Protocol Title:

Rollover Study; Multicentre, Phase III, Open-label Study to Further Evaluate the Safety and Efficacy of Palovarotene Capsules in Male and Female Participants Aged ≥14 Years with Fibrodysplasia Ossificans Progressiva (FOP) Who Have Completed Study PVO-1A-301 or PVO-1A-202/PVO-1A-204 and May Benefit from Palovarotene Therapy.

Protocol Number: CLIN-60120-452

Compound: Palovarotene (IPN60120)

Study Name: PIVOINE

Short Title:

A Rollover Study to Further Evaluate the Safety and Efficacy of Palovarotene Capsules in Male and Female Participants Aged ≥14 Years with Fibrodysplasia Ossificans Progressiva (FOP) Who Have Completed the Relevant Parent Studies.

Study Phase: III

Sponsor Name: Ipsen Pharma SAS

Legal Registered Address: 65, quai Georges Gorse
92100 Boulogne-Billancourt
Paris, France

Regulatory Authority Identifier Number(s):

IND number: 120181

EudraCT number: 2021-002244-70

Date: 13 November 2023

Version number: 4.0

Sponsor Signatory:

PPD

Ipsen Pharma SAS
Unit 9 Ash Road Wrexham Industrial Estate
LL139UF Wrexham
United Kingdom

Medical Monitor Name and Contact Information:

PPD

Ipsen Pharma SAS
Unit 9 Ash Road Wrexham Industrial Estate
LL139UF Wrexham
United Kingdom

Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in this study can be found in the study manual.

Principal Investigator Signature Page

I have read and agree to Protocol CLIN-60120-452 entitled 'Rollover Study; Multicentre, Phase III, Open-label Study to Further Evaluate the Safety and Efficacy of Palovarotene Capsules in Male and Female Participants Aged ≥14 Years with Fibrodysplasia Ossificans Progressiva (FOP) Who Have Completed Study PVO-1A-301 or PVO-1A-202/PVO-1A-204 and May Benefit from Palovarotene Therapy'. I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:

TITLE: [PRINCIPAL] INVESTIGATOR SIGNATURE:

DATE:

OFFICE:

SUMMARY OF CHANGES

The current version of the protocol was released on 13 November 2023 and includes Amendment 3. For the protocol amendment, an amendment form was prepared and is provided in Section 10.9.

List of Protocol Amendments

Amendment	Release date	Amendment form
1	**01 October 2021**	Section 10.7
2	**28 April 2022**	Section 10.8
3	**13 November 2023**	Section 10.9

Amendment #3 (13 November 2023)

This amendment is considered non-substantial.

Overall Rationale for the Amendment

This amendment aimed to:

- Update safety and efficacy background information;
- Provide clarification on remote follow-up and EOS/EW visits;
- Provide clarification on extra bone growth assessment;
- Remove the temporary measures related to the COVID-19 pandemic;
- Add the blister packaging and the packaging format for US patients (15 capsules packaged in bottle (5 mg))

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
ACVR1	Activin A Receptor Type-1
ADL	Activities of Daily Living
AE	Adverse Event
ALK2	Activin Receptor-like-kinase-2
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMP	Bone Morphogenetic Protein
CAJIS	Cumulative Analogue Joint Involvement Scale
CI	Confidence Interval
CIOMS	Council for International Organisations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP450	Cytochrome P450
DLCO	Diffusion Capacity of the Lung for Carbon Monoxide
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOS	End of Study
EU	European Union
EudraCT	European Clinical Trials Database
EW	Early Withdrawal
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in One Second
FKBP12	12-kDa FK506-binding Protein
FOCBP	Female of Childbearing Potential
FOP	Fibrodysplasia Ossificans Progressiva
FOP-PFQ	FOP Physical Function Questionnaire
FSH	Follicle-stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
HEENT	Head, Eyes, Ears, Nose and Throat

ABBREVIATION	Wording Definition
HED	Human Equivalent Dose
HO	Heterotopic Ossification
HRT	Hormonal Replacement Therapy
IB	Investigator's Brochure
ICC	International Clinical Council
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFOPA	International Fibrodysplasia Ossificans Progressiva Association
IND	Investigational New Drug
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LPLV	Last Participant Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of available observations
n	Number of nonmissing observations
NHS	Natural History Study
OMIM	Online Mendelian Inheritance in Man
PI	Principal Investigator
PP	Per Protocol
PPC	Premature Physeal Closure
PROMIS	Patient Reported Outcomes Measurement Information System
PT	Preferred Term
RARγ	Retinoic Acid Receptor Gamma
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SD	Standard Deviation
SI Unit	International System of Units
SoA	Schedule of Activities
SOC	System Organ Class
SP	Service Provider

ABBREVIATION	Wording Definition
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Events
TGF-β	Transforming Growth Factor Beta
ULN	Upper Limit of Normal
US	United States
WHODD	World Health Organization Drug Dictionary

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

Rollover Study; Multicentre, Phase III, Open-label Study to Further Evaluate the Safety and Efficacy of Palovarotene Capsules in Male and Female Participants Aged ≥14 Years with Fibrodysplasia Ossificans Progressiva (FOP) Who Have Completed Study PVO-1A-301 or PVO-1A-202/PVO-1A-204 and May Benefit from Palovarotene Therapy.

Short Title:

A Rollover Study to Further Evaluate the Safety and Efficacy of Palovarotene Capsules in Male and Female Participants Aged ≥14 Years with Fibrodysplasia Ossificans Progressiva (FOP) Who Have Completed the Relevant Parent Studies.

Rationale:

The aim of Study CLIN-60120-452 is to provide continued access to palovarotene once the ongoing clinical studies have ended. More specifically, the aim is to provide treatment continuity to participants who have completed one of the parent studies (Study PVO-1A-301 or PVO-1A-202 (Parts C and D correspond to Study PVO-1A-204 in France)) and, in the investigator's judgement, may benefit from palovarotene therapy until palovarotene is reimbursed in the country where the study is being conducted, or another access programme becomes available, or until the study end date of November 2024 is reached, whichever occurs first.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To further evaluate the safety of palovarotene in adult and paediatric participants with FOP.	• Incidence and description of all treatment-emergent adverse events (TEAEs) whether or not they are considered as related to the study intervention; • Incidence and description of all serious and nonserious treatment-related TEAEs; • Incidence and description of all serious TEAEs, whether or not they are considered as related to the study intervention; • Incidence and description of all nonserious TEAEs whether or not they are considered as related to the study intervention.
Secondary	
• To describe range of motion, as assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP, at the Inclusion Visit and over time under palovarotene treatment;	• Raw values and change from the Inclusion Visit in CAJIS total score at each Follow-up Visit;
• To describe the use of assistive devices and adaptations for daily living by FOP participants, at the Inclusion Visit and over time under palovarotene treatment;	• Raw values and shift from the Inclusion Visit in the use of assistive devices and adaptations for daily living at each Follow-up Visit;
• To describe physical function, using the adult form of the FOP Physical Function Questionnaire (FOP-PFQ), at the Inclusion	• Raw values and change from the Inclusion Visit in % of worst score for total score, upper extremities subscore and mobility subscore using the adult form of the

Visit and over time under palovarotene treatment;	FOP-PFQ for all participants, at each Follow-up Visit;
• To describe the FOP healthcare utilization in patients with FOP	• Type and frequency of healthcare utilization
• To describe the parameters of lung function (observed and % predicted forced vital capacity (FVC), observed and % predicted forced expiratory volume in one second (FEV_1), absolute and predicted FEV_1/FVC ratio, observed and % predicted diffusion capacity of the lung for carbon monoxide (DLCO)) at the Inclusion Visit and over time under palovarotene treatment;	• Raw values and change from the Inclusion Visit in observed and % predicted FVC at each Follow-up Visit; • Raw values and change from the Inclusion Visit in observed and % predicted FEV_1 at each Follow-up Visit; • Raw values and change from the Inclusion Visit in absolute and predicted FEV_1/FVC ratio at each Follow-up Visit; • Raw values and change from the Inclusion Visit in observed and % predicted DLCO at each Follow-up Visit;
• To describe physical and mental health, using the adult form of the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale, at the Inclusion Visit and over time under palovarotene treatment;	• Raw values and change from the Inclusion Visit in physical and mental function (mean global physical and mental health score converted into T-scores), using the adult form of the PROMIS Global Health Scale for all participants, at each Follow-up Visit;
• To describe the number of investigator-reported flare-ups, flare-up outcomes (extra bone growth, restricted movement) and flare-up duration by body location and overall;	• Raw values and change from the Inclusion Visit in number of investigator-reported flare-ups, flare-up outcomes (extra bone growth, restricted movement) and flare-up duration at each Follow-up Visit by body location and overall; • Percentage of participants with extra bone growth associated or not with a flare-up at each Follow-up Visit;
In relation to FOP: • To further understand and describe participants' experiences with FOP symptoms (e.g. flare-ups, joints being locked); • To describe the overall impact of the disease on participants living with FOP (e.g. physical functioning, emotional health, social functioning, work/school/daily life impacts); • To identify and rank the critical joints from a participant's perspective; In relation to patient experiences with palovarotene in the parent study: • To further understand and describe participant experience with palovarotene (e.g. decrease in number of flares up, delay in physical disability, overall satisfaction); • To describe the emotional benefit for participants of using palovarotene as a treatment for FOP; • To assess participants' perceptions of benefits and risks of palovarotene.	• Not applicable.

Overall Design:

Study CLIN-60120-452 is a multicentre, noncomparative rollover study with the aim of continuing to provide palovarotene to participants with FOP who have completed one of the parent studies (Study PVO-1A-301 or PVO-1A-202/PVO-1A-204) and, in the investigator's judgement, may benefit from palovarotene therapy. Participants who have completed the parent study are defined as those who have completed the parent End of Study (EOS) or End of Treatment Visit.

The study is designed primarily to further evaluate the safety of palovarotene and secondly, to collect efficacy data in male and female participants aged ≥14 years (qualifying as skeletally mature or, based on investigator's assessment, have reached final adult height) with FOP treated with palovarotene. Cross-sectional qualitative interviews will also be conducted by the principal investigator (PI)/qualified site staff, within 1 year (ideally within 1 month) following the Inclusion Visit, to inform on patient-centred outcomes such as perception of living with FOP and perceived treatment benefit of palovarotene.

Participants are eligible for the study whether they are receiving chronic or flare-up treatment in the parent study at the time of transition. Participants who previously interrupted/stopped palovarotene treatment and are currently under parent study follow-up due to the premature physeal closure (PPC) related partial clinical hold in participants <14 years, are eligible for the study if they are ≥14 years of age and skeletally mature/have reached final adult height based on investigator's assessment. There must be a current parent study signed informed consent (ICF) form for the participant to be eligible for Study CLIN-60120-452.

A maximum of 87 participants from studies PVO-1A-301, PVO-1A-202/PVO-1A-204 are eligible to be enrolled and will receive palovarotene once daily at the dose received during their participation in the parent study at the time of transition to Study CLIN-60120-452 or prior to interrupting/stopping palovarotene treatment.

The study will consist of an Inclusion Visit (Day 1) (which ideally corresponds to the parent EOS Visit), a continuous dosing treatment period (including a Follow-up Visit every six months), and an EOS/Early Withdrawal (EW) Visit.

Eligible participants will ideally enter the study directly after completing the EOS Visit of the parent study (Study PVO-1A-301 or PVO-1A-202/PVO-1A-204) and the ICF is signed. Any study assessments already performed at the parent EOS Visit will serve as the Inclusion Visit assessment for Study CLIN-60120-452 (maximum of one month allowed between the two visits). Treatment initiation for Study CLIN-60120-452 should ideally concur with the EOS Visit and the study intervention administration schedule of the parent study in order to ensure palovarotene treatment continuity for both chronic and flare-up treatment.

The Inclusion and EOS/EW Visit can be an in-clinic visit or performed remotely per study protocol schedule. However, to enable continued access to the Investigational Product and rollover of participants with impaired mobility [in the case(s) when, per investigator's judgement, this is considered as beneficial for the participant's medical condition], the parent EOS Visit, and consenting for CLIN-60120-452 and CLIN-60120-452 Inclusion Visit can be conducted remotely. In such case(s), both parts of remote consenting used by the site – i.e., Informing/Consenting discussion and ICF signature should be agreed with the IRB/EC, and the investigator's judgement should be sufficiently documented in the patient source notes. Follow-up Visits can be either in-clinic or performed remotely (e.g., at the participant's home by qualified SP in-home services and/or via video-conference or telephone contact from clinical site personnel). In-depth qualitative interviews, conducted in person or by telephone by the PI/qualified site staff within 1 year (ideally within 1 month) following the Inclusion Visit, will be proposed to all participants.

Patient-reported questionnaires (FOP-PFQ, PROMIS Global Health Scale and Healthcare Utilization) will be completed by the participant on paper. All other data collected in the study will be recorded in an electronic case report form (except for qualitative participant interview data).

Participants will continue to receive palovarotene until it is reimbursed in the country where the study is being conducted, or another access programme becomes available, or until the study end date of November 2024 is reached, whichever occurs first. At this time, investigational palovarotene will be discontinued to allow participants to transition to the commercially available drug, physician-prescribed palovarotene, or to another access programme, if available. Early access can only take place if it is allowed within the local laws, rules and regulations or specifically approved in writing by local authorities.

Participants can voluntarily withdraw from the study at any time for any reason.

The study intervention can be discontinued for individual participants by the investigator if he/she believes the participants' safety is at risk.

In the event of early study withdrawal or early discontinuation of the study intervention, all reasonable efforts should be made by the study personnel in-clinic or remotely to have the participants complete all study assessments of the EW Visit as per the schedule of activities.

Participants will be followed-up in-clinic or remotely for safety for 30 days after the last palovarotene dose of the study is received. If the study intervention was discontinued due to a safety concern, in the case of an adverse event (AE)/serious adverse event (SAE), the participant will be monitored until resolution, stabilisation or lost to follow-up and, in the case of pregnancy, the participant will be followed throughout the pregnancy and the health status of the baby verified up until one year of age.

An Independent Data Monitoring Committee will be set-up.

Intervention Groups and Duration:

This is a noncomparative rollover study.

Participants are eligible for the study whether they are receiving chronic or flare-up treatment in the parent study at the time of transition. Participants who previously interrupted/stopped palovarotene treatment and are currently under parent study follow-up are also eligible if they meet eligibility criteria. The dose of palovarotene administered will be individualised for each participant and based on the regimen (chronic or flare-up treatment), the dose received during their participation in the parent study at the time of transition to Study CLIN-60120-452 or prior to interrupting/stopping palovarotene treatment (to allow for dose modifications made to the standard chronic/flare-up regimen during the parent study).

Chronic/flare-up regimen:

Chronic treatment: oral palovarotene once daily, 5 mg, or at the dose received during participation in the parent study at the time of transition Study CLIN-60120-452 or prior to interrupting/stopping palovarotene treatment.

Flare-up treatment: increase in dose at the time of a flare-up (or substantial high risk traumatic event likely to lead to a flare-up) to 20 mg once daily for 4 weeks (28 days), followed by 10 mg once daily for 8 weeks (56 days) for a total of 12 weeks (84 days) even if symptoms resolve earlier.

Participants receiving flare-up treatment at the time of transition to Study CLIN-60120-452 will continue and complete the flare-up treatment as was planned in the parent study.

Flare-up treatment should begin at the onset of the first symptom indicative of a FOP flare-up or substantial high risk traumatic event likely to lead to a flare-up. Participants will be instructed to report potential flare-up symptoms to study site personnel. Symptoms of a FOP flare-up typically include but are not limited to localised pain, soft tissue swelling/inflammation, redness, warmth, decreased joint range of motion, and stiffness (only one symptom is required to define a flare-up). If these symptoms are consistent with previous flare-ups, include a participant-reported onset date, and are confirmed by the investigator as associated with a flare-up, participants will be instructed to immediately begin flare-up-based treatment.

