount of HO formed, and if using the same arguments as the Applicant, the difference in volume of HO may also be attributed to the complexity and heterogeneity of the disease, rather than to the treatment. The volume of HO formed in patients with new HO may also be more prone to (selection) bias.

2. Potential bias due to unequal observation periods with and without square root transformation
It is agreed with the Applicant that the pre-specified Bayesian model is biased by the unequal frequencies of CT scans (BL, 6-12-18-24 months in the active arm, versus BL, 12-24 months in the NHS), especially when applying the square root transformation on different observation periods and thereafter sum the result. For the NHS group the 12-month scan was compared to baseline, while for the palovarotene group the 12-month scan was compared to the previous 6 month scan and the 6 month scan to the baseline scan. To partially correct for this difference, the Applicant has provided the Bayesian analysis using 12-month collapsed data, meaning the increase from month 0-6 and from month 6-12 have been summed before applying the square root transformation. This is considered a useful correction.

However, the potential bias resulting from the method used to quantify HO remains, due to comparing two short observation periods in the palovarotene group (12 compared to 6 and 6 compared to 0 months in the palovarotene group) versus one longer observation period (12 compared to 0 months) in the NHS group. This bias is likely favouring the palovarotene group, as a small increase in new HO over two times a 6-month period may be more likely missed and scored as "no increase" in the qualitative analysis, while the same increase scored over a 1-year period has more chance to be visible and scored as "qualitative increase". In order to make both observation periods better comparable, the 12 months scans should have been compared to baseline for both groups.

3. Application of the square root transformation itself cannot be seen as an error

The square root transformation was implemented to decrease the impact of outliers. In the Day 180 report it was pointed out that it may be acceptable to present post-hoc modifications of the primary analysis because of errors in the pre-specified statistical methods or choice of clearly suboptimal statistical models. However, given the skewed distribution of the data, and the rationale of the Applicant for choosing this model, the square root transformation itself is not considered an error and should be taken into account when evaluating the strength of the evidence of the submitted data.

Several examples are provided by the Applicant to argue on the potential bias against palovarotene based on the sum of new HO volumes for hypothetical patient values, with and without square root transformation. However, the treatment effect parameter (γ) of the Bayesian model is the product term of the treatment effect on the mean number of regions presenting new HO with the treatment effect on new HO volume conditional on new HO occurring. Although the potential for bias is understood, the exact consequences on this parameter estimate is likely not as straightforward as

presented by the Applicant.

Moreover, the square-root transformation is not in itself objected to, as it was originally justified by the presence of higher than expected variability on the absolute scale. Therefore, the Applicant's opinion that the square-root transformation was an error is not supported. The rates of new HO appear to follow a rather skewed distribution, with a number of outlier values. It could therefore be argued that some data transformation might help improve model fit, and it is unclear whether this has been adequately investigated by the Applicant. Of note, a normal distribution is assumed for new HO volume in the Bayesian model. It could be questioned whether performing an analysis based on untransformed and heavily skewed data is appropriate. A different handling of other aspects of the statistical analysis (e.g. not relying on comparison versus previous scan, or an analysis that is not sensitive to differences in visit schedules – such as the one with 12-month collapsed visit schedules) may have allowed for data transformation without generating further bias.

As discussed above, the application of the square root transformation on unequal time periods can be considered an error warranting correction. As the effect of square root data transformation on the results is very large, the data without the transformation will also be considered.
As most analyses are post-hoc and may be data-driven, the error-corrected analysis closest to the originally pre-specified analysis should deserves the most value. In Figure 11, the Bayesian analysis with square root transformation using the 12 month collapsed data shows a 9.4% chance of a >30% reduction in new HO. Of note, the futility boundary set for the study was 5% chance of a >30% reduction. Hence the observed effect is close to the predefined futility boundary.

Nevertheless, this analysis also indicates that there is a 90.7% chance of any reduction of new HO (>0%). The clinical implications are uncertain as no minimally important clinical difference is defined for new HO and should be weighed against the safety profile of the product. Of note, with the right-skewed transformation, it is expected that the reduction in annualized change in new HO volume is smaller on the square-root scale than on the original scale without applying a transformation. The futility boundary of 30% seems to have been set on the square root scale, which cannot be directly applied to the original untransformed scale.

The wMLE analysis with negatives zeroed should be interpreted as a secondary analysis, in this analysis, palovarotene treatment is associated with a 31% reduction compared with the NHS however this analysis is also not statistically significant.

The tipping point analysis is of very limited relevance as it only applies to the post-hoc statistical analysis being investigated, which has no confirmatory value. Of note, a nominal two-sided significance threshold of 5% is used for the tipping point, whereas lower thresholds were to be used at each interim and final time points for the primary analysis.

4. Negative HO values are clinically implausible and the data is not suitable for valid conclusions

The applicant has provided a re-iteration of the conducted wMLE analyses for palovarotene, including the negative values. Further justification of the applicant to not transform and zero out the data is provided, stating that spontaneous regression of bone is observed in FOP. This by itself is not disputed, however, the study design and the way the HO was measured does not enable a robust conclusion about bone remodelling.
The inclusion of negative new HO values in the primary analysis is not supported. As based on the pre-specified hypothesis, negative values were not anticipated; on the scan first, a qualitative analysis was done (new HO yes/no), and if there was new bone formation, a quantitative assessment of the HO volume was performed. Therefore, a negative value conditional on a qualitative assessment of new HO is difficult to interpret and distinguish from a measurement error. Negative values may have been observed more often in the palovarotene group due to the different observation periods. Even if we

would ignore this potential bias, there is no clear, biologically plausible explanation for an effect of palovarotene on bone resorption.
On the other hand, it is not completely ruled out that it may represents a real and unexpected treatment effect. The only published literature related specifically to the role of RARgamma in bone resorption reports that RARgamma inhibits osteoclasts and this would argue against enhanced bone resorption due to palovarotene (Green et al 2015). However, the literature on the effects of retinoids on bone are ambiguous. As also expressed in the initial assessment, data suggestive of bone resorption under palovarotene treatment should be seen as hypothesis-generating at best and not as confirmatory evidence of efficacy. Ideally, a new study with appropriate design and analysis method should be conducted to confirm this hypothesis. Or at the very least, re-examination and analysis of all the scans could be considered. However, this would require a thorough evaluation and re-design of the analysis method.

Moreover, the applicant states that the negative values might be indicative of maturation of new HO, which is presented as a positive outcome by the applicant; however it seems that maturation of new HO is an undesirable outcome.

5. The external control arm

The Applicant argues that statistical comparisons of palovarotene against an external control arm (the natural history study – NHS) were adequate. It is acknowledged that using an external arm was considered acceptable at the time of scientific advice. However, this was discussed under the Applicant's assumption that the treatment effect would be "dramatic", thereby excluding the possibility that the anticipated bias associated with non-randomised comparisons could question the size of the treatment effect.

However, this is not the case in the presented results. Indeed, the primary analysis reached the futility criteria (so it failed to achieve statistical significance) and the post-hoc analyses provided by the Applicant are inconsistent given that results highly depend on the statistical model and on the assumptions made on the data (e.g. with/without data transformation, with/without the inclusion of negative values). In this situation, the uncertainties and challenges associated with using non-randomised comparisons is another severe limitation to the interpretability of study results and add to the list of uncertainties preventing any robust conclusions from being made from palovarotene efficacy results. Moreover, and as acknowledged by the Applicant, some differences are affecting the interpretability of comparisons against the NHS, notably the WBCT assessment schedule and the collection of flare-up data. In addition, some differences can also be noted in baseline characteristics, including age and flare-up distribution at baseline.

