PASS Information

Title	An International Observational Registry Study to Further Describe Long-term Safety and Effectiveness of Palovarotene in Patients with Fibrodysplasia Ossificans Progressiva (FOP)
Protocol version identifier	4.0
Date of last version of protocol	07 September 2023
European Union electronic register of post-authorisation studies (EU PAS register) number	Study not registered yet
Active substance	Palovarotene Pharmacotherapeutic group: other drugs for disorders of the musculo-skeletal system, ATC code: M09AX11
Medicinal product	Palovarotene
Product reference	H004867
Procedure number	-
Marketing Authorisation Holder (MAH)	Ipsen Pharma (EU) Ipsen Biopharmaceuticals, Inc (US)
Joint PASS	No

Research question and objectives	The aim of this registry study is primarily to collect and assess real-world safety data on paediatric and adult patients with FOP treated with palovarotene and secondly, to describe the effectiveness of this treatment, including its effect on physical function. Primary objective: To collect and assess real-world safety data in patients with FOP treated with palovarotene. Secondary objectives: • To describe the effect of palovarotene on range of motion (ROM) as assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP; • To describe the use of assistive devices and adaptations for daily living by FOP participants; • To describe the effect of palovarotene on physical function using age-appropriate forms of the Fibrodysplasia Ossificans Progressiva-Physical Function Questionnaire (FOP-PFQ); • 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 Baseline and over time under palovarotene treatment; • To describe the effect of palovarotene on physical and mental health (participants ≥15 years old) and overall quality of life (participants <15 years old) using age-appropriate forms of the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale; • To describe the flare-up frequency • To describe any movement mobility change by key body location and annually; • To describe the number of locations impacted per participant annually; • To describe the movement mobility outcomes (change in extra bone growth and change in movement), causes, associated symptoms with flare-up events by body location; • To describe the use (dose, frequency) of palovarotene in the real-world setting. For women: • Incidence of pregnancy; • Description of pregnancy outcomes. For growing children: • To describe height velocity; • To describe the difference between chronological age and bone age; • To describe the frequency, severity and descriptive details of premature physeal closure. For fractures (including vertebral fractures): • To describe the frequency, severity, outcome and descriptive details of any fractures.
Country(ies) of study	The registry study will be conducted in countries willing to participate and where palovarotene is registered/marketed at the time of the study.

Author	PPD Ipsen Pharma SAS Unit 9 Ash Road Wrexham Industrial Estate Wrexham LL13 9UF United Kingdom

Marketing Authorisation Holder(s)

MAH	EU: Ipsen Pharma 65, quai Georges Gorse 92100 Boulogne-Billancourt Paris, France US: Ipsen Biopharmaceuticals, Inc. One Main Street 7th Floor Cambridge, MA 02142 United States
MAH contact person	PPD Ipsen Innovation 5 avenue du Canada 91940 Les Ulis France

PROTOCOL SIGNATURES

Investigator Signature

I have read and agree to the post-authorisation safety study (PASS) protocol CLIN-60120-453 entitled "An International Observational Registry Study to Further Describe Long-term Safety and Effectiveness of Palovarotene in Patients with Fibrodysplasia Ossificans Progressiva (FOP)". I am aware of my responsibilities as an Investigator under the guidelines of Good Pharmacoepidemiology Practices (GPP), Good Pharmacovigilance Practices (GVP), any 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: _____

Full investigational site contact details, including telephone numbers, will be documented in the Trial Master File.

On behalf of the Sponsor:

NAME: PPD

TITLE: SIGNATURE: _____

DATE: _____

OFFICE: Ipsen Pharma SAS
Unit 9 Ash Road Wrexham Industrial Estate
Wrexham
LL13 9UF
United Kingdom

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2 LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
ACVR1	Activin A Receptor Type 1
ALK2	Activin Receptor-like-kinase-2
BMP	Bone Morphogenetic Protein
CA	Competent Authorities
CAJIS	Cumulative Analogue Joint Involvement Scale
CI	Confidence Intervals
CIOMS	Council for International Organizations of Medical Sciences
CO	Carbon Monoxide
CT	Computed Tomography
DLCO	Diffusion Capacity of the Lung for Carbon Monoxide
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FOP	Fibrodysplasia Ossificans Progressiva
FOP-PFQ	Fibrodysplasia Ossificans Progressiva-Physical Function Questionnaire
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GMPC	Global Medical Publications and Communications
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HO	Heterotopic Ossification
ICE	In Case of Emergency
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NHS	Natural History Study
OMIM	Online Mendelian Inheritance in Man
PASS	Post-authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PEP	Positive Expiratory Pressure
PI	Prescribing Information
PPC	Premature Physeal Closure
PROMIS	Patient Reported Outcomes Measurement Information System
PSUR	Periodic Safety Update Report
PT	Preferred Term
QoL	Quality of Life
QPPV	Qualified Person Responsible for Pharmacovigilance
RARγ	Retinoic Acid Receptor Gamma
ROM	Range of Motion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Service Provider
TEAE	Treatment-emergent Adverse Event
TGF-β	Transforming Growth Factor Beta
WBCT	Whole Body Computed Tomography
WHODD	World Health Organization Drug Dictionary
wLME	Weighted linear mixed effects

3 RESPONSIBLE PARTIES

A list of all Investigators, including contact details, will be in a stand-alone document, available upon request.