Chronic treatment should cease at the time of initiation of flare-up treatment, re-initiation of the chronic daily treatment should occur after completion of the flare-up treatment.

Flare-ups can occur in the absence of any apparent causative factor, but there is a high risk that substantial traumatic events (e.g. surgery, intramuscular immunisation, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, falls or influenza-like viral illnesses), can lead to a flare-up and result in heterotopic bone formation. Flare-up based treatment should also be initiated if the investigator confirms the presence of a substantial high-risk traumatic event likely to lead to a flare-up.

Persistent flare-up symptoms: treatment may be extended in 4-week intervals with 10 mg palovarotene and continued until the flare-up symptoms resolve.

Intercurrent flare-up: if the participant experiences an intercurrent flare-up (new flare-up location or marked worsening of the original flare-up) at any time during the flare-up treatment, then the 12-week flare-up treatment should be restarted.

In the case of any intolerable adverse reactions, the daily dose of the chronic/flare-up regimen can be reduced (see Table 5).

Flare-up only regimen:

If the participant experiences intolerable adverse reactions while taking chronic daily treatment and dose reduction does not alleviate the adverse reactions, then the participant may take palovarotene only at the time of flare-up (or substantial high-risk traumatic event).

Visit Frequency:

Every six months.

Study Participant and Intervention Duration:

Participants will enter ideally this study directly after completing the parent EOS Visit and continue to receive palovarotene until it is reimbursed in the country where the study is being conducted, or another access programme becomes available, or until the study end date of

November 2024 is reached, whichever occurs first. At this time, investigational palovarotene will be discontinued to allow participants to transition to the commercially available drug, physician-prescribed palovarotene.

The maximum duration is three years from enrolment to last study visit (November 2021 to November 2024).

Number of Participants:

A maximum of 87 participants from studies PVO-1A-301, PVO-1A-202/PVO-1A-204 are eligible to be enrolled.

Statistical Methods:

No formal statistical testing will be performed. All the analyses will be primarily descriptive in nature.

The Inclusion Visit is the first study visit (Day 1) and first administration of palovarotene in Study CLIN-60120-452 (and corresponds ideally to the EOS Visit of the parent study for assessments already performed in the parent study).

Sample Size determination

No formal sample size calculations have been performed as the sample size is dependent on the number of participants in the parent studies who are eligible. A maximum of 87 participants from studies PVO-1A-301, PVO-1A-202/PVO-1A-204 are eligible to be enrolled.

Primary Analysis

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by preferred term (PT) and system organ class (SOC). Adverse events listings will be presented by participant, SOC and PT.

The incidence of all reported TEAEs, serious and nonserious treatment-related TEAEs, serious and nonserious TEAEs, TEAEs leading to death and TEAEs leading to treatment discontinuation will be tabulated separately. In addition, summary tables for TEAEs will be presented by maximum intensity and study intervention relationship (investigator-reported causality assessment).

Secondary Analyses

All statistical analyses will be descriptive. For descriptive analyses, summary statistics will be presented at each scheduled visit. Summary statistics will include sample size, number of available observations (N), number of missing observations (missing), mean, 95% confidence intervals (CIs) of the mean/median, standard deviation, number of nonmissing observations (n), median and range for continuous variables and scores. For categorical or discrete variables, the absolute and relative (percentage) numbers based on the nonmissing number of observations for each category will be presented, including 95% CIs.

Participant Interview Analyses

Participant interviews will be performed within 1 year (ideally within 1 month) following the Inclusion Visit. No formal hypotheses will be tested given the qualitative nature of the analyses.

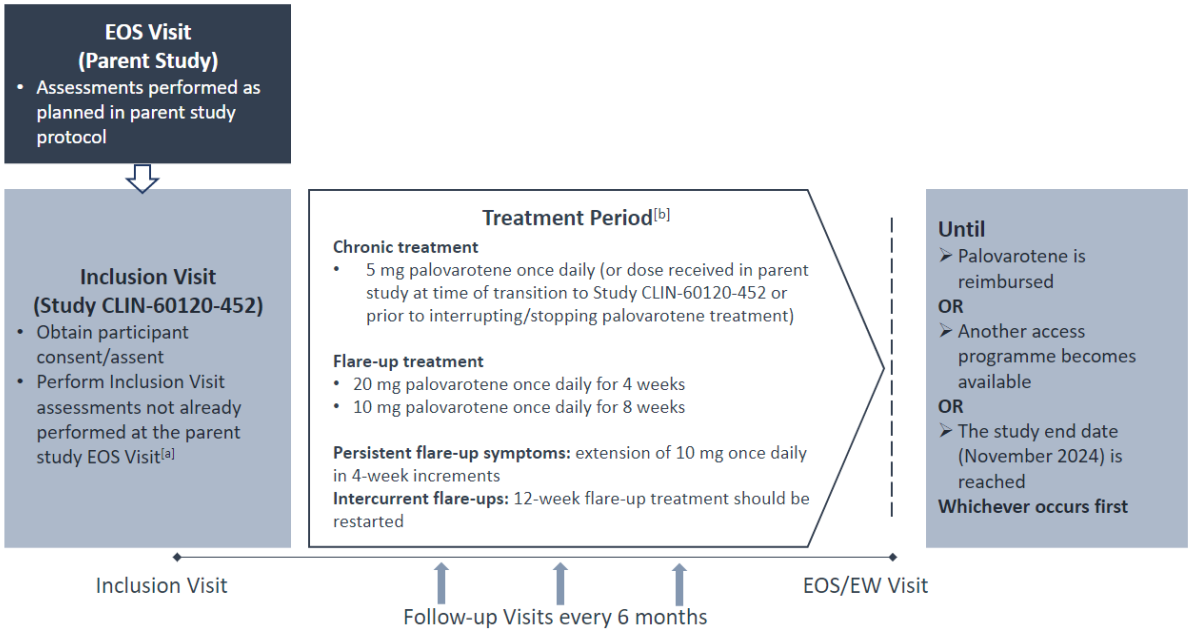
Initial thoughts will be recorded from each of the completed interviews. Key concepts raised by participants and dominant trends in interview data will be identified, with a particular focus on the study objectives and other potential insights emerging from the interviews. Additionally, once the interview transcripts are available, the interview data will be analysed according to the final qualitative analysis plan, using a thematic qualitative data analysis approach.

All qualitative and limited quantitative data will be summarised descriptively. Where applicable, Ns and %s will be provided.

Tables displaying the concepts described during the interviews will be developed to document the results of the interviews. Additionally, descriptive statistics based on the quantitative data obtained during the interviews (e.g. symptom improvements during the clinical study) will be computed and summarised.

1.2 Schema

Figure 1 Study Schema



eCRF=electronic case report form; EOS=End of Study; EW=Early Withdrawal.

a. For any assessments already performed at the parent study EOS Visit, the study site will enter the data again in the Study CLIN-60120-452 eCRF. Participants who completed the paediatric versions of the questionnaires at the EOS Visit of the parent study are required to complete the adult versions of the questionnaires at the CLIN 60120 452 Inclusion Visit.

b. Treatment will be individualised for each participant and based on the regimen (chronic or flare-up treatment) and the dose received in the parent study at the time of transition to Study CLIN-60120-452 or prior to interrupting/stopping palovarotene treatment. Participants will be supplied with chronic treatment as well as the appropriate dose of palovarotene to initiate flare-up treatment when a flare-up or traumatic event is confirmed by the investigator. If a participant is instructed by the investigator to reduce the daily dose of palovarotene due to intolerable adverse reactions but does not have the appropriate dose in his/her possession, the study site will make immediate arrangements to ship the appropriate palovarotene dose to the participant.

1.3 Schedule of Activities

The schedule of activities (SoA) planned in this study are presented in Table 1.

Table 1 Schedule of Activities

Assessment/Procedure	Inclusion Visit[a] Day 1			Follow-Up Visits Every 6 months (±1 month)[b]/ EOS/EW Visit[c]	
	Procedures already performed at the parent EOS Visit that will be transferred from parent study database	Procedures already performed at the parent EOS Visit to be entered in CLIN-60120-452 eCRF by the study site	Procedures to be performed at the CLIN-60120-452 Inclusion Visit	In-clinic Visit	Remote visit
Informed consent[d]			X		
Inclusion/exclusion criteria			X		
Study intervention administration/accountability[e]			X	X	X
Baseline demographics			X		
Physical examination			X		
Participant interview[f]			X		
Pregnancy testing and childbearing potential [g]		X[a]*		X	X
Linear height and body weight [h]		X[a]*		X	X
Vital signs [i]		X[a]*		X	X
Spinal health assessment [j]		X [a]**		X	
Lung function assessments [k]			X	X	
Flare-up assessment [l]			X	X	X [m]
Additional Extra bone growth assessment (without associated flare-up)			X	X	X
CAJIS [n]	X*			X	X
C-SSRS [n] [o]			X	X	X
FOP-PFQ assessment[p] [q]	X*		X [q]***	X	X
PROMIS Global Health Scale [p][q]	X*		X [q]***	X	X
FOP assistive devices assessment [p]			X	X	X
Healthcare Utilization [p]			X	X	X
Biochemistry (amylase, lipase, AST, ALT) and triglycerides	X*				
Disease and flare-up history	X				
Prior medications	X				
Concomitant medications		X		X	X
Concomitant procedures [r]		X		X	X
AEs [s]		X		X	X

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CAJIS=Cumulative Analogue Joint Involvement Scale for FOP; COVID-19=coronavirus disease 2019; C-SSRS=Columbia-Suicide Severity Rating Scale; DLCO=diffusion capacity of the lung for carbon monoxide; eCRF=electronic case report form; EOS=End of Study; EW=Early Withdrawal; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; FOP=fibrodysplasia ossificans progressiva; FOP-PFQ=FOP Physical Function Questionnaire; PROMIS=Patient Reported Outcomes Measurement Information System.

a. The Inclusion Visit should be in-clinic and corresponds ideally to the EOS Visit of the parent study (Study PVO-1A-301 or PVO-1A-202/PVO-1A-204). A maximum of one month is allowed between the two visits. For any assessments

from the parent EOS Visit performed outside this allowed time window, assessments will need to be performed again at the Study CLIN-60120-452 Inclusion Visit (flagged with *). However, to enable continued access to the Investigational Product and rollover of participants with impaired mobility [in the case(s) when per investigator's judgement this is considered as beneficial for the participant's medical conditions], the parent EOS Visit and consenting for CLIN-60120-452 and CLIN-60120-452 Inclusion Visit can be conducted remotely. In such case(s) both parts of remote consenting used by the site – i.e. Informing/Consenting discussion and ICF signature should be agreed with the IRB/EC, and the investigator's judgement should be sufficiently documented in the patient source notes.

For the spinal health assessment, a time window of 3 months post parent visit is allowed (flagged with **).

b. Follow-up Visits will be either in-clinic or performed remotely (e.g. at the participant's home by qualified SP in-home services, and/or via video-conference or telephone contact from clinical site personnel).

c. The EOS/EW Visit will be ideally an in-clinic visit (or remotely when permitted by the IRB/IEC) and will occur at the time of last study intervention intake. The EOS Visit must take place before the participant transitions to commercial treatment.

d. For participants <18 years, assent and legal guardian's consent will also be required.

e. Palovarotene status (treated or not treated) and regimen (chronic or flare-up treatment) at the time of transition to Study CLIN-60120-452 will be collected at the Inclusion Visit. Participants will be supplied with chronic treatment as well as the appropriate dose of palovarotene to initiate flare-up treatment when a flare-up or traumatic event is confirmed by the investigator. Participants will be instructed to report potential flare-up symptoms to study site personnel, only one symptom is required to define a flare-up (see Section 6.1). In the presence of persistent flare-up symptoms, treatment may be extended in 4-week intervals until the flare-up symptoms resolve. If the participant experiences an intercurrent flare-up, or substantial high-risk traumatic event likely to lead to a flare-up, at any time during the flare-up treatment, the 12-week flare-up treatment should be restarted.

f. Participant interviews will be conducted in person or by telephone by the PI/qualified site staff and can be carried out anytime within 1 year (ideally within 1 month) following the Inclusion Visit.

g. Participants will be assessed for child-bearing status and pregnancy prevention measures (females only). According to local practice, medically documented blood or urine pregnancy tests should be carried out prior to starting therapy, monthly as long as the participant receives palovarotene and one month after stopping (the results of pregnancy tests will be recorded in the eCRF). See Section 8.2.6 and 8.3.5 for procedure in case of a positive pregnancy test during the study.

h. For linear height, data from the parent EOS Visit will be used for the Study CLIN-60120-452 Inclusion Visit when available. Height at 6 to 12 months prior to the Inclusion Visit will be transferred from parent study database.

i. Vital signs to be collected are respiratory rate, blood pressure and heart rate.

j. The spinal health assessment must be performed at the Study CLIN-60120-452 Inclusion Visit ONLY if not already performed within the time window allowed (ie,, 3 months post-parent EOS Visit). The spinal health assessment will then be performed annually. The spinal health assessment should be performed using radiological imaging (e.g., CT, x-ray, scintigraphy, etc). This assessment may be performed locally.

k. Includes spirometry and the DLCO test. Spirometry obtains the lung function parameters of observed and % predicted FVC and FEV_1 and the absolute and predicted FEV_1/FVC ratio. The DLCO test obtains observed and % predicted DLCO which provides information on the efficiency of gas transfer from alveolar air into the bloodstream.

l. Includes extra bone growth assessment when associated with a flare-up

m. During remote visit performed at home by the SP in-home services, the participant will be asked if any flare-ups occurred since last visit. If yes, the homecare clinician will attempt to facilitate a call between the participant and the site to provide details.

n. In case of remote visit, the CAJIS and C-SSRS will be assessed via video-conference if possible or feasible or telephone contact from clinical site personnel. The homecare clinician will facilitate the call between the participant and Investigator.

o. 'Baseline' version of C-SSRS will be used at the Study CLIN-60120-452 Inclusion visit. 'Since Last Visit' version of C-SSRS will be used at Follow-Up Visits.

p. In case of remote visit, the questionnaires will be provided by the SP in-home services and completed by the participants.

q. Paper patient-reported questionnaires. Questionnaires completed at the parent EOS Visit will be used for the Study CLIN-60120-452 Inclusion Visit. The adult form (developed for participants ≥15 years old) of the FOP-PFQ and PROMIS Global Health Scale will be used for all participants. At in-clinic visits when multiple assessments are to be performed, the FOP-PFQ and the PROMIS Global Health Scale should be completed first, and in that order, before any other assessments are completed. Participants who completed the paediatric versions of the questionnaires at the EOS Visit of the parent study are required to complete the adult versions of the questionnaires at the CLIN-60120-452 Inclusion Visit (flagged with ***).

r. Any vaccinations received during the study (including COVID-19) should be recorded as concomitant procedures.

s. AEs first occurring during participation in the parent study and ongoing at the time of the Study CLIN-60120-452 Inclusion Visit will be entered again in the Study CLIN-60120-452 eCRF.

2 INTRODUCTION

Palovarotene is an orally bioavailable retinoic acid receptor gamma (RARγ) selective agonist that is being developed by Ipsen for the prevention of heterotopic ossification (HO) in adults and children with fibrodysplasia (myositis) ossificans progressiva (FOP).

2.1 Study Rationale

Currently there are no commercially available effective treatments to prevent the formation of heterotopic bone in FOP. Therapeutic approaches are limited to symptom management and flare-up prevention (Kaplan et al., 2019a; Meyers et al., 2019).