A number of post-hoc analyses are then provided to support the use of NHS as external control. The first one was an analysis focused on patients who transitioned from the NHS to Study 301, i.e. for the subset of 39 patients serving as their own control. There are known challenges with the interpretation of this analysis, given that patients were older at Study 301 baseline, with higher HO volume and a higher rate of a flare-up in the past 12 months. The results from the presented wLME analysis do not reach the 5% nominal significance level. Moreover, the analysis presented may be data-driven. Indeed, the analysis does not use square-root transformation or impute negative values to zero. It cannot be excluded that alternative analyses (e.g. different statistical models, or with data transformation or negative value imputation to zero) would have led to even less favourable results.

6. Matched analysis: residual confounding and selection bias cannot be excluded

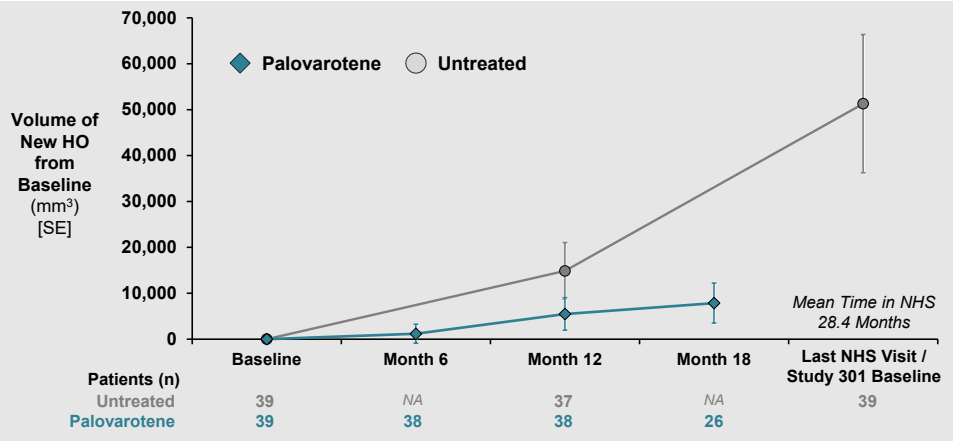
Three analyses have been provided to reduce confounding due differences between patients:
a). Subjects who transitioned from NHS to palovarotene; b). Subjects treated with palovarotene matched to untreated subjects (excluding patients who transitioned); c). A propensity score weighted

analysis

a. Subjects who transitioned from NHS to palovarotene

It is agreed with the applicant that subjects who transitioned to palovarotene could provide useful information for this complex heterogeneous disease, as a within-patient comparison can be made where patients serve as their own control. Therefore, confounding cannot be due to differences between patients in each study. However, selection bias of patients who opt for and are eligible for transitioning into the palovarotene group cannot be excluded.

At baseline in the NHS group the patients had on average 3.7 (SD 8.6) flare-ups in the past 12 months prior to enrolment, while this was 1.1 (SD 1.4) in the group that switched to the palovarotene group. This baseline difference and the potential impact are puzzling. The post-hoc wLME method showed a LS mean annualized new HO volume of 16,652 mm^3 in the untreated and 8,063 mm^3 in the untreated, a difference of 52%, nominal p-value 0.06. However, looking at Figure 19 there is an about 15,000 mm^3 increase in the first year in the NHS, with a much higher increase of 35,000 mm3 in the second year in the NHS. This unexplained large increase in the control group deserves further explanation and could potentially impact on the expected HO increase in the following year. The next year, there is a 5000 mm^3 increase during the first year of treatment and only a slight increase during month 12-18 of treatment. This decrease may be attributed to the treatment in NHS patients with increased bone formation, alternatively there might be impact (self)selection of subjects with much HO formation into the study, followed by regression to the mean.



b. Matched analysis of those who did not transition

The matched analysis of those who did not transition, matched for baseline characteristics, showed a 77% reduction in annualized new HO volume in Study 301 compared with no treatment in the NHS as shown in Figure 20 (nominal p-value <0.05). It is not stated what the age of the patients is in the matched analysis. Therefore, the relevance of this analysis for the final target population (patients with mature skeletons) is unclear.

c. Propensity score weighted analysis

For the propensity score weighting analysis, patients are weighted up or down to make the patients in the treatment group and the comparison group more similar to each other. There was a nominally statistically significant difference in annualised new HO volume among treated and untreated subjects. The mean (± SD) difference in annualised new HO volume between treatment groups was 19,430 (± 8,524) mm^3 after stabilised weighting (nominal $p < 0.05$). When reductions were coded as zero the effect was reduced (nominal p=0.09), and there was no significant difference when using the square

root of annualised HO (nominal p=0.55). As important limitations of this analysis, the Applicant mentioned that unobserved confounding could be excluded, the small sample size and a highly skewed outcome measure.

Given the highly skewed outcome measure, some form of transformation seems required.
In summary, when looking at the matched analysis a large reduction is estimated in all three studies. However, the analyses were performed post-hoc, which may have led to data-driven choices in the analysis. The results were nominal significant including negative values and without square root transformation. When reductions were set to zero the effect was no longer significant. When square root transformation was applied, the p-value was 0.55. Residual bias cannot be excluded in any of the three comparisons.

7. Secondary and tertiary endpoint results were not supportive of an effect of palovarotene

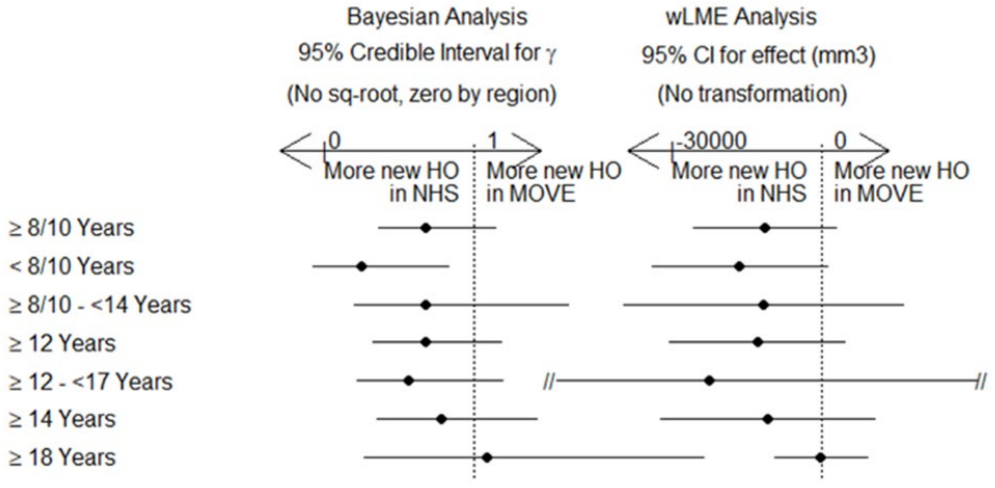
As discussed above, no difference was observed in the percentage of patients forming new HO in new regions. This is not consistent with the assumptions used for the sample size calculation.