The clinical safety and efficacy of palovarotene in reducing new HO in FOP has been evaluated and demonstrated in:

- Study PVO-1A-201 (complete), a phase II, randomised, double-blind, placebo-controlled study;
- Study PVO-1A-202 (Part A and B complete, Part C and D complete; Parts B, C and D correspond to Study PVO-1A-204 in France), an open-label extension of Study PVO-1A-201;
- Study PVO-1A-301 (Part A, B and C complete), a phase III, single-arm, open-label study.

The aim of this study is to provide continued access to an effective treatment for FOP for which there is no alternative once the ongoing clinical studies have ended. More specifically, the aim is to provide treatment continuity to participants who have completed one of the parent studies (Study PVO-1A-301 or PVO-1A-202/PVO-1A-204) and, in the investigator's judgement, may benefit from palovarotene therapy until palovarotene is reimbursed in the country where the study is being conducted, or another access programme becomes available, or until the study end date of November 2024 is reached, whichever occurs first.

2.2 Background

2.2.1 Disease Background

Fibrodysplasia ossificans progressiva (Online Mendelian Inheritance in Man (OMIM) #135100) is an ultra-rare genetic disorder, with an estimated prevalence of 1.36 per million individuals (Baujat et al., 2017).

FOP is caused by a spontaneous missense mutation in the activin A receptor type-1 (*ACVR1*)/activin receptor-like-kinase-2 (*ALK2*) gene, which encodes a receptor in the bone morphogenetic protein (BMP) signalling pathway (Pignolo et al., 2013; Zhang et al., 2013). Bone morphogenetic proteins are extracellular ligands belonging to the transforming growth factor beta (TGF-β) superfamily. Signal transduction studies show that receptor-regulated Smad proteins 1/5/8 are the immediate downstream molecules of BMP receptors and play a central role in BMP signal transduction (Sanchez-Duffhues et al., 2016; Shen et al., 2009).

Following ligand binding to BMP receptors, there is downstream activation of genes involved in the differentiation and activation of osteoblast and chondrocyte-like cells via phosphorylation of Smad proteins 1/5/8; this is regulated by the inhibitory factor 12-kDa FK506-binding protein (FKBP12), which binds to the BMP type 1 receptor and stabilises the inactive form (Sanchez-Duffhues et al., 2016; Shen et al., 2009). In the presence of the mutated *ACVR1/ALK2* gene, FKBP12 binding is reduced, leading to enhanced BMP signalling (Sanchez-Duffhues et al., 2016).

Patients with FOP experience sporadic and unpredictable episodes of soft-tissue swelling, pain, reduced movement, stiffness and fever, referred to as 'flare-ups' (Di Rocco et al., 2017; Kaplan et al., 2019a; Pignolo et al., 2013; Pignolo et al., 2016). Flare-ups appear spontaneously

or after muscle fatigue, minor trauma, intramuscular injections or influenza-like viral illnesses, and develop rapidly over several hours (Kaplan et al., 2019a); these inciting events induce local inflammation, which is followed by recruitment of bone progenitor cells that differentiate into chondrocytes (Shimono et al., 2011). Although some flare-ups regress spontaneously, many appear to lead to HO, which transforms soft and connective tissues (including aponeuroses, fascia, ligaments, tendons and skeletal muscles) into heterotopic bone (Kaplan et al., 2019a; Pignolo et al., 2013). Of patients with FOP, 95% manifest HO before reaching 15 years of age (Qi et al., 2017).

FOP is characterised by congenital malformation of the great toes and progressive HO in soft and connective tissues; it is a severely disabling HO disorder (Baujat et al., 2017; Pignolo et al., 2016). Other clinical features observed in patients with FOP are shortened thumbs, cervical spine malformations, short broad femoral necks and proximal medial tibial osteochondromas (Kaplan et al., 2009; Pignolo et al., 2013). Typically, HO begins in the dorsal, proximal, axial and cranial regions of the body (neck, shoulders and back) and progresses into ventral, caudal and distal regions (trunk and limbs) (Hüning and Gillessen-Kaesbach, 2014). Heterotopic ossifications develop into ribbons, sheets and plates of extra bone throughout the body and across joints, thereby progressively restricting movement (Baujat et al., 2017). Once ossification occurs, it is permanent; consequently, disability in FOP is cumulative, with most patients becoming immobilised and confined to a wheelchair by their third decade of life and requiring lifelong assistance in performing activities of daily living (ADL) (Baujat et al., 2017; Mattera et al., 2015; Ortiz-Agapito and Colmenares-Bonilla, 2015; Pignolo et al., 2013; Pignolo et al., 2020a).

FOP is not only an extremely disabling disease but also a condition of considerably shortened lifespan (Kaplan et al., 2010). Morbidity associated with FOP includes fractures (due to the increased risk of falls, immobility and prednisone use), limb swelling, pressure sores, hearing impairment, gastrointestinal issues and pain (Kaplan et al., 2019b; Peng et al., 2019). Patients with FOP reach a median survival of 56 (95% confidence interval (CI): 51; 60) years; death is often due to cardiorespiratory failure (as a result of respiratory insufficiency, which is usually caused by progressive restrictive chest-wall HO) or thrombosis (Baujat et al., 2017; Di Rocco et al., 2017; Kaplan et al., 2010; Pignolo et al., 2013).

There are currently no effective treatments to prevent the formation of heterotopic bone in FOP, with therapeutic approaches being limited to symptom management and flare-up prevention; consequently, there is a critical unmet need for definitive therapies for patients with FOP (Kaplan et al., 2019a; Meyers et al., 2019).

2.2.2 Treatment Background

Palovarotene is an orally bioavailable RARγ selective agonist.

RARγ is a nuclear hormone receptor that has a role in regulating skeletal development and growth; it is expressed in chondrogenic cells and chondrocytes (Koyama et al., 1999), where it operates as a transcriptional repressor (Williams, et al., 2009). Activation of the retinoid signalling pathway and RARγ has been demonstrated to inhibit both chondrogenesis and HO (Kaplan et al., 2017a). Given that chondrogenesis requires a decrease in retinoid signalling concurrent with upregulation of pro-chondrogenic pathways, including BMP signalling (Weston et al., 2002; Hoffman et al., 2006), RARγ agonists are likely to elicit anti-chondrogenic and anti-HO effects by maintaining retinoid signalling while reducing BMP signalling (Shimono et al., 2011).

RARγ agonists potently impede heterotopic endochondral ossification by inhibiting downstream effectors (namely Smad 1/5/8) of the mutated *ACVR1/ALK2* gene and by

redirecting pre chondrogenic mesenchymal stem cells from an osteoblast fate to a nonosseous soft-tissue fate (Shimono et al., 2011; Kaplan et al., 2011).

Palovarotene has been found to reduce new HO in animal models, and participants with FOP in phase II and III studies. A brief summary of clinical safety and efficacy of palovarotene in participants aged ≥8/10 years is provided in the sections that follow. To note, the target population for this study is ≥14 years which is aligned with the age of treated participants in the completed parent studies (Study PVO-1A-301 and PVO-1A-202/PVO-1A-204). A detailed description of the chemistry, pharmacology, nonclinical and clinical efficacy and safety of palovarotene is available in the Investigator's Brochure (IB).

2.2.3 Safety Profile of Palovarotene

Safety data from the FOP clinical studies reflect exposure to palovarotene in a total of 164 participants, including 139 participants aged 8 years and above for females and 10 years and above for males (≥8/10 years) for a mean duration of 94.1 weeks, to a maximum of 3.8 years. Participants received either:

- chronic/flare-up regimen: 5 mg daily dose of palovarotene with a 20/10 mg dose for 12 weeks at the time of flare-up (4 weeks of 20 mg once daily followed by 10 mg once daily for 8 weeks);
- flare-up regimen only: either the 20/10 mg dose for 12 weeks, a 10/5 mg dose for 6 weeks (10 mg once daily for 2 weeks followed by 5 mg once daily for 4 weeks) or a 5/2.5 mg dose for 6 weeks (5 mg once daily for 2 weeks followed by 2.5 mg once daily for 4 weeks).

In palovarotene-treated participants aged ≥8/10 years, the most commonly reported adverse reactions were in the *Skin and subcutaneous disorders* (98.8%), *Gastrointestinal disorders* (86.6%) and *Infections and infestations* (82.3%) System Organ Classes (SOC). The majority of adverse events (AEs) were mild or moderate (19.5% and 56.7% of participants, respectively) across all palovarotene FOP studies.

Serious adverse reactions reported in palovarotene-treated participants aged ≥8/10 years included PPC (preferred term (PT): epiphysis premature fusion) and cellulitis (13 participants each; 1.2%).

Adverse events leading to permanent discontinuation occurred in 9.8% of palovarotene-treated participants aged ≥8/10 years. No study discontinuations were reported in placebo/untreated participants due to AEs. Mucocutaneous AEs leading to dose reductions were more common during palovarotene 20/10 mg flare-up treatment than during chronic treatment.

Participants <18 years with open epiphyses were assessed for growth during the clinical studies. Twenty-seven of 87 skeletally immature FOP participants <18 years of age experienced PPC. In participants who received only chronic dosing, PPC, when observed, typically occurred between 12 and 18 months after exposure to palovarotene. The higher proportion of younger participants with PPC is expected given that pre-adolescent individuals are not expected to have physiologic growth plate closure. Thus, any narrowing, partial closure, or closure are likely to be assessed as premature by the clinician. However, the possibility that younger participants with specific risk factors are predisposed to developing PPC or are more sensitive to the effects of palovarotene cannot be excluded.

No pregnancies or deaths were reported during the clinical development programme. One death, due to restrictive lung disease from complications of FOP, occurred two and a half months after discontinuing palovarotene treatment. Efficacy of Palovarotene

2.2.4 Efficacy of Palovarotene

2.2.4.1 Phase II Studies

The flare-up only regimen was assessed in the phase II programme, including the double-blind, placebo-controlled Study PVO-1A-201 and the open-label extension, Study PVO-1A-202.

In Study PVO-1A-201, participants were randomised in a 3:3:2 fashion to palovarotene 10 mg for 2 weeks, then 5 mg for 4 weeks (10/5 mg treatment), palovarotene 5 mg for 2 weeks, then 2.5 mg for 4 weeks (5/2.5 mg treatment), or placebo for 6 weeks, followed by a 6-week observation period for all groups. The clinical endpoint of mean volume of new HO following a flare-up at Week 12 in evaluable flare-ups was assessed.

In Study PVO-1A-202 Part A, participants experiencing another flare-up received palovarotene 10/5 mg treatment in an open-label manner. In Part B, participants who were at least 90% skeletally mature received chronic 5 mg daily treatment with increased dosing at the time of a flare-up to 20 mg for 4 weeks followed by 10 mg for 8 weeks (chronic/flare-up regimen), with continuation of treatment in 4-week increments for persistent symptoms. Skeletally immature participants received the 20/10 mg flare-up treatment (weight-adjusted) in Part B.

The comparator group includes flare-ups imaged in untreated participants from the Natural History Study (NHS) (an international, 3-year, longitudinal, noninterventional study) and placebo-treated flare-ups from Study PVO-1A-201. These two sources of participants were similar with respect to demographics and baseline disease characteristics.

Based on pooled data from Studies PVO-1A-201, PVO-1A-202/Parts A and B, and PVO-1A-001 (NHS), there was a statistically significant 72% decrease (approximated *P* value of 0.02) in the new HO volume in the 15 flare-ups treated with the 20/10-mg flare-up only regimen (3045 mm^3) compared with the volume observed in untreated/placebo flare-ups (10,780 mm^3). Combining all flare-ups treated with the 20/10-mg regimen, regardless of whether they were preceded by chronic treatment with 5 mg, resulted in a 55% reduction in new HO (4818 mm^3 in 48 flare-ups) relative to untreated/placebo flare-ups (approximated *P* value of 0.24).

2.2.4.2 Phase III Study

The phase III study, PVO-1A-301, evaluated the efficacy and safety of the chronic/flare-up palovarotene treatment regimen in preventing new HO as compared to data from the NHS.

Participants received palovarotene 5 mg daily with increased dosing at the time of a flare-up defined as at least one symptom (e.g. pain, swelling, redness) consistent with a previous flare-up or a substantial high-risk traumatic event likely to lead to a flare-up to 20 mg once daily for 4 weeks followed by 10 mg once daily for 8 weeks (denoted as the chronic/flare-up regimen), with flare-up treatment extension in 4-week increments for persistent symptoms. Anytime during flare-up treatment, the 12-week treatment restarted if the participant had another flare-up or substantial high-risk traumatic event. The dosing was adjusted according to body weight in skeletally immature children (children who had not reached at least 90% skeletal maturity defined as a bone age of ≥12 years 0 months for girls and ≥14 years 0 months for boys).

The treatment groups assessed in the chronic/flare-up regimen were well matched for baseline demographics.

Post-hoc analyses showed that, for participants aged ≥8/10 years, the mean annualised new HO volume was 56% lower in palovarotene-treated participants (11 419 mm^3) (N=77) than that observed in untreated participants (25 796 mm^3) (N=79).

The weighted linear mixed effects analysis showed a 49% lower fitted mean annualised new HO volume in palovarotene treated participants (11 033 mm^3) versus untreated participants in the NHS (21 476 mm^3), yielding 2-sided nominal p-value p=0.1124.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of palovarotene may be found in the IB.

2.3.1 Risk Assessment

The key potential risks of clinical significance of participating in this study with palovarotene are summarised in Table 2 and are based on the current palovarotene IB, which is the safety reference document for this study. The list of potential risks may be revised if necessary, according to each new IB version published during Study CLIN-60120-452.