There was also no effect of palovarotene on the flare-up rate. In fact, the flare-up rate was even higher in the treated group compared with the NHS. The applicant has provided various explanations for this difference, including underreporting in the NHS. Since the flare-up rate in the NHS was lower than that reported in the literature, this might be a plausible explanation. However, even if this caused the difference, this indicates that the study design was not suitable to assess an effect on flare-ups.

Several PRO's were used as tertiary endpoints to assess the effect of palovarotene on functional mobility and HR-QoL. Unfortunately, even though patient testimonials were submitted claiming increased functional mobility and less pain, this did not translate in a clear effect on these scales.

8. Uncertainty of extrapolation of treatment effect to target population

When looking at the forest plots, it is important to note that the prespecified analysis did not show a difference in the primary endpoint between MOVE and NHS. However, one interpretation of the post-hoc Bayesian analysis (without transformation) in the figure below would be that there is a possible difference in younger age-groups but no effect in adults. Due to safety reasons, palovarotene is no longer proposed for the treatment of children <8/10 years, and combined with the limited understanding of the disease, this adds further uncertainty to the expected treatment effect in the target population.



9. Usefulness of the Phase II study data

Phase II study data was submitted to support the efficacy of palovarotene. This is complicated for numerous reasons. At first, the data for flare-up dosing is not applicable to the proposed chronic dosing and hence, data from Study 201 cannot be used to support efficacy as only flare-up dosing was used. Second, the applicant states that the study was not designed to use NHS data as an external comparator, and important limitations remain comparing two different populations, which is exactly what is provided. Third, as also indicated by the applicant, interpretation of the annualised new HO from Part B of the study is difficult and does not reflect the true palovarotene treatment effect due to key differences in patient enrolment characteristics, dosing regimens, and flare-up definitions compared with Study 301. Finally, interpretation is further complicated because not all flare-ups lead to new HO, and not all new HO is preceded by a flare up. This is supported by the data from Figure 21 reporting a relatively high volume of new HO in patients who did not report a flareup.

The fact remains, that no dose-response was visible in the phase II studies. The applicant reports that *"The Study 202B/C and 202C populations that best approximate the Study 301 population is the "All Treated and No Flares Combined" groups. The annualized new HO volume in these groups was similar to that observed in Study 301 (9,542 mm^3 in 202B/C and 8,731 mm^3 in 202C vs. 9,427 mm3 in 301), and less than in the NHS (23,656 mm^3)"*. However, as indicated by the applicant, no direct comparison can be made between the phase II data and the NHS.

A pooled analysis of Studies 201 and 202 flare-ups new HO data is presented, where treatment groups from both studies are compared against pooled data from placebo and the NHS. The results from an ANCOVA involving bootstrapping to account for patients contributing multiple flare-ups is also discussed. However, the value of such post-hoc pooled analysis is questioned, especially given the sparse data (the number of patients showing new HO volume is only a fraction of the already small population considered), and the possibility for analyses to be data-driven. Moreover, the reporting of flare-ups may be influenced by the knowledge of treatment, which could result in biased comparisons of treated vs untreated flare-ups.

The Applicant argues that Study 202 Part C cannot be directly compared with Study 301 or NHS, which led the Applicant to perform additional post-hoc analyses: analyses in "subjects optimally treated", analyses in subjects who transferred from NHS to Study 202 and matched-pairs and propensity score weighting analyses. However, it is unclear why the analysis of Study 202 Part C requires the definition of population subsets to improve comparability to Study 301 or the NHS, as the same categorisation does not seem to have been investigated for Study 301. Another limitation is the very limited sample size for each Study 202 category. The same can be said about the analysis of patients who transferred from NHS to Study 202, as it includes only 6 subjects. It is also difficult to interpret propensity score matching/weighting analyses: there are serious limitations associated with these analyses (as discussed above for phase 3 results), and none of them reached nominal statistical significance (all $p>0.4$). More generally, the potential for data-driven analyses precludes any meaningful conclusions to be made.

10. Long term data do not support efficacy

Analysis of annualised new HO volume in the ITT period (baseline to last visit) in Study 301 vs. NHS, including patients who were off treatment for a substantial amount of time, showed a 44% reduction in raw mean annualised new HO volume in palovarotene-treated subjects in Study 301 (13,316 mm^3) compared with untreated subjects in NHS (23,656 mm^3) – in an adjusted analysis this difference was not significant.
Data from the post-restart patients included only 17 subjects. Annualised new HO volume was less with palovarotene treatment during Study 301 compared with the NHS, but did not indicate a statistically significant effect of palovarotene.

Conclusion on Ground 2. Based on the data provided, CHMP do not agree with the Applicant that robust confirmatory evidence on the efficacy of palovarotene has been provided, as multiple uncertainties remain and bias of a relevant magnitude cannot be excluded. There is a risk of data-driven analyses, especially as several aspects of the methodology (e.g. statistical model, data transformation and negative value imputation) are associated with essential discrepancies in study results. The uncertainties associated with using non-randomised comparisons is another serious limitation to the interpretability of study results. The clinical relevance of the observed effect is unknown.

Point not resolved

Ground #3

Due to its mechanism of action, one can expect that the safety profile of palovarotene will be comparable to systemic retinoids. The safety data provided by the applicant confirmed this, with, among other things, a predominance of mucocutaneous adverse effects and a number of cases of premature epiphyseal closure, fractures, and psychiatric disorders. The applicant reflected in the SmPC the well-known adverse effects for systemic retinoids, such as hyperostosis, which have not occurred in the ongoing clinical studies at present, without forgetting their teratogenic potential. All known adverse effects following the administration of systemic retinoids, but not currently occurring, would require long-term monitoring of palovarotene as part of a pharmacovigilance plan. The applicant proposes to ensure this monitoring through a registry study.

The main safety issue identified during the clinical development of palovarotene concerns premature physeal closure (PPC) reported in subjects under the age of 14, particularly in the proposed indication range by the applicant (8 years and older for girls and 10 years and older for boys).

In their grounds for re-examination, the applicant has submitted an argumentation to justify a positive benefit/risk in both the paediatric population aged 8 (f) and 10 (m) years of age at the start of therapy, and a restricted population aged 12 (f) and 14 (m) years of age at treatment start.

Throughout the palovarotene clinical development program, 13 patients under 14 years of age from the initially proposed target population were diagnosed with PPC. Among the 13 cases of PPC, growth retardation was reported in 8 of them. Five patients (out of the 8) had scoliosis before treatment and the applicant argues that this could contribute to height deceleration. However, the 3 other patients (out of the 8), had no risk factor for growth retardation. In addition, for 3 other patients (out of the 13) whose growth was slowed, PPC was diagnosed after treatment discontinuation, arguing the irreversibility of PPC upon treatment cessation. The applicant's conclusion that the potential consequences of PPC have not been shown with the available data is not agreed. In addition, the conclusion that the potential consequences of PPC are not as severe as leaving the patient untreated is not shared.

In term of risk minimisation measures, the applicant proposes measures such as warnings in the SmPC, educational brochures, an international registry study to better characterise the risk of PPC, and radiological monitoring of growth according to a predetermined frequency to detect PPC early. The applicant's proposal is to perform a radiograph every 3 months for a subject undergoing treatment for HO flare-ups and every 6 to 12 months for subjects on chronic treatment. However, for an immature skeleton subject, the applicant provided no arguments that could justify the frequency of radiological growth monitoring according to palovarotene treatment (chronic or HO flare-ups).

As mentioned in the initial assessment, the proposed risk minimisation measures are not considered adequate and feasible. The proposed measures are also not considered useful to predict the PPC in time as they may be performed relatively late.

Even though the applicant argues that no severe consequences of PPC were observed during the studies, this is not considered sufficient as palovarotene, if approved, would be a long term (maybe even lifelong) therapy. Therefore, the CHMP does not agree with the applicant that PPC is not of major concern.

However, CHMP considers that the risk of PPC could be mitigated by narrowing the use of palovarotene to patients above 14 years of age with mature skeletons.

During the oral explanation on 23 May 2023, the applicant stated that they would accept to narrow the indication in older children (≥ 14 years or skeletally mature). No specific wording was submitted.

Conclusion on Ground 3

Narrowing the indication to children above 14 years of age with mature skeletons would address the major safety concerns of PPC. However, the uncertainty on the clinical benefit due to the severe deficiencies in the clinical program also applies to older children precluding demonstration of efficacy.

5.1. Risk Management Plan

5.1.1. Safety concerns

Table SVIII.1: Summary of safety concerns (RMP version 4.0, dated 22 March 2023)

Summary of safety concerns	
Important identified risks	• Teratogenicity • Premature physeal closure including inhibition of long bone growth (in growing children) • Radiologically observed vertebral fractures • Mucocutaneous effects
Important potential risks	• Fractures and impaired fracture healing
Missing information	• Long term safety

5.1.2. Pharmacovigilance plan

Table Part III.3: On-going and planned additional pharmacovigilance activities (RMP version 4.0, dated 22 March 2023)

Study status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3: Required additional pharmacovigilance activities				
Study Short Name: Global Registry Study (CLIN-60120-453)	*Primary Objective:* The objective of this registry study is primarily to collect and assess real-world safety data on paediatric and adult patients with FOP treated with	• Teratogenicity • Premature Physeal closure • Radiologically observed	Study start date:	Participant enrolment will start from the date of palovarotene availability in said country and once the investigational site has been activated.

An International Observational Registry Study to Further Describe Long term Safety and Effectiveness of Palovarotene in Patients with Fibrodysplasia Ossificans Progressiva (FOP). (Planned)	palovarotene and secondly, to describe the effectiveness of this treatment, including its effect on physical function. As part of data collected in this registry, incidence of pregnancies and their outcome will be reported, recorded and analysed. Pregnant women who have previously received and discontinued palovarotene at any time during the pregnancy will be included for safety follow-up. Also, frequency, severity and descriptive details of any fractures, and PPC will be measured along with height velocity and difference between chronological age and bone age for growing children.	vertebral fractures • Mucocutaneous effects • Fractures and impaired fracture healing • Long term safety	Study end date (LPO):	Approximately 10 years (from first participant, first visit) with a minimum of 1-year data collected for participants who enrolled within that period.
			Target start date of data collection:	May 2023 in Canada
			Interim reports:	Every 2 years
			Planned end of data collection:	May 2034
			Protocol submission due date	Within 6 months of Ethics Committee (EC) decision

5.1.3. Risk minimisation measures

Table V.3 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern (RMP version 4.0, dated 22 March 2023)

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Teratogenicity (Important identified risk)	Routine risk minimisation measures: • *A black box warning* • *Prescription-only medicine* • *SmPC Section 4.2, 4.3, 4.4 and 4.6* • *Package Leaflet Section 2* Additional risk minimisation measures: • *Educational Programme*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Global Registry Study (CLIN-60120-453)*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Premature physeal closure including inhibition of long bone growth (in growing children) (Important identified risk)	Routine risk minimisation measures: • *Continued monitoring is recommended every 6-12 months during chronic treatment and every 3 months during flare-up treatment until patients reach skeletal maturity or final adult height* • *In the case of any signs or symptoms of epiphyses premature fusion following treatment initiation, the decision to continue Sohonos® to limit heterotopic ossifications consequences versus temporarily or permanently interrupting the treatment should be based on a benefit-risk assessment discussed between the treating physician, the patient (or legal representative) with the advice of an expert in growth if needed* • *Prescription-only medicine* • *SmPC Section 4.2, 4.4, and 4.8* • *Package Leaflet Section 2* Additional risk minimisation measures: • *Educational Programme*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Global Registry Study (CLIN-60120-453)*
Radiologically observed vertebral fractures (Important identified risk)	Routine risk minimisation measures: • *Periodic radiological assessment of the spine is recommended* • *Prescription-only medicine* • *SmPC Section 4.4, 4.8, and 5.3* • *Package Leaflet Section 2 and 4* Additional risk minimisation measures: *Educational Programme*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: *Global Registry Study (CLIN-60120-453)*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Mucocutaneous effects (Important identified risk)	Routine risk minimisation measures: • *SmPC Section 4.4, 4.8 and 5.3* • *Prescription-only medicine* Additional risk minimisation measures: *Educational Programme*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: *Global Registry Study (CLIN-60120-453)*
Fractures and impaired fracture healing (Important potential risk)	Routine risk minimisation measures: • *Periodic radiological assessment of the spine is recommended* • *Prescription-only medicine* • *SmPC Section 4.8 and 5.3* • *Package Leaflet Section 2 and 4* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: *Global Registry Study (CLIN-60120-453)*
Long term safety (Missing information)	Routine risk minimisation measures: • *None* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Global Registry Study (CLIN-60120-453)*

5.1.4. Conclusion

The CHMP, having considered the data submitted by the applicant, were of the opinion that, due to the concerns identified with this application, as above outlined, the RMP cannot be agreed at this stage.

5.2. Pharmacovigilance

5.2.1. Pharmacovigilance system

The CHMP and PRAC, having considered the data submitted by the applicant, were of the opinion that, due to the concerns identified with this application, as above outlined, the pharmacovigilance system summary cannot be agreed at this stage.

5.2.2. Periodic Safety Update Reports submission requirements

Not applicable.

5.3. Product information

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

5.3.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

However, in light of the negative opinion, a satisfactory package leaflet cannot be agreed at this stage.

6. Benefit-risk balance following re-examination

6.1. Therapeutic Context

6.1.1. Disease or condition

The proposed indication in the latest submitted product information for palovarotene therapy is:

"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 (myositis) ossificans progressiva (FOP)."

Of note, during the oral explanation on 23 May 2023, the applicant also proposed to narrow the indication to older children (i.e. ≥14 years or skeletally mature) to address the safety concern of premature physeal closure (PPC). No specific wording was submitted.

FOP is an ultra-rare, severely disabling disease characterised by painful, recurrent episodes of soft tissue swelling (flare-ups) and abnormal bone formation. Lesions begin in early childhood. There are approximately 800 confirmed cases of FOP globally. The prevalence is estimated at approximately 1.36 per million individuals, with no geographic, ethnic, racial, or sex preference. The result of recurrent extra-skeletal bone formation, HO is cumulative immobility, with patients becoming wheelchair-bound or bedridden by the third decade of life. Life-threatening complications include severe weight loss due to ankylosis of the jaw, and respiratory insufficiency due to ankylosis ossification of thorax and progressive spinal deformity. Thoracic insufficiency commonly causes complications such as pneumonia and right-sided heart failure, leading to markedly shortened survival (Kaplan-Meier median survival is 56 years).

Palovarotene is an orally bioavailable RARγ agonist. RARγ are expressed in chondrogenic cells and chondrocytes where they operate as unliganded transcriptional repressors. The aim of the treatment is to prevent HO formation and improve symptoms.