Table 2 Summary of Potential Risks of Study Participation and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention		
Contraindications		
Teratogenicity	The teratogenic potential of systemic retinoids is well established regarding the risk to the developing embryo and foetus. Although there were no pregnancies in the palovarotene development programme, 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.	**Participant selection:** Participants who are pregnant or breastfeeding will not be included in the study. FOCBP are only eligible to participate in the study if they have met all the conditions of pregnancy prevention (Section 5.1). **Participant monitoring:** During the study, pregnancy testing will be carried out monthly until one month after stopping treatment (Section 8.2.6). **Study intervention withdrawal criteria:** If a participant becomes pregnant during the study, palovarotene will be immediately discontinued (Section 8.3.5).
Radiological vertebral fracture	In clinical trials, palovarotene has resulted in decreased vertebral bone mineral content, decreased bone density and decreased bone strength as well as an increased risk of radiologically observed vertebral (T4 to L4) fractures in treated adult and paediatric patients compared with untreated patients.	**Participant selection:** Participants who have any symptomatic vertebral fracture will not be included in the study (Section 5.2). **Instruction:** Assessment of 25-OH Vitamin D levels is recommended and supplementation with Vitamin D for good bone health should be considered as per the ICC on FOP guideline [ICC FOP 2022] and local guidelines. **Participant monitoring:** Spinal health assessment will be performed annually using radiological imaging (e.g., CT, x-ray, scintigraphy, etc).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypersensitivity to palovarotene	Not applicable	**Participant selection:** Participants with a known allergy to palovarotene will not be included in the study (Section 5.2). **Participant monitoring:** During the study, participants will be monitored for signs of hypersensitivity/allergy and any events will be recorded as AEs (Section 8.3). **Study intervention withdrawal criteria:** The daily dose of palovarotene can be reduced for any intolerable adverse effects. If already receiving the lowest dose, palovarotene can be temporarily or permanently discontinued or the participant switched to flare-up treatment only (Section 6.5).
Special warnings and precautions for use		
Mucocutaneous effects	Mucocutaneous toxicities are the most common side effects of systemic retinoids and are generally treatable, dose-dependent, and reversible. The most frequently reported AEs during FOP clinical studies with palovarotene were primarily mucocutaneous in nature, including cheilitis/dry lips, dry skin, pruritus and alopecia, and were generally assessed as related to palovarotene.	**Participant selection:** Participants who were intolerant to prior treatment with palovarotene will not be included in the study (Section 5.2). **Instruction:** Participants will be instructed to utilise symptomatic therapy (e.g. analgesics, skin emollients, lip moisturisers, artificial tears, or other helpful treatments), to minimize these side effects, or as prophylaxis in the study. **Participant monitoring:** During the study, participants will be monitored for signs of mucocutaneous effects and any events will be recorded as AEs (Section 8.3). **Study intervention withdrawal criteria:** The daily dose of palovarotene can be reduced for any intolerable adverse effects. If already receiving the lowest dose, palovarotene can be temporarily or permanently discontinued or the participant switched to flare-up treatment only (Section 6.5).
Photosensitivity	Photosensitivity reactions, such as exaggerated sunburn reactions (e.g. burning, erythema, blistering) involving areas exposed to the sun have been associated with the use of retinoids. Although palovarotene has not been proven to be phototoxic, precautionary measures for phototoxicity are recommended.	**Participant selection:** Participants who were intolerant to prior treatment with palovarotene, or any other medical condition that would expose the participant to undue risk, will not be included in the study (Section 5.2). **Instructions:** Participants should avoid excessive exposure to sun and use protection from sunlight when it cannot be avoided (use of sunscreens, protective clothing, and use of sunglasses). **Participant monitoring:** During the study, participants will be monitored for signs of photosensitivity and any events will be recorded as AEs (Section 8.3).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Study intervention withdrawal criteria: The daily dose of palovarotene can be reduced for any intolerable adverse effects. If already receiving the lowest dose, palovarotene can be temporarily or permanently discontinued or the participant switched to flare-up treatment only (Section 6.5).
Psychiatric disorders	Systemic retinoids have been associated with psychiatric side effects, including depression, suicide, aggression and psychosis. During FOP clinical studies, AEs related to psychiatric disorders were reported in a third of all participants with irritability, anxiety and depressed mood reported most frequently.	**Participant selection:** Participants with suicidal ideation (type 4 or 5) or any suicidal behaviour at the Study CLIN-60120-452 Inclusion Visit defined by the C-SSRS, will not be included in the study (Section 5.2). **Participant monitoring:** During the study, will be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour and any events will be recorded as AEs (Section 8.2.1). **Study intervention withdrawal criteria:** If participants experience signs of suicidal ideation or behaviour, consideration should be given to discontinuing the study intervention.

AE=adverse event; C-SSRS=Columbia-Suicide Severity Rating Scale; EOS=End of Study; FOCBP=female of childbearing potential; FOP=fibrodysplasia ossificans progressiva.

2.3.2 Benefit Assessment

Palovarotene has been demonstrated in clinical studies to be effective in reducing new HO in FOP participants. Currently, available therapeutic approaches for FOP are limited to symptom management and flare-up prevention. None of them have demonstrated reduction in HO formation.

Therefore, the benefit afforded to participants with FOP enrolled in this study is continued access to a definitive, effective treatment for FOP for which there is no alternative, until palovarotene is reimbursed in the said participants country or another access programme becomes available.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to participants, the potential risks identified in association with palovarotene are justified by the anticipated benefits that may be afforded to participants with FOP.

3 OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To further evaluate the safety of palovarotene in adult and paediatric participants with FOP.	• Incidence and description of all treatment-emergent adverse events (TEAEs) whether or not they are considered as related to the study intervention; • Incidence and description of all serious and nonserious treatment-related TEAEs; • Incidence and description of all serious TEAEs, whether or not they are considered as related to the study intervention; • Incidence and description of all nonserious TEAEs whether or not they are considered as related to the study intervention.
Secondary	
• To describe range of motion, as assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP, at the Inclusion Visit and over time under palovarotene treatment;	• Raw values and change from the Inclusion Visit in CAJIS total score at each Follow-up Visit;
• To describe the use of assistive devices and adaptations for daily living by FOP participants, at the Inclusion Visit and over time under palovarotene treatment;	• Raw values and shift from the Inclusion Visit in the use of assistive devices and adaptations for daily living at each Follow-up Visit;
• To describe physical function, using the adult form of the FOP Physical Function Questionnaire (FOP-PFQ), at the Inclusion Visit and over time under palovarotene treatment;	• Raw values and change from the Inclusion Visit in % of worst score for total score, upper extremities subscore and mobility subscore using the adult form of the FOP-PFQ for all participants, at each Follow-up Visit;
• To describe the FOP healthcare utilization in patients with FOP	• Type and frequency of healthcare utilization
• To describe the parameters of lung function (observed and % predicted forced vital capacity (FVC), observed and % predicted forced expiratory volume in one second (FEV_1), absolute and predicted FEV_1/FVC ratio, observed and % predicted diffusion capacity of the lung for carbon monoxide (DLCO)) at the Inclusion Visit and over time under palovarotene treatment;	• Raw values and change from the Inclusion Visit in observed and % predicted FVC at each Follow-up Visit; • Raw values and change from the Inclusion Visit in observed and % predicted FEV_1 at each Follow-up Visit; • Raw values and change from the Inclusion Visit in absolute and predicted FEV_1/FVC ratio at each Follow-up Visit; • Raw values and change from the Inclusion Visit in observed and % predicted DLCO at each Follow-up Visit;
• To describe physical and mental health, using the adult form of the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale, at the Inclusion Visit and over time under palovarotene treatment;	• Raw values and change from the Inclusion Visit in physical and mental function (mean global physical and mental health score converted into T-scores), using the adult form of the PROMIS Global Health Scale for all participants, at each Follow-up Visit;

• To describe the number of investigator-reported flare-ups, flare-up outcomes (extra bone growth, restricted movement) and flare-up duration by body location and overall;	• Raw values and change from the Inclusion Visit in number of investigator-reported flare-ups, flare-up outcomes (extra bone growth, restricted movement) and flare-up duration at each Follow-up Visit by body location and overall; • Percentage of participants with extra bone growth associated or not with a flare-up at each Follow-up Visit;
In relation to FOP: • To further understand and describe participants' experiences with FOP symptoms (e.g. flare-ups, joints being locked); • To describe the overall impact of the disease on participants living with FOP (e.g. physical functioning, emotional health, social functioning, work/school/daily life impacts); • To identify and rank the critical joints from a participant's perspective; In relation to patient experiences with palovarotene in the parent study: • To further understand and describe participant experience with palovarotene (e.g. decrease in number of flares up, delay in physical disability, overall satisfaction); • To describe the emotional benefit for participants of using palovarotene as a treatment for FOP; • To assess participants' perceptions of benefits and risks of palovarotene.	• Not applicable.

4 STUDY DESIGN

4.1 Overall Design

Study CLIN-60120-452 is a multicentre, noncomparative rollover study with the aim of continuing to provide palovarotene to participants with FOP who have completed one of the parent studies (Study PVO-1A-301 or PVO-1A-202/PVO-1A-204) and, in the investigator's judgement, may benefit from palovarotene therapy. Participants who have completed the parent study are defined as those who have completed the parent End of Study (EOS) or End of Treatment Visit.

The study is designed primarily to further evaluate the safety of palovarotene and secondly, to collect efficacy data in male and female participants aged ≥14 years (qualifying as skeletally mature or, based on investigator's assessment, have reached final adult height) with FOP treated with palovarotene. Cross-sectional qualitative interviews will also be conducted by the principal investigator (PI)/qualified site staff, within 1 year (ideally within 1 month) following the Inclusion Visit, to inform on patient-centred outcomes such as perception of living with FOP and perceived treatment benefit of palovarotene.

Participants are eligible for the study whether they are receiving chronic or flare-up treatment in the parent study at the time of transition. Participants who previously interrupted/stopped palovarotene treatment and are currently under parent study follow-up due to the PPC related partial clinical hold in participants <14 years, are eligible for the study if they are ≥14 years of age and skeletally mature/have reached final adult height based on investigator's assessment. There must be a current parent study signed informed consent form (ICF) for the participant to be eligible for Study CLIN-60120-452.

A maximum of 87 participants from studies PVO-1A-301, PVO-1A-202/PVO-1A-204 are eligible to be enrolled and will receive palovarotene once daily at the dose received during their participation in the parent study at the time of transition to Study CLIN-60120-452 or prior to interrupting/stopping palovarotene treatment.

The study will consist of an Inclusion Visit (Day 1) (which corresponds ideally to the parent EOS Visit), a continuous dosing treatment period (including a Follow-up Visit every six months), and an EOS/Early Withdrawal (EW) Visit. The study design is illustrated in Figure 1.

Eligible participants will ideally enter the study directly after completing the EOS Visit of the parent study (Study PVO-1A-301 or PVO-1A-202/PVO-1A-204) and the ICF is signed. Any study assessments already performed at the parent EOS Visit will serve as the Inclusion Visit assessment for Study CLIN-60120-452 (maximum of one month allowed between the two visits). For assessments not performed in the parent study (i.e. spirometry), assessments will be performed at the Study CLIN-60120-452 Inclusion Visit.

Treatment initiation (at the Inclusion Visit) for Study CLIN-60120-452 should ideally concur with the EOS Visit and the study intervention administration schedule of the parent study in order to ensure palovarotene treatment continuity for both chronic and flare-up treatment.

The Inclusion and EOS/EW Visit can be an in-clinic visit or performed remotely per study protocol schedule. However, to enable continued access to the Investigational Product and rollover of participants with impaired mobility [in the case(s) when per investigator's judgement this is considered as beneficial for the participant's medical conditions], the parent EOS, consenting for CLIN-60120-452 and CLIN-60120-452 Inclusion Visit can be conducted remotely. In such case(s) both parts of remote consenting used by the site – i.e. Informing/Consenting discussion and ICF signature should be agreed with the IRB/EC, and the investigator's judgement should be sufficiently documented in the patient source notes. Follow-up Visits can be either in-clinic or performed remotely (e.g., at the participant's home by

qualified SP in-home services, or via video-conference or telephone contact from clinical site personnel). In-depth qualitative interviews, conducted in person or by telephone by the PI/qualified site staff within 1 year (ideally within 1 month) following the Inclusion Visit, will be proposed to all participants.

Participants will undergo the procedures and assessments specified in the SoA (Table 1). Patient-reported questionnaires (FOP-PFQ, PROMIS Global Health Scale, Healthcare Utilization and FOP Assistive Device Assessment) will be completed by the participant on paper. All other data collected in the study will be recorded in an electronic case report form (eCRF) (except for qualitative participant interview data).

Participants will continue to receive palovarotene until it is reimbursed in the country where the study is being conducted, or another access programme becomes available, or until the study end date of November 2024 is reached, whichever occurs first. At this time, investigational palovarotene will be discontinued to allow participants to transition to the commercially available drug, physician-prescribed palovarotene, or to another access programme, if available. Early access can only take place if it is allowed within the local laws, rules and regulations or specifically approved in writing by local authorities.

Participants can voluntarily withdraw from the study at any time for any reason.

The study intervention can be discontinued for individual participants by the investigator if he/she believes the participants' safety is at risk.

In the event of early study withdrawal or early discontinuation of the study intervention, all reasonable efforts should be made by the study personnel in-clinic or remotely to have the participants complete all study assessments of the EW Visit as per the SoA.

Participants will be followed-up in-clinic or remotely for safety for 30 days after the last palovarotene dose of the study is received. If the study intervention was discontinued due to a safety concern, the participant will be monitored for safety (see Section 8.3.3 for follow-up of AEs/serious adverse events (SAEs) and Section 8.3.5 for follow-up of pregnancies).

The EOS for an individual participant will be the date of study completion due to palovarotene becoming reimbursed in the country where the study is being conducted, or another access programme becoming available, or the study end date of November 2024 being reached, whichever occurs first.

The maximum duration of the study is three years from enrolment to last study visit (November 2021 to November 2024).

An Independent Data Monitoring Committee (IDMC) will be set-up, as described in Section 10.1.5.

4.2 Scientific Rationale for Study Design

Firstly, this study was designed to provide treatment continuity to participants who have completed one of the parent studies (Study PVO-1A-301 or PVO-1A-202/PVO-1A-204) and, in the investigator's judgement, may benefit from palovarotene therapy until palovarotene is reimbursed in the country where the study is being conducted, or another access programme becomes available.

In addition, the study will primarily further evaluate the safety of palovarotene and secondly, collect efficacy data in participants with FOP treated with palovarotene. Cross-sectional qualitative interviews will also be conducted by the principal investigator (PI)/qualified site staff, within 1 year (ideally within 1 month) following the Inclusion Visit, to inform on patient-centred outcomes such as perception of living with FOP and perceived treatment benefit of palovarotene.

The primary endpoint is the standard description and incidence of all TEAEs, serious and nonserious treatment-related TEAEs, all serious TEAEs and all nonserious TEAEs, which will permit the AE profile of palovarotene to be further characterised.

As secondary endpoints, this study will continue to collect efficacy data which was collected in the parent studies; range of motion, physical impairment, physical and mental health and the number of flare-ups experienced and their outcome and duration. As in the parent studies, range of motion will be assessed by CAJIS, physical impairment by the FOP-PFQ and physical and mental function by the PROMIS Global Health Scale.

The CAJIS is a disease-specific, objective measure of joint movement completed by the investigator to document total joint involvement. CAJIS scores have been shown to provide an accurate and reproducible overview of total body and regional mobility burden of FOP that correlates with age and functional status (Kaplan et al., 2017b; Pignolo et al., 2019).

The FOP-PFQ is a disease-specific patient-reported outcome measure of physical impairment. It was developed by Clementia (an Ipsen Company) based on the FDA Guidance for Industry, 'Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims' to assess the relationship between patient reports of physical impairment due to HO, thereby providing evidence of HO as a clinically meaningful endpoint. FOP-PFQ scores have been shown to provide a consistent and reproducible measure of physical function and ability to conduct ADL, correlated with age, functional status and HO volume (Pignolo et al., 2019; Pignolo et al., 2020b).

The PROMIS Global Health Scale is a patient-reported outcome measure of physical and mental function. HO burden substantially impacts quality of life and physical functioning. A strong, statistically significant association between total PROMIS Global Health Scale scores and the number of anatomic sites subjectively reported as being affected by HO has been shown. In addition, a statistically significant association between the total PROMIS score and the FOP-PFQ has been shown. When stratified by gender, this relationship holds only for females (Pignolo et al., 2020c).

The lung function parameters of FVC, FEV_1 and FEV_1/FVC ratio as well as the DLCO, a measure of the efficiency of gas transfer from alveolar air into the bloodstream, has not been collected in previous clinical studies but will inform on the effect of palovarotene on lung function. Patients with FOP often experience respiratory insufficiency, which is usually caused by progressive restrictive chest-wall HO and is often the cause of death (Kaplan et al., 2010).

Further information on the use of assistive devices and adaptations for daily living will be collected using a list compiled by the International Fibrodysplasia Ossificans Progressiva Association (IFOPA) of assistive devices and adaptations for daily living used by patients with FOP.

The target population for this study is ≥14 years (at the time the informed consent is signed) which is aligned with the age of treated participants in the completed parent studies (Study PVO-1A-301 and PVO-1A-202/PVO-1A-204).

4.2.1 Participant Input into Design

None.

4.3 Justification for Dose

The proposed dosing for palovarotene consists of 5 mg once daily (chronic treatment) with an increase in dose at the time of a flare-up to 20 mg once daily for 4 weeks (28 days), followed by 10 mg once daily for 8 weeks (56 days) for a total of 12 weeks (84 days) (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 palovarotene and continued until

the flare-up symptoms resolve. Should the participant experience an intercurrent flare-up (new flare-up location or marked worsening of the original flare-up) at any time during flare-up treatment, the flare-up 12-week treatment should be restarted (see Section 6.1). In the case of adverse reactions, the daily dose can be reduced (see Section 6.5). If dose reduction does not alleviate the adverse reactions, then the participant may take palovarotene only at the time of a flare-up (or substantial high-risk traumatic event) (Section see 6.1).