6.1.2. Available therapies and unmet medical need

Currently, there are no effective medical treatment options to prevent flare-ups, HO, or disease progression in FOP. Surgical resection of heterotopic bone is not recommended as it can exacerbate flare-ups and further HO formation. Current pharmacologic intervention for FOP is limited to palliative management and is not known to be disease-modifying. Medications used to treat FOP include high-dose corticosteroids, oral or topical acetaminophen, NSAIDs in combination with a proton pump inhibitor, cyclooxygenase-2 (COX-2) inhibitors, muscle relaxants, opioids, gabapentin, pregabalin, or tricyclic antidepressants.

6.1.3. Main clinical studies

The application is based on a single pivotal clinical study PVO-1A-301 (MOVE).

This is a multicentre, single-arm, open-label, phase 3 study in 107 adult and paediatric subjects with FOP. The results are compared with data collected from a 3-year, longitudinal, non-interventional NHS in 114 subjects with FOP due to the R206H mutation.

A phase 2 open-label extension study PVO-1A-202/204 study enrolled 54 subjects and provides important follow-up data up with palovarotene treatment up to 3 years. The results from this study may also be compared with NHS as similar doses were used and similar endpoints were recorded in this study. An earlier placebo-controlled dose-finding study PVO-1A-201 tested two active doses 5/2.5mg and 10/5mg at flare-up.

Based on the serious identified risk of PPC, a partial clinical hold was implemented on subjects <14 years old on 04 December 2019 in the ongoing palovarotene program, including main study PVO-1A-301 and PVO-1A-202/204. Shortly after, the sponsor paused dosing for all subjects (14 years and older) in the FOP palovarotene program on 24 January 2020; based on the pre-specified analysis, futility was declared. After that, the sponsor became unblinded to all study data. However, re-analyses presented indicated a potential benefit. The Data Safety Monitoring Board (DSMB) acknowledged the dilemma created by the highly disparate results, which in their opinion precludes a confident conclusion about futility. In May 2020 the DMSB recommended palovarotene to be continued in skeletally mature children ≥ 14 years. For the group of girls ≥8<14 and boys ≥10<14 years of age, who may also be at a risk of permanent, premature epiphyseal closure, they recommended these children could be re-started on palovarotene, provided the informed consent was done in a manner that fully elucidates the issues about safety and efficacy.

6.2. Favourable effects

In two *in vivo* studies using a mouse model for the disease, palovarotene, when administered prior to the injury, reduced or eliminated HO formation and a dose-response relationship was demonstrated.

The first dose-finding study PVO-1A-201 did not meet its primary responder endpoint; nearly all participants had "no or minimal new HO" at week 6. Sparse data from 9 participants by week 12 indicated, however, that palovarotene could have an effect on new HO volume.

The primary endpoint in studies PVO-1A-301 (main study) and PVO-1A-202/204 Part C was the radiological mean observed annualised new HO volume. The prespecified primary analyses did not show clinically or statistically significant differences in the mean observed annualised new HO volume (square root transformed data zeroed out by body region) between the phase 3 study PVO-1A-301 and NHS. In this analysis, the observed annualised new HO volume for PVO-1A-301 was 140 mm^3 (mean SEM) or 137 mm^3 (LSmean) in treated patients and 150 mm^3 (mean SEM) or 130 mm^3 (LSmean) in

untreated subjects. These numbers correspond to a non-significant difference of approximately 6%, p=0.52.

In this pre-defined analysis, the square root transformation was used to limit the effect of outliers. Only regions with new HO in a qualitative examination were measured quantitatively. Negative quantitative values were to be zeroed as they were likely considered as measurement errors. The applicant argued, however, that the wLME analysis without square-root transformation would be the appropriate analysis method of results, including negative values, and that the pre-specified Bayesian analysis with implementation of a square root transformation was an error. In this wLME post-hoc analysis presented by the applicant, the LS mean (SEM) of new HO was 9,427 mm^3 in study PVO-1A-301 compared to 23720 mm^3 in NHS. This corresponds to a reduction of new HO by 60%. The nominal statistical significance of the Wilcoxon test was p=0.0003.

Using this "without square-root transformation negatives included" approach, no annualised new whole-body HO volumes was reduced in PVO-1A-202/204 Parts B and C compared to NHS. HO volumes in this study were numerically even higher compared to untreated subjects. The mean annualised new HO was 27.967 mm^3 in Study PVO-1A-202/Part B, 24.290 mm^3 in Part C and 23.720 mm^3 in the NHS.

In the grounds for re-examination, the applicant provided a "corrected" Bayesian analysis i.e. with the data from study 301 collapsed over 12 months to better match the visit schedule in the NHS. A non-significant reduction of 16% compared to the NHS (0.84 (0.64-1.09)), with a 90% chance of any reduction between 0 and 30% was observed.

6.3. Uncertainties and limitations about favourable effects

The population PK analysis performed to support the initially proposed weight-adjusted posology in children below 14 years of age (skeletally immature children) could not demonstrate that the targeted exposure corresponds to an efficacious and safe dosing regimen. The proposed dosing appears to result in a similar exposure in all weight groups but higher fluctuations in the smaller children. Potential clinical relevance of increased fluctuation is not possible to assess. The overall benefit-risk assessment with the proposed posology must be based on the efficacy and safety data from patients included in the clinical studies which is currently negative.

Due to interruptions due to safety and futility in the pivotal study (PVO-1A-301), final submitted efficacy analyses were carried out at a different time point and much less data were analysed than originally planned. The single-arm design and primary endpoint were previously accepted by CHMP as the disease course was considered relatively stable during a couple of years. However, comparative data with the NHS is principally available only at month 12. The short study duration makes the single-arm design questionable and the interpretation of results unreliable.

There was no difference between the pivotal study (PVO-1A-301) and NHS in the primary endpoint, (i.e. in the prespecified analysis using square root transformed data zeroed out by body region). There were no differences between these two studies in the secondary endpoints either: there was no substantial difference in the number of new body regions with new HO between the palovarotene treated subjects (1.3) and the subjects in the NHS (1.5); the proportion of subjects reporting flare-ups at month 12 was 65 % in the palovarotene treated study and 54 % in the NHS i.e. there was no improvement in the number of flare-ups with the treatment with palovarotene; the flare-up rate per month was higher in the palovarotene treated study than in the NHS where subjects were untreated. The exploratory endpoints also did not provide support for palovarotene efficacy.

The fact that the main studies were not placebo-controlled increases the uncertainty of results due to potential biases in external comparisons. There were considerable differences at baseline HO between cohorts that could indicate more active disease in the NHS. In addition, the great discrepancy of the results based on analysis methods seriously questions the overall robustness and reliability of the HO data. It is noted that there was a considerable intra- and interindividual variability in the assessments of new HO indicating these measurements are challenging to perform. The palovarotene clinical program had a focus on preventing new HO. Therefore, the whole-body HO was not systematically quantitively measured after baseline. Only regions with qualitatively detectable new HO were measured. It is reasonable to expect these values to be positive. Negative values in these measurements could reflect uncertainties in the method of measuring HO or at best be hypothesis-generating, that palovarotene could affect existing HO. To study such a hypothesis further, existing lesions should have been systematically followed. Such data does not exist. Assessment of existing lesions (which could generate possible negative values) was not pre-planned and was not performed systematically, comprehensively, clinically or scientifically soundly. This is one of the concerns in the post-hoc approach presented by the applicant.