Participants are eligible for the study whether they are receiving chronic or flare-up treatment in the parent study at the time of transition. Participants who previously interrupted/stopped palovarotene treatment and are currently under parent study follow-up are also eligible if they meet eligibility criteria. As this is a rollover study with the aim of providing treatment continuity, the dose of palovarotene administered will be individualised for each participant and based on the regimen (chronic or flare-up treatment) and dose they received during their participation in the parent study at the time of transition to Study CLIN-60120-452 or prior to interrupting/stopping palovarotene treatment (to allow for dose modifications made to the standard chronic/flare-up during the parent study).

The proposed chronic/flare-up regimen was selected based on nonclinical and clinical data.

In a non-injury-based mouse model of FOP that recapitulates much of the clinical phenotype observed in patients, including spontaneous HO formation, chronic daily treatment with palovarotene at a human equivalent dose (HED) of approximately 5 mg prevented HO formation. Importantly, in this animal model, the dosing regimen did not impair long bone growth but partially normalised the abnormal growth plate histology and shortened long bones that are key phenotypic features of this model. The results raised the possibility that chronic daily palovarotene dosing may be a major component of an optimised clinical dosing strategy.

The rationale for increasing the chronic palovarotene dose at the time of a flare-up comes from nonclinical data from two different mouse models of FOP which demonstrated a dose-related decrease in HO volume; and suggested that flare-up-based treatment using an HED of 20 mg may be necessary to optimally prevent HO following an injury (equivalent to a flare-up in humans).

The chronic/flare-up regimen was assessed in Study PVO-1A-301. The flare-up only regimen was assessed in the phase II studies PVO-1A-201 and PVO-1A-202. Both regimens were demonstrated to significantly reduce new HO volume versus untreated/placebo-treated participants (see Section 2.2.4)

While it is recognised that flare-ups can occur in the absence of any apparent causative factor, there is a high risk that substantial traumatic events such as surgery, intramuscular immunisations, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, falls, or influenza-like viral illnesses can induce flare-ups and progressive HO formation (Kaplan et al., 2008). In one survey of patients with FOP, flare-ups were induced in two-thirds of falls and resulted in permanent loss of movement in 93% of patients (Glaser et al., 1998). Therefore, flare-up-based treatment should also be initiated if the investigator confirms the presence of a substantial high-risk traumatic event likely to lead to a flare-up.

4.4 End of Study Definition

The EOS for an individual participant will be the date of study completion; the participant is considered to have completed the study if he/she has stopped study intervention due to palovarotene becoming reimbursed in the country where the study is being conducted, or another access programme becoming available, or the study end date of November 2024 being reached, whichever occurs first.

The EOS Visit can be an in-clinic visit or performed remotely and must take place before the participant transitions to commercial treatment.

Study end is defined as the date of last contact with the last participant in the study (Last Participant Last Visit (LPLV)).

Criteria for study intervention discontinuation and participant discontinuation/withdrawal from the study are described in Section 7.1 and Section 7.2, respectively. Loss to follow-up is described in Section 7.3.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Participants enrolling will have fulfilled the inclusion and exclusion criteria for Study PVO-1A-301 or PVO-1A-202/PVO-1A-204.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Participant has completed the EOS or End of Treatment Visit of Study PVO-1A-301 or PVO-1A-202 (PVO-1A-202 Parts C and D correspond to Study PVO-1A-204 in France) and did not previously withdraw consent from any of the parent studies to be eligible for Study CLIN-60120-452.

In the investigator's judgment, the participant may benefit from continued participation in a palovarotene study.

Age

1. Participant must be ≥14 years of age (aligned with the age of treated participants in the ongoing parent studies PVO-1A-301 and PVO-1A-202/PVO-1A-204) and qualify as 100% skeletally mature (if <18 years, based on assessments carried out at parent EOS Visit; if ≥18 years, automatically considered 100% skeletally mature) or have reached final adult height based on investigator's assessment*, at the time the Study CLIN-60120-452 informed consent is signed.

**The above criteria can be reached at any point after parent study end for the participant to be eligible for Study CLIN-60120-452, as long as it is prior to palovarotene becoming reimbursed in the country where the study is being conducted.*

Sex

2. Male, or female who is not pregnant or breastfeeding and has met all of the following conditions:
   - Females of child-bearing potential (FOCBP) (defined in Section 10.2.1) must have a negative blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) prior to administration of palovarotene;
   - FOCBP must agree to remain abstinent from heterosexual sex during treatment and for one month after treatment or, if sexually active, to use two effective methods of birth control (described in Section 10.2.2) during and for one month after treatment;
   - Additionally, sexually active FOCBP must already be using two effective methods of birth control one month before treatment is to start;
   - Specific risk of the use of retinoids during pregnancy, and the agreement to remain abstinent or use two effective methods of birth control will be clearly defined in the informed consent and the participant or legally authorised representatives (e.g. parents, caregivers or legal guardians) must specifically sign this section.

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Guidance for contraception and collection of pregnancy information is provided in Section 10.2.

Requirements for pregnancy testing are located in Section 8.2.6.

Informed Consent and Assent

3. Capable of giving signed informed consent or providing assent as described in Section 10.1.3.

5.2 Exclusion Criteria

Participants will not be included in the study if any of the following criteria apply:

Medical conditions

1. History of allergy or hypersensitivity to retinoids, gelatin, lactose (note that lactose intolerance is not exclusionary) or palovarotene, or unresponsiveness to prior treatment with palovarotene.
2. Uncontrolled cardiovascular, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease.
3. Symptomatic vertebral fracture.
4. Any other medical condition/clinically significant abnormalities that would expose the participant to undue risk or interfere with study assessments.
5. Amylase or lipase >2× above the upper limit of normal (ULN) or with a history of chronic pancreatitis.
6. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5× ULN.
7. Fasting triglycerides >400 mg/dL with or without therapy.
8. Suicidal ideation (type 4 or 5) or any suicidal behaviour at the Inclusion Visit as defined by the Columbia-Suicide Severity Rating Scale (C-SSRS).

Prior/concomitant therapy (see Section 6.8)

9. Current use of 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.
10. Exposure to synthetic oral retinoids other than palovarotene within 4 weeks of the Inclusion Visit.
11. Concurrent treatment with tetracycline or any tetracycline derivatives due to the potential increased risk of pseudotumor cerebri.
12. Use of concomitant medications that are strong inhibitors or inducers of cytochrome P450 (CYP450) 3A4 activity (see Section 6.8 and 10.5); or kinase inhibitors such as imatinib.

Other exclusion criteria

13. Palovarotene is reimbursed in the country where the study is being conducted.
14. Any reason that, in the opinion of the investigator, would lead to the inability of the participant and/or family to comply with the protocol.

5.3 Lifestyle Considerations

No lifestyle restrictions are required for this study.

5.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from

regulatory authorities. Minimal information includes date of informed consent, demography, reason for screen failure, eligibility criteria and any SAE at the time.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6 STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention is defined as the investigational intervention intended to be administered to the study participant according to the study protocol.

6.1 Study Intervention Administered

The study intervention administered is palovarotene. Participants are eligible for the study whether they are receiving chronic or flare-up treatment in the parent study at the time of transition. Participants who previously interrupted/stopped palovarotene treatment and are currently under parent study follow-up are also eligible if they meet eligibility criteria. As this is a rollover study with the aim of providing treatment continuity, the dose of palovarotene administered will be individualised for each participant and based on the regimen (chronic or flare-up treatment) and the dose they received during their participation in the parent study at the time of transition to Study CLIN-60120-452 or prior to interrupting/stopping palovarotene treatment (to allow for dose modifications made to the standard chronic/flare-up regimen during the parent study).

In the completed parent studies PVO-1A-202/PVO-1A-204 and PVO-1A-301, participants received the chronic/flare-up regimen detailed in Table 4 below (or the weight-based equivalent for <90% skeletally immature participants), with flare-up treatment extension in 4-week increments for persistent symptoms. In Study PVO-1A-301, anytime during flare-up treatment, the 12-week treatment restarts if the participant has another flare-up or a substantial high-risk traumatic event. In both parent studies, the daily dose of palovarotene can be reduced if the participant experiences AEs that are not tolerated.

Participants receiving flare-up treatment at the time of transition to Study CLIN-60120-452 will continue and complete the flare-up treatment as was planned in the parent study. Chronic daily treatment should then be re-initiated at 5 mg, or the dose received during participation in the parent study prior to the flare-up.

Treatment initiation (at the Inclusion Visit) for Study CLIN-60120-452 should ideally concur with the EOS Visit and the study intervention administration schedule of the parent study in order to ensure palovarotene treatment continuity for both chronic and flare-up treatment.

Details of the study intervention are provided in Table 4.

Table 4 Study Intervention Administered

Intervention Name	Palovarotene
Intervention Description	Palovarotene hard capsules, taken once daily as chronic/flare-up treatment
Type	Drug
Dose Formulation	Capsule
Unit Dose Strength(s)	Each capsule contains 1 mg, 1.5 mg, 2.5 mg, 5 mg or 10 mg of palovarotene as active ingredient
Dosage Level(s)	**Chronic/flare-up regimen:** **Chronic treatment** 5 mg once daily (or at the dose received during participation in the parent study at the time of transition to Study CLIN-60120-452, or prior to interrupting/stopping palovarotene treatment) **Flare-up treatment** 20 mg once daily for 4 weeks (28 days) 10 mg once daily for 8 weeks (56 days) **Persistent flare-up symptoms:** extension of 10 mg once daily in 4-week increments **Intercurrent flare-ups** (new flare-up location or marked worsening of original flare-up): 12-week flare-up treatment should be restarted **Chronic treatment:** once daily, 5 mg or at the dose received during participation in the parent study at the time of transition to Study CLIN-60120-452 or prior to interrupting/stopping palovarotene treatment. **Flare-up treatment:** increase in dose at the time of a flare-up (or substantial high risk traumatic event likely to lead to a flare-up) to 20 mg once daily for 4 weeks (28 days), followed by 10 mg once daily for 8 weeks (56 days) for a total of 12 weeks (84 days) (20/10 mg flare-up treatment) even if symptoms resolve earlier. Flare-up treatment should begin at the onset of the first symptom indicative of a FOP flare-up or substantial high-risk traumatic event likely to lead to a flare-up. Symptoms of a FOP flare-up typically include but are not limited to localised pain, soft tissue swelling/inflammation, redness, warmth, decreased joint range of motion, and stiffness. Chronic treatment should cease at the time of initiation of flare-up treatment, re-initiation of the chronic daily treatment should occur after completion of the flare-up treatment. Flare-ups can occur in the absence of any apparent causative factor, but there is a high risk that substantial traumatic events (e.g. surgery, intramuscular immunisation, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, falls or influenza-like viral illnesses), can lead to a flare-up and result in heterotopic bone formation. Flare-up treatment should be initiated at the time of such events. ***Persistent flare-up symptoms:*** treatment may be extended in 4-week intervals with 10 mg palovarotene and continued until the flare-up symptoms resolve. ***Intercurrent flare-up:*** if the participant experiences an intercurrent flare-up (new flare-up location or marked worsening of the original flare-up) at any time during the flare-up treatment, then the 12-week flare-up treatment should be restarted. In the case of any intolerable adverse reactions, the daily dose of the chronic/flare-up regimen can be reduced (see Section 6.5). **Flare-up only regimen:** If the participant experiences intolerable adverse reactions while taking chronic daily treatment and dose reduction does not alleviate the adverse reactions, then the participant may take palovarotene only at the time of flare-up (or substantial high-risk traumatic event).
Route of Administration	Oral
Use	Active study intervention
IMP and NIMP/AMP.	IMP
Sourcing	Centrally by sponsor

Packaging and Labelling	Study intervention will be provided in bottle or blister packaging: - 90 capsules packaged in a bottle (1 mg, 1.5 mg, 2.5 mg, 5 mg and 10 mg). - 14 capsules packaged in a blister (1 mg, 1.5 mg and 5 mg) - 15 capsules packaged in a bottle (5 mg) for US patients only. Each carton will be labelled as required per country requirement.
Storage requirements	To be stored at room temperature (between 15°C and 30°C) and protected from light and humidity.
Former Names/Alias(es)	None

AMP=auxiliary medicinal product; FOP= fibrodysplasia ossificans progressiva; IMP=investigational medicinal product; NIMP=non investigational medicinal product.

Participants will be instructed to report potential flare-up symptoms to study site personnel. Only one symptom is required to define a flare-up. If these symptoms are consistent with previous flare-ups, include a participant-reported onset date, and are confirmed by the investigator as associated with a flare-up, participants will immediately begin flare-up-based treatment. Flare-up based treatment should also be initiated if the investigator confirms the presence of a substantial high-risk traumatic event likely to lead to a flare-up.

Based on clinical signs and symptoms as determined by the investigator, flare-up treatment may be extended in 4-week intervals while on-treatment with 10 mg palovarotene and continue until the flare-up resolves and the 4-week extension treatment has been completed.

Participants will be supplied with chronic treatment as well as the appropriate dose of palovarotene to initiate flare-up treatment when a flare-up or traumatic event is confirmed by the investigator (during in-clinic or remote visit, or by telephone contact).

Participants will be instructed to contact study site personnel immediately in case of intolerable adverse reactions during palovarotene treatment. The investigator will assess the adverse reaction and, if appropriate, will instruct the participant to reduce the daily dose of palovarotene as described in Section 6.5. If the participant does not have the appropriate dose in his/her possession, the study site will make immediate arrangements to ship the appropriate palovarotene dose to the participant.

Palovarotene should be taken with food preferably at the same time each day. Palovarotene may be swallowed whole, or capsules may be opened and the contents emptied onto a teaspoon of soft food and taken immediately.

6.2 Preparation, Handling, Storage and Accountability

Women who are pregnant or intend to become pregnant should avoid contact with palovarotene. Additionally, to avoid unintended exposure, caregivers administering palovarotene by emptying the capsule contents onto soft food should wear disposable gloves when handling and use disposable paper towels and a container to collect waste (e.g. a resealable bag).

Palovarotene capsules may be opened, and the contents emptied on a teaspoon of soft food and taken immediately. If not taken immediately, it can be taken after a maximum of one hour after the sprinkling provided it was maintained at room temperature and not exposed to direct sunlight.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorised site staff may supply study intervention. All study intervention must be stored in a secure, environmentally controlled and monitored (manual or automated) area in

accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

- The investigator, institution or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- The sponsor will provide guidance on the destruction of unused study intervention. If destruction is authorised to take place at the investigational site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy and any special instructions provided by the sponsor. All destruction must be adequately documented.

Further guidance and information for the receipt, preparation, management and disposal/return of the study intervention are provided in the 'Investigational Medicinal Product Handling Manual'.

At each dispensation (at scheduled and unscheduled visits, if applicable), treatment number(s) will be assigned by the Interactive Web Response System (IWRS). The IWRS will also manage all logistical aspects of the study treatment (e.g. replacement, drug supplies and expiry dates) and the recording of drug accountability/destruction. This service provides the investigator, investigational site coordinators and project team members with a service that is available 24 hours a day, 7 days a week. Additional details may be found in the IWRS reference manual provided to each investigational site. In case of technical or dispensation queries, a 24-hour helpline is available. If a participant discontinues the study before any intake of study treatment, his/her assigned treatment number(s) will not be reused.

In addition to the information provided in the IWRS, drug accountability paper records will be maintained by the investigator.

6.3 Measures to Minimise Bias: Randomisation and Blinding

6.3.1 Randomisation

Not applicable as this is a nonrandomised study.

6.3.2 Maintenance of Blinding

This is an open-label study therefore no procedures for blinding are applicable.

6.4 Study Intervention Administration/Accountability

Study intervention bottles and blisters will be brought back to the site and accountability performed. Accountability will be documented in the source documents and IWRS.

A record of the quantity of palovarotene dispensed to and administered by each participant must be maintained and reconciled with study intervention and accountability records.

Palovarotene status (treated or not treated) and regimen (chronic or flare-up or intercurrent flare-up or persistent flare up symptoms treatment) at the time of transition to Study CLIN-60120-452 will be collected at the Inclusion Visit.

6.5 Dose Modification

Participants will be instructed to contact study site personnel immediately in case of intolerable adverse reactions during palovarotene treatment. The investigator will assess the adverse reaction and, if appropriate, will instruct the participant to reduce the daily dose to the next lower dosage as shown in Table 5; additional dose reduction should occur if adverse reactions continue to be intolerable. If the participant is already receiving the lowest possible dose, then consideration should be given to discontinue therapy temporarily or permanently or switching

to flare-up treatment only (see Section 6.1). Subsequent flare-up treatment should be initiated at the same reduced treatment that was tolerated previously.

Table 5 Dose Reduction of Palovarotene

Dose Prescribed	Reduced Dose
20 mg	15 mg
15 mg	12.5 mg
12.5 mg	10 mg
10 mg	7.5 mg
7.5 mg	5 mg
5 mg	2.5 mg
2.5 mg	1 mg

6.6 Continued Access to Study Intervention after the End of the Study

The aim of this rollover study is to provide continued access to treatment to participants who have completed one of the parent studies until palovarotene is reimbursed in the country where the study is being conducted, or another access programme becomes available, or until the study end date of November 2024 is reached, at which point the study will end. Therefore, participants will not receive any additional study intervention following the EOS.

6.7 Treatment of Overdose

For this study, any dose of palovarotene greater than those specified in Section 6.1 will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose; any overdose should be treated with supportive care according to the signs and symptoms exhibited by the participant.

In the event of an overdose, the investigator/treating physician should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until palovarotene can no longer be detected systemically (at least 30 days).
- Document the quantity of the excess dose as well as the duration of the overdose. See Section 10.3.1 for reporting requirements concerning overdose.

6.8 Prior and Concomitant Therapy

The following medications are not allowed during palovarotene treatment (chronic or flare-up-based treatment):

- Vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, herbal preparations, or fish oil are not permitted from the day before the start of treatment until the last day of treatment.
- Synthetic oral retinoids other than palovarotene are not permitted in the 30 days prior to treatment until the last day of treatment.
- Concomitant use of tetracyclines and retinoids has been associated with benign intracranial hypertension. Therefore, use of tetracycline or tetracycline derivatives is prohibited during the study. If the participant experiences a medical condition that requires treatment with tetracycline and/or doxycycline, the study intervention should be discontinued for the duration of tetracycline treatment and the medical monitor should be notified. Prior to restarting treatment with palovarotene, an appropriate wash-out period of 3 days must be considered.

- Strong inhibitors of CYP450 3A4 are known to alter the metabolism of palovarotene. Thus, concurrent oral medications identified as strong inhibitors of CYP450 3A4 (see Section 10.5) are excluded. If during the study, the participant must take a strong inhibitor of CYP450 3A4, the study intervention is to be discontinued for the duration of treatment. Prior to restarting treatment with palovarotene, an appropriate wash-out period (five half-lives) must be considered (see Section 10.5).
- Strong inducers of CYP450 3A4 are also known to alter the metabolism of palovarotene. Thus, concurrent oral medications identified as strong inducers of CYP450 3A4 (see Section 10.5) are excluded. If during the study, the participant must take a strong inducer of CYP450 3A4, the study intervention may continue, but the medical monitor should be notified.
- Kinase inhibitors such as imatinib, and other drugs used off-label as potential treatments for FOP such as rapamycin, as reported in the literature. A washout period of 5 half-lives is required prior to enrolment into the study.

Prior medications will not be collected or recorded in the Study CLIN-60120-452 eCRF. These data will be transferred from the final parent study database and summarised at the Inclusion Visit.

Any medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, herbal supplements and vaccines (e.g. COVID-19)) or other specific categories of interest that the participant receives during the study will be collected at the Inclusion Visit, the Follow-up Visits and the EOS/EW Visit along with:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

The following data on concomitant procedures will be collected at the Inclusion Visit and at the Follow-up/EOS/EW Visits:

- Surgical procedure name;
- Indication;
- Reason for concomitant surgery;
- Date of surgery.

6.8.1 Preventive Medication

Assessment of 25-OH Vitamin D level is recommended and supplementation with Vitamin D for good bone health should be considered as per the ICC on FOP guideline [ICC FOP 2022] and local guidelines.

6.8.2 Rescue Medicine

Mucocutaneous toxicities are the most common side effects of systemic retinoids. The most frequently reported AEs during FOP clinical studies with palovarotene were primarily mucocutaneous in nature, including cheilitis/dry lips, dry skin, pruritus and alopecia, and were generally assessed as related to palovarotene.

Participants will be instructed to utilise symptomatic therapy (e.g. analgesics, skin emollients, lip moisturisers, artificial tears, or other helpful treatments), to minimize these side effects, or as prophylaxis in the studies.

Although palovarotene has not been proven to be phototoxic, precautionary measures for phototoxicity are recommended. Participants should avoid excessive exposure to sun and use protection from sunlight when it cannot be avoided (use of sunscreens, protective clothing, and use of sunglasses).

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.9.

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention before the EOS. Palovarotene treatment for individual participants can be discontinued by the investigator if he/she believes the participants' safety is at risk. In the event of pregnancy, palovarotene treatment must be discontinued (Section 8.3.5).

If palovarotene is permanently discontinued, the participant will be withdrawn from the study.

All reasonable efforts should be made by the study personnel to have the participants complete all study assessments of the EW Visit as per the SoA (see Table 1).

If palovarotene is permanently discontinued due to a safety concern, the participant will be monitored for safety (see Section 8.3.3 for follow-up of AEs/SAEs and Section 8.3.5 for follow-up of pregnancies).

7.1.1 Liver Chemistry Stopping Criteria

Not applicable to this study.

7.1.2 QTc Stopping Criteria

Not applicable to this study.

7.1.3 Treatment Interruption

Palovarotene can be temporarily discontinued if, after the daily dose of palovarotene has already been reduced to the lowest possible dose (see Section 6.5), the participant continues to experience intolerable adverse effects.

If palovarotene is temporarily interrupted, the participant will remain in the study and assessments performed as planned per the SoA.

If palovarotene is permanently discontinued, the participant will be withdrawn from the study and all reasonable efforts should be made by the study personnel to have the participant complete all study assessments of the EW Visit as per the SoA.

In case of suspected or confirmed COVID-19 (SARS-CoV-2) infection, the intervention administration may be temporarily discontinued depending on the participant clinical presentation. In some cases, the investigator may request a participant be retested before the intervention administration is resumed.

7.1.4 Rechallenge

If palovarotene is temporarily interrupted due to a safety related event, once the event resolves, treatment can resume at the discretion of the investigator. If the event reoccurs, palovarotene treatment may be temporarily interrupted again or permanently discontinued.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or compliance reasons. Participants meeting exclusion criteria during the course of the study will be withdrawn.
- The legal guardian and the paediatric participant have the right to withdraw permission (consent or assent, respectively) at any time during the study. If the study staff identify any reluctance in the legal guardian or paediatric participant (e.g. signs of verbal or physical dissent) about continued participation in the study, the paediatric participant's

continuation in the study should be re-evaluated. The same principles that govern permission/assent/consent also govern its withdrawal. A participant will be withdrawn from the study if consent or assent if applicable (a paediatric participant's dissent should be respected) is withdrawn.

- At the time of discontinuing from the study, all reasonable efforts should be made by the study personnel to have the participants complete all study assessments of the EW Visit if possible, as shown in the SoA. See SoA (Table 1) for data to be collected at the time of study discontinuation and any evaluations that need to be completed.
- The reason for discontinuation will be recorded in the eCRF.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such withdrawal of consent.
- If the participant requests to permanently discontinue the study intervention, they will be withdrawn from the study. In the case of ongoing AE/SAEs or pregnancy, they will be asked to be followed for safety (see Section 8.3.3 for follow-up of AEs/SAEs and Section 8.3.5 for follow-up of pregnancies).
- If the participant withdraws consent for any further contact, the investigator will explain in the medical records as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or post-study intervention follow-up. This information must be entered in the eCRF.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return/be present for scheduled in-clinic or remote visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic or be present remotely for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The site should counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (see Table 1). Protocol waivers and exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- Procedures conducted as part of the participant's parent EOS Visit will be utilised for screening and Inclusion Visit assessments. All evaluations must be reviewed to confirm that potential participants meet all eligibility criteria.

Eligible participants will enter this study ideally directly after completing the EOS Visit of the parent study (Study PVO-1A-301 or PVO-1A-202/PVO-1A-204) and after having signed the ICF. Any study assessments already performed at the parent EOS Visit will serve as the Inclusion Visit assessment for Study CLIN-60120-452; the data will be either transferred from the parent study database or will be entered again in the Study CLIN-60120-452 eCRF by the study site (see details in Table 1). For assessments not performed in the parent study (i.e. spirometry) or assessments performed out of allowed time window, assessments will be performed in-clinic or remotely at the Study CLIN-60120-452 Inclusion Visit.

8.1 Efficacy Assessments

At in-clinic visits when multiple assessments are to be performed, the FOP-PFQ and the PROMIS Global Health Scale should be completed first, and in that order, before any other assessments are completed.

8.1.1 FOP-PFQ

Physical function will be assessed using the FOP-PFQ at the Inclusion Visit, Follow-up Visits and the EOS/EW Visit.

The FOP-PFQ is a disease-specific patient-reported outcome measure of physical impairment which includes questions related to ADL and physical performance. The adult form (developed for participants ≥15 years old) will be used for all participants.

The adult FOP-PFQ consists of 28 questions which are scored on a scale of 1 to 5, with lower scores indicating that the participant has more difficulty completing those tasks. A total score, upper extremities subscore and a mobility subscore is calculated. Score calculations are described in Section 9.4.3.1.

8.1.2 PROMIS Global Health Scale

Physical and mental function will be assessed using the PROMIS Global Health Scale at the Inclusion Visit, at the Follow-up Visits and the EOS/EW Visit.

The PROMIS Global Health Scale is a patient-reported outcome measure of physical and mental function. The adult form (developed for participants ≥15 years old) will be used for all participants.

The PROMIS Global Health Scale consists of 10 questions from which two scores are calculated: the global physical health score and the global mental health score, both ranging from 4 (worse health) to 20 (better health). Scores are converted to T-scores, with a higher T-score value indicating better health. Score calculations and conversion to T-scores are described in Section 9.4.3.2.

8.1.3 CAJIS

The CAJIS for FOP will be performed at the Inclusion Visit, Follow-up Visits and the EOS/EW Visit.

The CAJIS is an objective measure of joint movement completed by the investigator to document total joint involvement (Kaplan et al., 2017b). This scale, which was developed by the investigators from the Center for Research in FOP and Related Disorders, assesses functional disability by categorising range of motion across 12 joints (both right and left shoulder, elbow, wrist, hip, knee and ankle joints) and three body regions (cervical spine, thoracic/lumbar spine and jaw), with each joint/region assessed as: 0=normal (<10% deficit); 1=partially impaired (10% to 90% deficit); 2=functionally ankylosed (>90% deficit). The CAJIS total score is calculated as the sum of the scores of all joints/regions and ranges from 0 (no involvement) to 30 (maximally involved).

The examiner must also note and record (yes/no) if the participant:

- Can walk;
- Uses a wheelchair;
- Needs some help with ADL;
- Needs complete help with ADL.

8.1.4 FOP Assistive Devices Assessment

The use of assistive devices and adaptations for daily living will be collected using the FOP assistive devices assessment at the Inclusion Visit, Follow-up Visits and the EOS/EW Visit.

Assistive devices and adaptations for daily living include:

- Mobility aids (cane/crutch, walker, manual wheelchair, motorised scooter, customised motorised wheelchair, adapted vehicle for driving or for motorised wheelchair);
- Eating tools (adapted eating utensils, customised height table for eating/customised chair for eating, customised table for eating attached to wheelchair, straws for drinking, blender for pureeing foods, adapted cooking utensils);
- Personal care tools (hearing aids, reaching stick, dressing stick, compression socks, customised clothing, standard shoe lift for support, customised shoe soles, portable urinal for male and females, adapted comb/brush/bathing tools/toothbrush/shaver/cosmetic application tools, pill crusher, medical alert bracelet with annual emergency membership, 'In Case of Emergency' Taggisar with annual membership and label for emergency care, customised dental care tools);
- Bathroom aids and devices (barrier-free roll in shower, shower seat/chair, handicap height toilet, washlet toilet, portable commode, lift seat on toilet, adapted sink counter/height/faucet handles/piping, shower grab bars, shower handheld sprayer, tub lift, bathroom grab bars);
- Bedroom aids and devices (memory foam bed mattress/pillows, bed with motorised lift system, airflow mattress, waterbed, bed safety rails, bed pull/strap for self-positioning, remote control devices for lights/window treatment/shades);
- Home adaptions (floor level threshold on all doorways, wide doorways to allow wheelchair access, transfer lift for bathing and mobility around the house, portable transfer lift, permanent built in ramp for home, portable ramp for use in home/office/travel, automatic light switches, customised furniture, customised counters in your kitchen/bathroom/work area, lift chair, durable/easy care flooring due to wheelchair weight, padded flooring for protection for children, handicapped emergency

exits, sliding/pocket interior doors, remote control/hands free exterior door opener and closer, combination emergency fire/carbon monoxide detectors and alert)

- Work environment adaptions (customised desk/office chair/workstation/office tools, use of handicapped bathroom facilities);
- Technology adaptions (adapted keyboard, voice activated computer software, wireless keyboard and mouse, trackball, adapted stand for computer use, typing stick, onscreen keyboard that is not normally part of the device);
- Sports and recreation adaptions (protective helmet/body gear, adapted bicycle, other adapted recreational gear);
- School adaptions (adapted desk, adapted chair, reaching tools, special electronics for learning, adapted curriculum);
- Medical therapies for daily living (supplemental oxygen, physical therapy, hydrotherapy, energy medicine therapy, occupational therapy, lymphoedema massage treatments and wraps, wound care specialist, positive expiratory pressure mask or spirometer for breathing exercises).

8.1.5 Healthcare Utilisation

The healthcare utilisation information that will be collected does not rely on specific validated questionnaires, but on tailored questions which will assess the type and frequency of health services used in the past 6 months/since the last visit.

8.1.6 Lung Function Assessments

Lung function will be assessed at the Inclusion Visit, Follow-up Visits and at the EOS/EW Visit.

The lung function parameters of observed FVC (litres) and % predicted FVC, observed FEV_1 (litres) and % predicted FEV_1 and the absolute and predicted FEV_1/FVC ratio are obtained by spirometry.

The parameters of observed (traditional unit of mL/min/mmHg or International System of Units (SI unit) of mmol/min/kPa) (Graham et al., 2017) and % predicted DLCO is obtained by the DLCO test. This provides information on the efficiency of gas transfer from alveolar air into the bloodstream. Carbon monoxide has a high affinity for haemoglobin, and it follows the same pathway as that of oxygen to finally bind with haemoglobin. Inhaled carbon monoxide is used for this test due to its high affinity for haemoglobin which is 200-250 times that of oxygen (Modi and Cascella, 2020).