Although the "corrected" Bayesian analysis provided by the applicant is considered an improvement, it is uncertain what the effect would be in patients above 14 years of age with mature skeletons. This view was also shared by the ad hoc expert group. In the re-examination, the applicant presented their view that the best analysis in their opinion is the wLME analysis without square root transformation. Although there is no objection to the wLME analysis itself, bias is introduced by the differences in visit schedules which is not accounted for. Since the data is heavily skewed, data transformation is considered appropriate.

Based on different dosing regimens studied in the phase 2 program, an exploratory analysis was conducted to describe the relationship between palovarotene exposure and the increase in HO volume after flare-up in subjects with FOP. There was no dose-response trend across the flare-up doses utilised in the phase 2 program to support that the drug would be effective in FOP and support the proof of concept in humans. In the analysis of flare-up outcomes comparing phase 2 data with untreated, there was no evidence that palovarotene would reduce clinical symptoms of pain and swelling during flare-up.

During the assessment, new data from the ongoing PVO studies: PVO-1A-301 and Study PVO-1A-202/204 Part C was submitted by the applicant consisting of 45 patients from study PVO-1A-301 and 26 patients from PVO-1A-202/204. The available longer term new efficacy data from these studies did not indicate that PVO treatment would decrease new HO volume. The numbers reported were similar or higher compared to those from the natural history cohort. Furthermore, PVO treatment had no effect on flare-up rates as numbers reported during on and- off treatment periods were similar.

6.4. Unfavourable effects

During the main study (MOVE), the rates of TEAEs and SAEs were higher in the group of subjects who received treatment for HO flare-ups [20/10 mg] compared to those reported in the group of subjects who received chronic treatment (5 mg).

Due to its mechanism of action, palovarotene has a safety profile comparable to that of systemic retinoids characterised by the occurrence of mucocutaneous effects, skeletal effects, ocular system abnormalities such as persistent dry eye, teratogenicity, and poor pregnancy outcomes.

Mucocutaneous effects were seen in almost all patients treated with palovarotene during clinical studies and included dry skin, lip dry, pruritis, alopecia, rash, erythema, skin exfoliation, dry eye, drug eruption and skin irritation, in decreasing order of frequency, which may contribute, due to a

diminished skin barrier, to an increased risk of skin and soft tissue infections, particularly paronychia and decubitus ulcer.

Just like with systemic retinoids, long-term bone demineralisation can lead to potential fractures. Radiologically observed vertebral fracture was identified as an important identified risk associated with palovarotene based on analyses performed on whole body computed tomography (WBCT) data in FOP subjects in the phase 3 (MOVE) study.

Teratogenicity is an important identified risk in the palovarotene clinical program and a well-known class effect of systemic retinoids. Although there were no pregnancies in the palovarotene development program, findings in toxicology studies demonstrate characteristic patterns of foetal malformations typical of retinoids (e.g., cleft palate, misshapen skull bones, short/long bones). At higher dosages, these effects resulted in reduced foetal survival. Therefore, similar to other systemic retinoids, palovarotene is assumed to be a potent teratogen and has the potential to adversely affect development of an embryo or foetus if given to a pregnant female patient and lead to adverse pregnancy outcomes. Consequently, if authorised, palovarotene would have been an absolute contraindication during pregnancy and for females of childbearing potential unless all of the conditions of pregnancy prevention are met or they are not at risk for pregnancy. The applicant had also proposed guidance and warnings in the label and additional risk minimisation measures in the form of a pregnancy prevention program.

Premature Physeal Closure (PPC) has been demonstrated to be an important identified risk associated with palovarotene treatment in growing children with FOP. In clinical studies, epiphyses premature fusion was identified as a serious irreversible risk associated with palovarotene treatment and has been reported in children< 14 years. PPC was identified in 26 of 102 subjects (26%) <18 years of age in the FOP-FAS, including 22 subjects with treatment-emergent events and 4 subjects with post-treatment events. The incidence of PPC varied across FOP-FAS paediatric age categories, from 12% for subjects ≥8/10 to <18 years, to 23% for ≥8/10 to <14 years, to 56% for <8/10 years. No PPC events were reported in subjects over the age of 14 years.

6.5. Uncertainties and limitations about unfavourable effects

The safety profile of palovarotene is generally well reflected; however, some uncertainties and limitations about some unfavourable effects remain.

According to the applicant, the median age at which HO begins in individuals with FOP is 6 years, which would justify an early treatment initiation to preserve physical function. For this reason, the applicant had proposed an indication age of 8 years and older for girls and 10 years and older for boys, which would correspond to the ages at which 80% of the subject's final height is reached.

Throughout the palovarotene clinical development program, 13 patients under 14 years of age from the initially proposed target population were diagnosed with PPC. Among the 13 cases of PPC, growth retardation was reported in 8 of them. Five patients (out of the 8) had scoliosis before treatment and the applicant argues that this could contribute to height deceleration. However, the 3 other patients (out of the 8), had no risk factor for growth retardation. In addition, for 3 other patients (out of the 13) whose growth was slowed, PPC was diagnosed after treatment discontinuation, arguing the irreversibility of PPC upon treatment cessation. The applicant’s conclusion that the potential consequences of PPC have not been shown with the available data is not agreed. In addition, the conclusion that the potential consequences of PPC are not as severe as leaving the patient untreated is not shared.

In addition, in the FOP-FAS clinical program, PPC appeared as early as Month 6, which is earlier than what is reported in the general retinoid class literature. No clear characteristics define or predict who will develop PPC, over what period, or after what duration of palovarotene exposure. Therefore, given the high incidence of PPC over relatively short periods of time, it is assumed that upon initiation of treatment with palovarotene, all growing children are considered at risk for PPC. Moreover, there is the potential for longer-term consequences, including growth arrest, leg length discrepancy, disproportionate growth (epiphyseal growth plate closure preferentially affecting the lower extremities), angular deformity in affected joints, and gait disturbance. Given the relatively short follow-up times to date, these longer-term consequences have not been identified in subjects treated with palovarotene.

In terms of risk minimisation measures for PPC, the applicant proposed measures such as warnings in the SmPC, radiological monitoring of growth according to a predetermined frequency to detect PPC early, educational brochures, and planned to further characterise the risks by means of an international registry study post authorisation. Several uncertainties and limitations concern this radiological monitoring. During the ad hoc expert group meeting, the experts mentioned that radiological assessments are considered suitable to assess growth plates however they are not an effective tool to mitigate the risk of PPC (as when PPC is diagnosed on X-rays damage is already in place).

During the oral explanation on 23 May 2023, the applicant proposed to narrow the indication to older children (≥ 14 years or skeletally mature). Narrowing the indication to children above 14 years of age with mature skeletons would address the major safety concerns of PPC. However, the uncertainty on the clinical benefit due to the severe deficiencies in the clinical program also applies to older children precluding demonstration of efficacy.

Chronic toxicities from long-term therapy with other retinoids are known to increase the risk for the occurrence of skeletal abnormalities, usually mimicking diffuse idiopathic hyperostosis syndrome (DISH). In contrast to other side effects of retinoids, which are dose-dependent and reversible upon withdrawal of the drug, it seems unlikely that bone abnormalities will resolve after discontinuing the medication. Even though no DISH or DISH-like symptoms were reported in the FOP population, this is considered a class effect. To date, the studied palovarotene population is very limited. Furthermore, unlike e.g., isotretinoin, palovarotene is intended for long-term, even life-long, treatment. Thus, it seems probable that cases may occur if the drug is approved.