8.1.7 Flare-up Assessment

For each flare-up, the location of the flare-up, flare-up cause, flare-up start and stop date, whether it is ongoing, flare-up concomitant medication, symptoms and outcome (resulted in extra bone growth, restricted movement) will be collected at the Inclusion Visit (for ongoing flare-up, data from parent EOS Visit will be entered again in the Study CLIN-60120-452 eCRF), the Follow-up Visits and the EOS/EW Visits.

Symptoms of a flare-up typically include, but are not limited to, localised pain, soft tissue swelling/inflammation, redness, warmth, decreased joint range of motion and stiffness. Only one symptom is required to define a flare-up. Flare-ups can occur in the absence of any apparent causative factor, but there is a high risk that substantial traumatic events (e.g. surgery, intramuscular immunisation, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, falls or influenza-like viral illnesses) can lead to a flare-up and result in heterotopic bone formation.

At each visit, the investigator will ask the participant if they experienced any flare-ups since their last visit, the location of the flare-ups, the start and stop date or whether it is ongoing, if any flare-up concomitant medication was taken and whether the flare-up resulted in extra bone growth and/or restricted movement. When extra bone growth occurred, the location will be specified and the investigators will ask the participant how the extra bone growth affected their movement.

Bone growth, loss of mobility and audiology impact that occurs as a consequence of a flare-up will be reported as an AE or SAE (see Section 10.3.1).

8.1.8 Extra Bone Growth Assessment (without associated flare-up)

For each extra bone growth (without associated flare-up) the location of the extra bone growth, whether it was preceded by injury, illness, vaccination and/or other events ("yes", "no" or "unknown"), extra bone growth start date, duration and whether it is ongoing, will be collected at the Inclusion Visit and Follow-up/EOS/EW Visits.

At each visit, the investigator will ask the participant if they experienced any extra bone growth (without associated flare-up) since their last visit and the details of these extra bone growths.

8.1.9 Qualitative Participant Interviews

In-depth qualitative interviews will be proposed to all participants and will be conducted in person or by telephone by the PI/qualified site staff. Interviews can be carried out anytime within 1 year (ideally within 1 month) following the Inclusion Visit with consenting participants.

Participants will be asked to describe her/his past experience with FOP (e.g. symptoms, joint being locked) and with palovarotene (e.g. decrease in number of flare-ups, delay in physical disability, overall satisfaction).

Participants will also be asked to describe:

- the overall impact of the disease on them (e.g. physical functioning, emotional health, social functioning, work/school/daily life impacts);
- the critical joints involved;
- the emotional benefit of using palovarotene as a treatment for FOP;
- the perceptions of benefits and risks of palovarotene.

The conduct of the qualitative interviews and all related procedures will be described in the interview guide. For the collection and reporting processes of the AEs/SAEs during the qualitative interviews, please refer to Section 8.3.

8.2 Safety Assessments

The assessment of AEs/SAEs is detailed in Section 8.3.

8.2.1 Spinal Health Assessment

Participants' spinal health should be assessed for the risk of 'radiological vertebral fracture'.

The spinal health will be assessed using radiological imaging (e.g., CT, x-ray, scintigraphy, etc) at the Inclusion Visit, at the Follow-Up Visit annually and at the EOS/EW Visit. This assessment may be performed locally.

The data from the spinal health assessment performed in the parent study (less than 3 months before entry in CLIN-60120-452 study) should be entered in the CLIN-60120-452 eCRF by the study site for the Inclusion Visit. If the spinal health assessment was performed more than 3 months before entry in CLIN-60120-452 study, a new spinal health assessment should be performed at the Inclusion Visit. Spinal health assessment should then be performed annually.

The radiological imaging can be done locally and the spinal health assessment will be done by the PI and the data should be collected in the eCRF. If any vertebral fractures are identified, these should be reported as AEs and the corresponding eCRF page should be completed.

8.2.2 C-SSRS and Suicidal Ideation and Behaviour Risk Monitoring

Suicidal ideation and behaviour will be collected using the C-SSRS ('Baseline' version) at the Inclusion Visit for screening purposes. At Follow-up visits, the C-SSRS 'Since Last Visit' version will be used.

The adult form (designed for participants ≥12 years of age) will be used for all participants. Any participant reporting type 4 or 5 suicidal ideation or any suicidal behaviour within the past month prior to the Inclusion Visit, will not be eligible to participate in the study.

Although there was no treatment-related increase in suicidal ideation, suicidal behaviour or psychiatric disorders overall relative to untreated participants with FOP in clinical trials, depression, depression aggravated, anxiety, mood alterations and suicidal thoughts and behaviours have been reported in patients treated with systemic retinoids. In addition, there is a relatively high background prevalence (24%) of depression in untreated patients with FOP.

Therefore, participants being treated with palovarotene should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of suicidal ideation or behaviour should undergo a risk assessment. All factors contributing to suicidal ideation and behaviour should be evaluated and consideration should be given to discontinuation of the study intervention.

When informed consent or assent has been given, families and caregivers of participants being treated with palovarotene should be alerted about the need to monitor participants for the emergence of unusual changes in behaviour, as well as the emergence of suicidal ideation and behaviour and to report such symptoms immediately to the study investigator. Suicidal ideation and behaviour will be captured as an AE/SAE.

8.2.3 Biochemistry and Triglycerides

Amylase, lipase, AST, ALT and triglyceride levels from the EOS of parent studies and centrally measured will be used at the Inclusion Visit for screening purposes.

For participants being screened more than one month after EOS visit of parent study, blood samples will be collected under fasting conditions when possible and testing preformed at a local, qualified laboratory.

The participant will not be eligible to participate in the study if:

- Any of the exclusion criteria apply (Section 5.2);
- Amylase or lipase is >2× above the ULN;
- AST or ALT is >2.5× above the ULN;
- Fasting triglycerides levels are >400 mg/dL with or without therapy.

8.2.4 Linear Height and Body Weight

Linear height and body weight will be collected for all participants at the Inclusion Visit, the Follow-up Visits and the EOS/EW Visit.

Height at 6 to 12 months prior to the Inclusion Visit will also be collected.

8.2.5 Vital Signs

Respiratory rate, blood pressure and heart rate will be collected at the Inclusion Visit, the Follow-up Visits and the EOS/EW Visit.

- Blood pressure and pulse measurements will be assessed by manual techniques. An automated device should not be used due to the risk of over-inflation and potential tissue injury in participants with FOP. To minimise the potential for a flare-up at the cuff site when measuring blood pressure, the cuff should be pumped slowly to a maximum of 140 mm Hg. Blood pressure should not be measured on an arm with a flare-up.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones).
- Vital signs will be measured after 5 minutes rest and will include respiratory rate, systolic and diastolic blood pressure and pulse.

8.2.6 Pregnancy Testing

Female participants are assessed for child-bearing status and pregnancy prevention measures prior to receiving palovarotene. Refer to Section 5.1 for pregnancy testing entry criteria.

Pregnancy tests may be performed either with the assistance from a study nurse at home or self-administered by the participant.

According to local practice, medically documented blood or urine pregnancy tests should be performed, as follows (the results of which will be recorded in the eCRF):

- **Prior to starting therapy:** at least one month after the participant has started using contraception, and shortly (preferably a few days) prior to the first prescription, the participant should undergo a pregnancy test. This test should ensure the participant is not pregnant when she starts treatment with palovarotene and should be documented within the patient medical records.
- **Follow-up pregnancy testing during treatment:** follow-up pregnancy tests should be done monthly. The need for repeated medically documented pregnancy tests every month is required and should be determined according to local practice including consideration of the participant's sexual activity and extent of FOP disease burden.
- **End of treatment:** one month after stopping treatment, women should undergo a final pregnancy test.

Palovarotene is strictly contraindicated during pregnancy, therefore if the pregnancy test is positive at the Inclusion Visit, the participant will not be eligible to participate in the study. Any positive pregnancy test during the study will result in immediate discontinuation of palovarotene. If a participant becomes pregnant during the study, she will be followed throughout her pregnancy and the health status of the baby will be verified up until one year of age (see Section 8.3.5).

8.3 AEs and SAEs and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legal guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs or their sequelae (any AE, based on the investigator’s opinion, not only those assessed

as related) that persist after the date of palovarotene discontinuation, or that caused the participant to discontinue palovarotene (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs (including SAEs) will be collected from the signing of the ICF until last study intervention intake + 30 days at the time points specified in the SoA (Table 1).

All AEs that first occurred during participation in the parent study and are ongoing at the time of transition to Study CLIN-60120-452 will be collected and entered again as ongoing AEs/SAEs in the Study CLIN-60120-452 eCRF at the signing of the ICF.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of awareness of the event, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation (unless any AEs/SAEs or their sequelae persist after this date, follow-up is required until the event or its sequelae resolve or stabilise, or the participant is lost to follow-up). However, if the investigator learns of any SAE, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor (through pharmacovigilance).

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. Follow-up of the AE/SAE after the date of palovarotene discontinuation is required until the event or its sequelae resolve or stabilise at a level acceptable to the investigator and the sponsor's clinical monitor or his/her designated representative, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board (IRB)/independent ethics committee (IEC), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

- Investigator safety reports must be prepared by the sponsor for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor's policy and forwarded to investigators as necessary.

8.3.5 Pregnancy

- Details of all pregnancies in female participants will be collected from the signing of the ICF and until one year after the end of treatment within Study CLIN-60120-452.
- Any female participant who becomes pregnant while participating in the study will discontinue the study intervention and be withdrawn from the study.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate forms (AE form, in the eCRF and 080479-FOR Drug Exposure for Pregnancy Form – paper form) and submit it to the sponsor within 24 hours of learning of the female participant's pregnancy (detailed in Section 10.2).
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and follow-up information on the neonate up until one year of age and the information will be forwarded to the sponsor using the appropriate forms.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- For female participants who have not reached legal age and who become pregnant, this information will be shared with the participant's legal guardian if and as required by local regulations.

8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.7 Adverse Events of Special Interest

No Adverse Events of Special Interest have been formally defined during palovarotene clinical development.

8.3.8 Reporting of Study Intervention Errors Including Misuse/Abuse

- Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a study intervention (medicinal product) while under the control of a healthcare professional, participant or consumer (EMA definition).
- Misuse refers to situations where the study intervention is intentionally and inappropriately used not in accordance with the protocol.
- Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- Study intervention errors and uses outside of what is foreseen in the protocol will be recorded in the eCRF in the AE section. It will be reported in the safety database only if associated with an SAE.

- Misuse or abuse will be collected and reported (via SAE form) in the safety database, whether associated or not with an AE/SAE, within 24 hours of investigator's or qualified designees' awareness.

8.4 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5 Genetics

Genetics are not evaluated in this study.

8.6 Biomarkers

Biomarkers are not evaluated in this study.

8.7 Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.8 Medical Resource Utilisation and Health Economics

Medical resource utilisation and health economics parameters are not evaluated in this study.

8.9 Demographic and Baseline Characteristics

The following data will not be collected or recorded in the Study CLIN-60120-452 eCRF; these data will be transferred from the final parent study database and summarised:

- Disease history including the date of symptom onset, date of diagnosis by a physician, method of diagnosis, date of genetic test if performed and type of FOP genetic mutation.
- Flare-up history over the past 12 months prior to the Inclusion Visit including: location of flare-ups, cause, flare-up start and stop date, flare-up concomitant medication and outcome (resulted in extra bone growth, restricted movement). Symptoms of a flare-up typically include, but are not limited to, localised pain, soft tissue swelling/inflammation, redness, warmth, decreased joint range of motion and stiffness.

The following will be collected at the Inclusion Visit:

- Baseline demographics including age, gender and race.
- Physical examination including a general assessment, skin, lymph nodes, head, eyes, ears, nose and throat (HEENT), thorax, lung, cardiovascular system, abdomen, extremities, musculoskeletal system, neurological system and other.

Any post-Inclusion Visit abnormal findings considered clinically significant by the investigator will be collected as an AE/SAE.

9 STATISTICAL CONSIDERATIONS

The first draft of the statistical analysis plan (SAP) will be made available within the first three months following the first participant first visit and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.1 Statistical Hypotheses

No hypotheses are planned to be tested as the primary endpoint of this study is descriptive.

9.1.1 Multiplicity Adjustment

Adjustment for multiplicity is not applicable to this study.

9.2 Sample Size Determination

No formal sample size calculations have been performed as the sample size is dependent on the number of participants in the parent studies who are eligible. A maximum of 87 participants from studies PVO-1A-301, PVO-1A-202/PVO-1A-204 are eligible to be enrolled.

9.3 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Screened Set	All participants who signed the ICF
Enrolled Set	The Enrolled Set will contain all participants who were assigned to receive palovarotene in Study CLIN-60120-452.
Full Analysis Set (FAS)/Safety Set	The FAS/Safety Set will contain all participants who received at least one dose of palovarotene during Study CLIN-60120-452.
Per Protocol (PP) Set	The PP set will contain all participants from the FAS who did not experience any major protocol deviations that may interfere with safety/efficacy evaluations

9.4 Statistical Analyses

9.4.1 General Considerations

Statistical evaluation will be performed using Statistical Analysis System (SAS®) (Version 9.4 or higher).

No formal statistical testing will be performed. All the analyses will be primarily descriptive in nature. If p-values are presented, they will be for exploratory purposes only.

For descriptive analyses, summary statistics will be presented at each scheduled visit and will include sample size, number of available observations (N), number of missing observations (missing), mean, 95% CIs of the mean/median, standard deviation (SD), number of nonmissing observations (n), median and range for continuous variables and scores. For categorical or discrete variables, the absolute and relative (percentage) numbers based on the nonmissing number of observations for each category will be presented, including 95% CIs.

Missing data will not be replaced but will be displayed in all relevant tables.

The Inclusion Visit is the first study visit (Day 1) and first administration of palovarotene in Study CLIN-60120-452 (and corresponds to the EOS Visit of the parent study for assessments already performed in the parent study).

All analyses will be performed by parent study (PVO-1A-301 or PVO-1A-202/PVO-1A-204), by palovarotene status at the time of transition to Study CLIN-60120-452 (treated, not treated) and treatment regimen (chronic treatment only, flare-up treatment only, chronic & flare-up treatment) and overall.

9.4.2 Analysis of Primary Endpoint

The primary endpoint is the incidence and description of all TEAEs, serious and nonserious treatment-related TEAEs, all serious TEAEs and all nonserious TEAEs.

A TEAE is defined as any AE that occurs after signing the ICF of Study CLIN-60120-452 or an ongoing AE from the parent study with a worsening in severity or relationship to the study intervention following transition to Study CLIN-60120-452.

Ongoing AEs from the parent study with no change in severity or relationship to the study intervention following transition to Study CLIN-60120-452 will not be considered TEAEs.

Any event that first occurred during participation in the parent study and is ongoing at the time of transition to Study CLIN-60120-452 will therefore be a (non-TEAE) AE.

All ongoing AEs from the parent study and all TEAEs that occur following the signing of the ICF until last study intervention intake + 30 days will be included in the participant data listings using the Full Analysis Set (FAS)/Safety Set. Primary endpoint analyses and summary tables will be presented by parent study, by palovarotene status at the time of transition to Study CLIN-60120-452 and treatment regimen and overall for the FAS/Safety Set.

Adverse events/TEAEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by PT and SOC. Adverse events/TEAE listings will be presented by participant, SOC and PT.

The incidence of all reported TEAEs, serious and nonserious treatment-related TEAEs, all serious TEAEs, all nonserious TEAEs, TEAEs leading to death and TEAEs leading to treatment discontinuation will be tabulated separately. In addition, summary tables for TEAEs will be presented by maximum intensity and study intervention relationship (investigator-reported causality assessment).

9.4.3 Analysis of Secondary Endpoints

Data related to the secondary endpoints will be included in the participant data listings using the FAS/Safety Set. Secondary endpoint analyses and summary tables will be presented by parent study, by palovarotene status at the time of transition to Study CLIN-60120-452 and treatment regimen and overall for the FAS/Safety Set.

Analyses of the secondary endpoints will be repeated on the Per Protocol (PP) Set if ≥10% of participants are excluded from the FAS/Safety Set.

Data will be tabulated descriptively, i.e. the number and percentage of participants for each category for categorical parameters, and the number, mean, SD, 95% CIs of the mean/median, median, minimum and maximum for continuous parameters will be tabulated.

9.4.3.1 FOP-PFQ

The adult FOP-PFQ consists of 28 questions which are scored on a scale of 1 to 5. A total score, upper extremities subscore and a mobility subscore is calculated as follows:

- Total score: the sum of the scores from each question which will range from 28 × 1 = 28 to 28 × 5 = 140.
- Upper extremities subscore: the sum of the scores from 15 questions (Questions 1-12, 14, 25 and 26) which will range from 15 × 1 = 15 to 15 × 5 = 75.
- Mobility subscore: the sum of the scores from 13 questions (Questions 13, 15-24, 27 and 28) which will range from 13 × 1 = 13 to 13 × 5 = 65.

Missing scores for individual questions will not be imputed, but they will be taken into account according to the rules described below:

(1) If more than 20% of the questions contributing to the total score are missing, the total score will not be calculated. It will be considered as missing.

(2) If less than 20% of the questions contributing to the total score are missing, the total score will be calculated by summing all observed question scores, divided by the number of questions that were answered and by multiplying this average score by the total number of questions that were meant to be answered (i.e. × 28).

The two rules described above also apply to the upper extremities subscore and the mobility subscore.

The scores will be transformed to reflect a percentage of worst score. The percentage of worst score ranges from 0% to 100% with 0% indicating the best possible function and 100% indicating the worst possible function.

The % of worst scores (for total score, upper extremities subscore and mobility subscore) as well as the change from the Inclusion Visit will be presented for each visit.

9.4.3.2 PROMIS Global Health Scale

The PROMIS Global Health Scale consists of 10 questions from which the global physical health score and the global mental health score, both ranging from 4 (worse health) to 20 (better health), is calculated as follows:

- Global physical health score: the sum of scores from Questions 3, 6, 7 and 8 and will range from 4 (worse health) to 20 (better health).
- Global mental health score: the sum of scores from Questions 2, 4, 5 and 10 and will range from 4 (worse health) to 20 (better health).

In the calculation of the above scores, the Question 7, 8 and 10 will be rescaled as shown in Table 6.

If a participant is missing any of the contributing raw scores, the corresponding score (global physical health or global mental health score) will not be calculated for that participant.

Table 6 Rescaled Global Physical and Mental Health Scores for the Adult Version of the PROMIS Global Health Scale

Questions	Raw Score	Rescaled Score
7	0	5
	1-3	4
	4-6	3
	7-9	2
	10	1
8 and 10	1	5
	2	4
	3	3
	4	2
	5	1

PROMIS=Patient Reported Outcomes Measurement Information System.

The global physical health score and the global mental health score will be converted into T-scores (see Table 7). T-score distributions are standardised such that a value of 50 represents the average (mean) for the general population and increments of ±10 points represent ±1 SD away from the norm. Higher T-scores indicate better physical/mental health. A T-score <50 indicates worse health than the general population, while a T-score >50 indicates better health.

For example, a participant who has a T-score of 60 is 1 SD better (healthier) than the general population.

Table 7 PROMIS Global Health Scale T-Score Conversions for Global Physical and Mental Health Scores

Global Physical Health			Global Mental Health		
Raw Score	**T-Score**	**Standard Error**	**Raw Score**	**T-Score**	**Standard Error**
4	16.2	4.8	4	21.2	4.6
5	19.9	4.7	5	25.1	4.1
6	23.5	4.5	6	28.4	3.9
7	26.7	4.3	7	31.3	3.7
8	29.6	4.2	8	33.8	3.7
9	32.4	4.2	9	36.3	3.7
10	34.9	4.1	10	38.8	3.6
11	37.4	4.1	11	41.1	3.6
12	39.8	4.1	12	43.5	3.6
13	42.3	4.2	13	45.8	3.6
14	44.9	4.3	14	48.3	3.7
15	47.7	4.4	15	50.8	3.7
16	50.8	4.6	16	53.3	3.7
17	54.1	4.7	17	56	3.8
18	57.7	4.9	18	59	3.9
19	61.9	5.2	19	62.5	4.2
20	67.7	5.9	20	67.6	5.3

PROMIS=Patient Reported Outcomes Measurement Information System.

Actual values as well as the change from the Inclusion Visit in mean global physical and mental health score converted into T-scores will be presented for each visit.

9.4.3.3 CAJIS

Actual values as well as the change from the Inclusion Visit in CAJIS total score will be presented for each visit.

9.4.3.4 FOP Assistive Devices

Actual values as well as the shift from the Inclusion Visit in the use of assistive devices and adaptions for daily living will be presented for each visit.

9.4.3.5 Healthcare Utilization

Descriptive statistics will be presented for each visit.

9.4.3.6 Lung Function Parameters

Actual values as well as the change from the Inclusion Visit in observed and % predicted FVC, observed and % predicted FEV_1, absolute and predicted FEV_1/FVC ratio and observed and % predicted DLCO will be presented for each visit.

The DLCO value is reported in either traditional units (mL/min/mmHg) or SI units (mmol/min/kPa). Values in SI units can be multiplied by 2.987 to obtain values in traditional units (Graham et al., 2017).

9.4.3.7 Flare-ups

Actual values as well as the change from the Inclusion Visit in number of investigator-reported flare-ups, flare-up outcomes (extra bone growth, restricted movement) and flare-up duration will be presented for each visit by body location and overall.

9.4.3.8 Extra Bone Growth

The percentage of participants with extra bone growth (associated with a flare-up and not associated with a flare-up) will be presented for each visit.

9.4.3.9 Qualitative Participant Interviews

No formal hypotheses will be tested given the qualitative nature of the analyses.

The service Provider (SP) will begin the analysis process based on the PI/qualified site staff debrief and record of initial thoughts from each of the completed interviews. Specifically, using field notes (where available), the PI/qualified site staff will identify key concepts raised by participants and dominant trends in interview data with a particular focus on the study objectives and other potential insights emerging from the interviews. Additionally, once the interview transcripts are available, the SP will analyse the interview data according to the final qualitative analysis plan, using a thematic qualitative data analysis approach.

All qualitative and limited quantitative data will be summarised descriptively. Where applicable, Ns and %s will be provided.

Tables displaying the concepts described during the interviews will be developed to document the results of the interviews. Additionally, descriptive statistics based on the quantitative data obtained during the interviews (e.g. symptom improvements during the clinical study) will be computed and summarised.

9.4.4 Other Analyses

9.4.4.1 Demographic and Baseline Characteristics

Disease and flare-up history will be summarised using the data transferred from the final parent study database.

Baseline demographic and physical examination data will be included in the participant data listings and descriptive statistics presented using the FAS/Safety Set.

Physical examination findings will be coded using MedDRA and summarised.

9.4.4.2 Prior and Concomitant Medication

Prior medication will be summarised at the Inclusion Visit using the data transferred from the final parent study database.

Concomitant medication will be included in the participant data listings using the FAS/Safety Set.

Descriptive statistics of concomitant medication will be presented for the FAS/Safety Set.

Concomitant medication will be coded using the World Health Organization Drug Dictionary (WHODD) and summarised by drug categories.

9.4.4.3 Concomitant Procedures

Concomitant procedure data will be included in the participant data listings using the FAS/Safety Set.

Descriptive statistics of concomitant procedures will be presented for the FAS/Safety Set.

9.4.4.4 Spinal Health Assessment

Spinal health assessment data will be included in the participant data listings using the FAS/Safety Set.

Descriptive statistics of spinal health assessment will be presented for the FAS/Safety Set.

9.4.4.5 Linear Height and Body Weight

Linear height and body weight will be included in the participant data listings using the FAS/Safety Set.

Actual values and mean changes from the Inclusion Visit in linear height and body weight will be presented at each visit for the FAS/Safety Set.

Height velocity and z-scores will be derived for participants <18 years of age. Actual values and mean changes from the Inclusion Visit in height velocity and z-scores will be presented at each visit for the FAS/Safety Set.

9.4.4.6 Vital Signs

Vital signs (respiratory rate, blood pressure and heart rate) will be included in the participant data listings using the FAS/Safety Set.

Actual values and mean changes from the Inclusion Visit in respiratory rate, blood pressure and heart rate will be presented at each visit for the FAS/Safety Set.

9.4.4.7 Participant Disposition and Withdrawals

The numbers and percentages of participants included in the analysis sets will be tabulated overall, by parent study and by country and site. The reasons for participant exclusions from each of the analysis sets will also be tabulated.

In addition, the number of participants who discontinued treatment or withdrew from the study will be presented with the primary reasons for discontinuation/withdrawal.

9.4.5 Subgroups Analyses

Subgroup analyses will be performed by parent study (PVO-1A-301 or PVO-1A-202/PVO-1A-204), palovarotene status at the time of transition to study CLIN-60120-452 (treated, not treated), and treatment regimen (chronic treatment only, flare-up treatment only, chronic & flare-up treatment).

Further details on the statistical analysis will be provided in the SAP.

9.5 Interim Analyses

No interim analyses are planned.

A stand-alone final report for the qualitative participant interview will be made available once enrolment and all interviews have been completed at the Inclusion Visit.

11 REFERENCES

Baujat G, Choquet R, Bouée Set et al. Prevalence of fibrodysplasia ossificans progressiva (FOP) in France: an estimate based on a record linkage of two national databases. Orphanet J Rare Dis 2017;12:123.

Di Rocco M, Baujat G, Bertamino M et al. International physician survey on management of FOP: a modified Delphi study. Orphanet J Rare Dis 2017;12:110.

Glaser DL, Rocke DM, Kaplan FS. Catastrophic falls in patients who have fibrodysplasia ossificans progressiva. Clin Orthop 1998;(346):110-116.

Graham BL, Brusasco V, Burgos F et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J 2017;49(1):1600016.

Hoffman LM, Garcha K, Karamboulas K et al. BMP action in skeletogenesis involves attenuation of retinoid signaling. J Cell Biol 2006;174:101–13.

Hüning I, Gillessen-Kaesbach G. Fibrodysplasia ossificans progressiva: clinical course, genetic mutations and genotype-phenotype correlation. Mol Syndromol 2014;5:201–11.

The International Clinical Council on FOP (ICC). The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations. January 2022.

Kaplan FS et al. In: J Bilezikian et al., editors. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 9th ed. Washington, DC: American Society for Bone and Mineral Research 2019a:865–70.

Kaplan FS, Al Mukaddam M, Baujat G et al. The International Clinical Council on FOP (ICC) and Consultants. The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations. Proc Intl Clin Council FOP 2019b;1:1–111.

Kaplan FS, Pignolo RJ, Al Mukaddam MM et al. Hard targets for a second skeleton: therapeutic horizons for fibrodysplasia ossificans progressiva (FOP). Expert Opin Orphan Drugs 2017a;5:291–4.

Kaplan FS, Al Mukaddam M, Pignolo RJ. A cumulative analogue joint involvement scale (CAJIS) for fibrodysplasia ossificans progressiva (FOP). Bone 2017b;101;123-128.

Kaplan FS, Zasloff MA, Kitterman JA et al. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. J Bone Joint Surg Am 2010;92:686–91.

Kaplan FS, Lounev VY, Wang H et al. Fibrodysplasia ossificans progressiva: a blueprint for metamorphosis. Ann N Y Acad Sci 2011;1237:5–10.

Kaplan FS, Xu M, Seemann P et al. Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1. Hum Mutat 2009;30:379–90.

Kaplan FS, Le Merrer M, Glaser DL, et al. Fibrodysplasia ossificans progressiva. Best Pract Res Clin Rheumatol 2008;22(1).

Koyama E, Golden EB, Kirsch T et al. Retinoid signaling is required for chondrocyte maturation and endochondral bone formation during limb skeletogenesis. Dev Biol 1999;208:375–91.

Mattera MS, Kaplan FS, Pignolo RJ et al. Patient-reported physical function outcome measure for adults with Fibrodysplasia Ossificans Progressiva: intelligent test design based on Promis item banks. Value Health 2015;8:A165.

Meyers C, Lisiecki J, Miller S et al. Heterotopic Ossification: A Comprehensive Review. JBMR Plus 2019;3:e10172.

Modi P, Cascella M. Diffusing Capacity of The Lungs for Carbon Monoxide. [Updated 2020 Apr 15]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556149/ (Accessed March 2021).

Peng K, Cheung K, Lee A et al. Longitudinal Evaluation of Pain, Flare-Up, and Emotional Health in Fibrodysplasia Ossificans Progressiva: Analyses of the International FOP Registry. JBMR Plus 2019;3:e10181.

Ortiz-Agapito F, Colmenares-Bonilla D. Quality of life of patients with fibrodysplasia ossificans progressiva. J Child Orthop 2015;9: 489–93.

Pignolo RJ, Cheung K, Kile S et al. Self-reported baseline phenotypes from the International Fibrodysplasia Ossificans Progressiva (FOP) Association Global Registry. Bone 2020a;134:115274.

Pignolo RJ, Kimel M, Whalen J, et al. Validity and reliability of the fibrodysplasia ossificans progressiva physical function questionnaire (FOP-PFQ), a patient-reported, disease-specific measure [Poster presentation]. ASBMR Annual Meeting Virtual Event, 2020b, 11-15 September.

Pignolo RJ, Cheung K, Kile S, et al. Self-reported baseline phenotypes from the International Fibrodysplasia Ossificans Progressiva (FOP) Association Global Registry. Bone 2020c;134:115274.

Pignolo RJ, Baujat G, Brown MA, et al. Natural history of fibrodysplasia ossificans progressiva: cross-sectional analysis of annotated baseline phenotypes. Orphanet J Rare Dis 2019;14(1):98.

Pignolo RJ, Bedford-Gay C, Liljesthröm M et al. The Natural History of Flare-Ups in Fibrodysplasia Ossificans Progressiva (FOP): A Comprehensive Global Assessment. J Bone Miner Res 2016;31:650–6.

Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: diagnosis, management, and therapeutic horizons. Pediatr Endocrinol Rev 2013;10 Suppl 2:437–48.

Qi Z, Luan J, Zhou X et al. Fibrodysplasia ossificans progressiva: Basic understanding and experimental models. Intractable Rare Dis Res 2017;6:242–8.

Sanchez-Duffhues G, de Gorter DJ, Ten Dijke P. Towards a cure for Fibrodysplasia ossificans progressiva. Ann Transl Med 2016;4 Suppl 1:S28.

Shen Q, Little SC, Xu M et al. The fibrodysplasia ossificans progressiva R206H ACVR1 mutation activates BMP-independent chondrogenesis and zebrafish embryo ventralization. J Clin Invest 2009;119:3462–72.

Shimono K, Tung WE, Macolino C et al. Potent inhibition of heterotopic ossification by nuclear retinoic acid receptor-γ agonists [published correction appears in Nat Med. 2012 Oct;18(10):1592] Nat Med 2011;17:454–60.

Weston AD, Chandraratna RA, Torchia J et al. Requirement for RAR-mediated gene repression in skeletal progenitor differentiation. J Cell Biol 2002;158:39–51.

Williams JA, Kondo N, Okabe T et al. Retinoic acid receptors are required for skeletal growth, matrix homeostasis and growth plate function in postnatal mouse. Dev Biol 2009;328:315–27.

Zhang W, Zhang K, Song L et al. The phenotype and genotype of fibrodysplasia ossificans progressiva in China: a report of 72 cases. Bone 2013;57:386–91.