A signal on Bone Safety was raised by the applicant to assess the possible causal relationship between palovarotene treatment in Study 301 compared with standard of care only (i.e., palovarotene untreated) in Study 001 (NHS) and selected bone safety outcomes in subjects with FOP. No validation for the methods, baseline data or discussion of the clinical relevance of the results were provided. Nonetheless, the data indicate a negative impact of palovarotene treatment on bone strength and mineralisation, and a threefold higher risk of new-onset radiological vertebral fractures in palovarotene treated versus untreated FOP subjects. The consequences for bone safety during longer, potentially life-long, treatment are not known.

There is currently no evidence in the palovarotene studies to suggest an impact on fracture healing with palovarotene treatment; however, palovarotene's mechanism of action is compatible with a negative impact on fracture healing. Therefore, fractures and impaired fracture healing are considered an important potential risk of palovarotene.

Literature suggests that retinoids may interact with the nuclear receptor RXR and lead to central hypothyroidism. This effect is observed in nearly 100% of the patients treated with high-dose retinoids (e.g., Bexarotene) prompting routine concomitant L-T4 treatment. For palovarotene, however, both

increasing and decreasing thyroxine levels have been reported and there is no general indication of increased risk for central hypothyroidism, as both low and high TSH has been reported.

6.6. Effects Table

Table 54 Effects Table for the pivotal study (PVO-1A-301) vs NHS cohort for Sohonos in the treatment of FOP (data cut-off: 28/02/2020)

Effect	Short Description	Treatment N=97	Control N=101	Uncertainties/ Strength of evidence	
Favourable effects				Effect Bayesian posterior with 95% credible interval % reduction wLME, treatment effect with 95% confidence interval	
Annualised new HO volume	Original primary Bayesian analyses (with varying follow-up duration). Sqrt transformation, negatives zeroed out by body region, wLME analysis: LSmean (SEM)	137 (20.7)	129.5 (15.7)	0.95 (0.74, 1.22), -5.9%, 7.6 (-45.17, 60.32)	Marginal difference favouring treatment in comparison to untreated historical controls, non-significant.
	Post-hoc: Bayesian analyses with sqrt transformation, collapsed over 12-month interval ("corrected" intervals)			0.84 (0.64, 1.09)	
	Post-hoc: Bayesian analyses without sqrt transformation, "corrected interval" wLME analysis: LSmean (SEM)	14,901 (4,027)	22,017 (3,300)	0.61 (0.42, 0.87)	
	Post-hoc: wLME analysis without the square-root transformation negatives included	8,969	20,579	-56% -11,610 (-21,977, -1,243)	
Proportion of subjects with any new HO	at month 12, n (%)	59 (64.1%)	56 (62.2%)	Small uncertain difference favouring control	

Effect	Short Description	Treatment N=97	Control N=101	Uncertainties/ Strength of evidence
Number of body regions with new HO	per subject, mean (SD)	1.3 (1.4)	1.5 (1.6)	Small uncertain difference favouring treatment
Proportion of subjects reporting flare-ups	at Month 12, n (%)	64 (64.6%)	60 (54.1%)	Favours control
Flare-up rate through Month 24	per subject-month exposure (95% CI)	0.13 (0.09, 0.17)	0.07 (0.05, 0.08)	Favours control
Unfavourable effects				
Proportion of subjects with PPC in FOP-FAS population	n/N (%)	<18 y: 24/102 (24%) <8/10 y: 14/25 (56%) ≥8/10 to <14 y: 9/39 (23%) >14 y: 0	0	Reported exclusively in palovarotene treated subjects with immature skeleton.
Dry skin	n/N (%)	109/139 (78)	3/20 (15)	≥8/10 Years (FOP-FAS)

Effect	Short Description	Treatment N=97	Control N=101	Uncertainties/ Strength of evidence
Dry lips	n/N (%)	78/139 (56)	1/20 (5)	≥8/10 Years (FOP-FAS)
Pruritus	n/N (%)	56/139 (40)	1/20 (5)	≥8/10 Years (FOP-FAS)
Erythema	n/N (%)	47/139 (34)	0	≥8/10 Years (FOP-FAS)

Abbreviations: HO: heterotopic ossification, PPC: Premature physeal closure, y: years

Table 55 Effects Table for trials PVO-1A-202/Parts B and C vs Natural history cohort for Sohonos in treatment of FOP

Effect	Short Description	Treatment Part B N=37	Treatment Part C N=32	Control N=101	Uncertainties/ Strength of evidence
Favourable effects					
New whole body HO volume	Mean, mm^3 (SD)	27967 (82436)	24290 (63290)	23720 (48741)	Small uncertain difference favouring control

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

In the palovarotene clinical programme, results of single-arm studies have been compared with an external natural history cohort. The uncertainties of results from external comparisons due to potential biases are well known. There were considerable differences at baseline HO between cohorts that could indicate more active disease in the NHS. The active treatment studies were interrupted for futility, and data was unblinded. It is clear from the interim data submitted that the main study PVO-1A-301 did not meet its primary predefined radiological endpoint (mean observed annualised new HO volume). The methodological issues preclude a reliable effect size estimate. In addition, the great discrepancy of the results based on analysis methods seriously questions the overall robustness of the HO data. The different results seem to be strongly dependent on the higher number of negative volumes in the treatment group without a good understanding whether these reduced volumes would come from a potential treatment effect. Descriptive presentations of the radiological data show a great overlap between treated and non-treated cohorts. There was no substantial difference in secondary endpoints such as the number of new body regions with new HO in treated and untreated cohorts either.

Therefore, any potential beneficial radiological effects would be expected to be supported by clinical endpoints at least to some extent. However, there was no substantial difference in patients reporting flare-ups or any of the patient-reported outcomes Cumulative analogue joint involvement scale (CAJS), FOP-Physical function questionnaire, PROMIS Global health scale or flare-up outcomes pain and swelling. Therefore, any clinically relevant effect of palovarotene in any of the main symptoms of FOP is questioned.

The major safety issues identified with palovarotene treatment are PPC, bone safety and teratogenicity. Teratogenicity can be adequately handled by contraindicating the medicinal product in pregnant women, together with a strong cautionary wording in the label and additional risk minimisation measures in the form of a pregnancy prevention program. Likewise, different aspects of bone safety may be mitigated with adequate wordings in the SmPC and with additional Pharmacovigilance activities. For PPC, however, all subjects with growing skeleton seem to be at risk and radiological assessments are not an effective tool to mitigate the risk of PPC (as when PPC is diagnosed on X-rays damage is already in place). During the oral explanation on 23 May 2023, the applicant proposed to narrow the indication to older children (≥ 14 years or skeletally mature). Narrowing of the indication to children above 14 years of age with mature skeletons would address the major safety concerns of PPC. However, the uncertainty on the clinical benefit due to severe deficiencies in the clinical program also applies to older children precluding demonstration of efficacy. Extrapolation of a potential affect to children aged 14 years and above therefore adds further uncertainty, also due to the limited number of subjects included and limited understanding of this complex and heterogeneous disease.

For other safety issues with palovarotene, including class effects for systemic retinoids, proposed SmPC wordings and additional Pharmacovigilance activities are deemed sufficient, and these issues are not considered to affect the benefit/risk ratio of palovarotene.

6.7.2. Balance of benefits and risks

The applicant's position that palovarotene reduce the formation of new HO cannot be agreed on. The application is based on a post-hoc analysis of primary endpoint radiological data, that has not been not sufficiently scientifically or clinically justified.

Efficacy of palovarotene on new HO volume formation, compared to natural history cohort PVO- 1A-001, is not robustly established. The predefined primary analysis failed in the main single arm study PVO-1A-301, efficacy data from the other clinical study PVO-1A-202/204 was not supportive, data from secondary endpoints (flare-up rate, PROs) did not show efficacy and available longer-term clinical data after clinical hold did not support efficacy. Overall, the robustness and clinical relevance of the presented results have not been shown in any of the age groups comprising the indication. This is unfortunate as FOP is a devastating disease with a high unmet medical need.

On the other hand, major safety concerns were identified with palovarotene treatment (e.g. Premature physeal closure (PPC)). During the oral explanation on 23 May 2023, the applicant proposed to narrow the indication to older children (≥ 14 years or skeletally mature). Narrowing the indication to children above 14 years of age with mature skeletons would address the major safety concerns of PPC. However, the uncertainty on the clinical benefit due to the severe deficiencies in the clinical program also applies to older children precluding demonstration of efficacy.

Considering that the efficacy of palovarotene has not sufficiently been demonstrated and the important safety concerns in the claimed indication the benefit-risk balance is negative.

6.7.3. Additional considerations on the benefit-risk balance

The applicant submitted a letter from key opinion leaders and patient testimonies which have been considered and acknowledged in the assessment. The CHMP also considered in its assessment patient testimonies received via a third-party intervention.

In addition, the following criteria were taken into account to assess the comprehensiveness of the data submitted by the applicant.

1. Quality of evidence; many methodological weaknesses have been identified in the clinical study program for palovarotene. The study design, a single-arm externally controlled study, is associated with many limitations and forms of bias. The study failed its primary endpoint and futility was declared at the first interim analysis. Many post hoc analyses were conducted after unblinding. It cannot be excluded that these analyses were data-driven. Therefore, quality of evidence is considered limited.
2. The precision of the effect size estimate; due to the many methodological issues and the heterogeneity of the disease, the uncertainty on the treatment effect is large and the final results are inconclusive.
3. The clinical meaningfulness of the endpoints; the primary endpoint in the clinical studies was the formation of new heterotopic ossification. As HO progressively impairs joint mobility/motion and thereby greatly affects Health related Quality of Life (HRQoL), this is considered a clinically meaningful endpoint. However, no Minimal Clinically Important Difference (MICD) has been defined for new HO formation.
4. Duration of efficacy; as there are currently concerns about the efficacy in general, it is difficult to conclude on the duration of any efficacy.

5. Safety exposure: The safety of palovarotene has been examined in 164 subjects with FOP receiving at least one dose of the drug and including 139 subjects ≥8/10 years. Considering the rarity of the disease this is considered a substantial number of patients. Nevertheless, rare side effects will not be picked up in this population.
6. Safety length of follow-up; as of the 31 July 2021 cut-off date, more than 95% of the subjects in the ≥8/10 years group were on study for at least 12 months and 76% were on study drug for >30 months. Again, considering the rarity of the disease, this follow-up duration is considered substantial. A major concern was identified regarding PPC, the follow-up is not considered sufficient to fully characterise this risk and to assess potential long-term consequences of PPC.
7. Target population versus the study population; patients with FOP were included in the main study who did not have a flare-up in the 4 weeks preceding screening. This might indicate that patients with most active disease were not included in the study and the impact of this on the overall interpretation of the results is unclear.
8. Pharmacological rationale; palovarotene is a RARγ agonist. 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 pharmacological rationale is therefore fairly clear although the exact role of palovarotene in different phases and aspects of the disease is not clear.
9. Natural history: a natural history study was conducted by the applicant to serve as an external comparator for the phase III study. In general, the natural history of FOP is not well described. It is considered a very complex and heterogenous disease.

In conclusion, the data package is not considered comprehensive, primarily based on the lack of good quality data, uncertainties about the treatment effect estimate, the complexity and heterogeneity of the disease and the risk of PPC which is not fully characterised during the study follow-up.

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances was requested by the applicant in the initial submission.

The CHMP considers that the absence of comprehensive data cannot be addressed by considering the benefit-risk balance in the context of a marketing authorisation under exceptional circumstances, as the applicant has not sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use.

In the grounds for re-examination, the applicant has not sufficiently justified on which grounds a marketing authorisation under exceptional circumstances is requested (i.e. inability to provide comprehensive efficacy and safety data due to rarity of the indication, or inability to provide comprehensive information due to the present state of scientific knowledge, or inability to collect such information because it would be contrary to medical ethics). Therefore, based on the justifications on the grounds for approval under exceptional circumstance submitted by the applicant, such marketing authorisation cannot be agreed.

6.8. Conclusions

The overall benefit/risk balance of Sohonos is negative.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by consensus that the quality, safety and efficacy of Sohonos are not sufficiently demonstrated, and therefore recommends the refusal of the granting of the marketing authorisation under exceptional circumstances for the above-mentioned medicinal product. The CHMP considers that:

- There is an outstanding issue on the quality of the active substance pertaining to the redefinition of two starting materials. This concern was raised with the applicant during the procedure but has not been adequately addressed. The CHMP considers that the quality of the medicinal product is currently not acceptable but could be considered acceptable if this outstanding issue would be satisfactorily addressed in a new marketing application. The applicant's proposal to address it as a post-approval commitment is not relevant since the product is not approvable due to negative benefit/risk balance. Therefore, the quality issue remains unresolved.
- The applicant's conclusion of the data that palovarotene effectively reduces new heterotopic ossifications (HO) cannot be agreed on. The applicant's conclusion is based on a post-hoc analysis of primary endpoint radiological data that is neither scientifically nor clinically justified.

  Effects of palovarotene on new HO volume formation were investigated in the main single-arm study PVO-1A-301 and the results compared to the natural history cohort from study PVO- 1A-001. The predefined primary analysis failed to demonstrate efficacy of palovarotene and there are limitations of the comparison against the natural history cohort in light of baseline differences and primary endpoint assessments. In addition, results on secondary efficacy endpoints (flare up rate, patient reported outcomes), data from the other clinical study PVO-1A-202/204 and available longer-term clinical data after clinical hold did not support efficacy. Overall, robustness and clinical relevance of the presented results have not been shown.
- The results suggest that all skeletally immature subjects receiving palovarotene are at risk for premature physeal closure (PPC), which is a known safety risk for all retinoids. PPC is an irreversible serious risk which may be associated with growth arrest, leg length discrepancy, disproportionate, angular deformity in affected joints, and gait disturbance. PCC was reported with palovarotene treatment in children< 14 years. Therefore, the proposed indication in females> 8 years and males >10 years cannot be supported and risk minimisation measures for PPC in subjects with an immature skeleton are not considered adequate to minimise the risk. Narrowing the indication to children ≥ 14 years of age with mature skeletons would address this major safety concern. However, the uncertainty on the clinical efficacy due to the severe deficiencies in the clinical program also applies to older children precluding demonstration of efficacy.

The CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the quality, efficacy and safety of Sohonos are not properly or sufficiently demonstrated. Therefore, the CHMP has recommended the refusal of the granting of the marketing authorisation under exceptional circumstances for Sohonos.