4 ABSTRACT

Title	
Registry Study Title:	An International Observational Registry Study to Further Describe Long-term Safety and Effectiveness of Palovarotene in Patients with Fibrodysplasia Ossificans Progressiva (FOP)
Protocol Version N°:	4.0
Date of the Last Version of the Protocol:	07 September 2023
Author:	PPD

Rationale and Background

Fibrodysplasia ossificans progressiva (FOP; Online Mendelian Inheritance in Man (OMIM) #135100) is an ultra-rare genetic disorder, with an estimated prevalence of 1.36 per million individuals; however, the number of confirmed cases varies by country. FOP affects all races, and there is no ethnic, sex-linked or geographic predisposition. Median patient age at time of FOP diagnosis is 6.4 years.

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. Bone morphogenetic proteins are extracellular ligands belonging to the 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.

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 FKBP12, which binds to the BMP type I receptor and stabilises the inactive form.

Most patients with FOP have classic FOP (~97%), but a minority are affected by atypical FOP (~3%). In classic FOP, approximately 90% of patients carry the same specific *ACVR1/ALK2* gene mutation (c.617G>A; p.R206H) in the glycine and serine activation domain of the gene. In the presence of the mutated *ACVR1/ALK2* gene, FKBP12 binding is reduced, leading to enhanced BMP signalling. FOP diagnosis is clinical but requires genetic confirmation.

Patients with FOP experience sporadic and unpredictable episodes of soft-tissue swelling, pain, reduced movement, stiffness and fever, referred to as “flare-ups”. Flare-ups appear spontaneously or after muscle fatigue, minor trauma, intramuscular injections or influenza-like viral illnesses, and develop rapidly over several hours; these inciting events induce local inflammation, which is followed by recruitment of bone progenitor cells that differentiate into chondrocytes. Although some flare-ups regress spontaneously, many appear to lead to heterotopic ossification (HO), which transforms soft and connective tissues (including aponeuroses, fascia, ligaments, tendons and skeletal muscles) into heterotopic bone. Of patients with FOP, 95% manifest HO before reaching 15 years of age.

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. Other clinical features observed in patients with FOP are shortened thumbs, cervical spine malformations, short broad femoral necks and proximal medial tibial osteochondromas. 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). Heterotopic ossifications develop into ribbons, sheets and plates of extra bone throughout the body and across joints, thereby progressively restricting movement. 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.

FOP is not only an extremely disabling disease but also a condition of considerably shortened lifespan. 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. Patients with FOP reach a median survival of 56 (95% 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.

Misdiagnosis and delayed diagnosis contribute to the accumulation of disability in patients with FOP. There is often a delay in the diagnosis of FOP because of lack of physician awareness and inadequate description in most medical textbooks. The median delay from onset of symptoms to the correct diagnosis is 1.1 years (range: <1 month to 49 years), after consultation with a median of six different healthcare professionals. FOP is misdiagnosed in up to 87% of individuals, with the most common incorrect diagnoses including cancer, aggressive juvenile fibromatosis, ankylosing spondylitis and bunions.

Until recently, there were no effective treatments to reduce the formation of heterotopic bone in FOP, with therapeutic approaches being limited to symptom management and flare-up prevention; consequently, as well as an imperative to improve early diagnosis and to reduce iatrogenic harm, there is a critical unmet need for definitive therapies for patients with FOP.

Palovarotene is being developed by Ipsen for the treatment of FOP. Palovarotene was first approved by Health Canada for the treatment of patients with FOP for both chronic uses, and for flare-ups, in adults and children aged 8 years and above for females and 10 years and above for males with FOP. Then, the FDA approved palovarotene for the reduction in volume of new heterotopic ossification in adults and paediatric patients aged 8 years and older for females and 10 years and older for males with FOP. Palovarotene is an orally bioavailable retinoic acid receptor gamma (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, where it operates as a transcriptional repressor. Activation of the retinoid signalling pathway and RARγ has been demonstrated to inhibit both chondrogenesis and HO. Given that chondrogenesis requires a decrease in retinoid signalling concurrent with upregulation of pro-chondrogenic pathways, including BMP signalling, RARγ agonists are likely to elicit anti-chondrogenic and anti-HO effects by maintaining retinoid signalling while reducing BMP signalling.

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 non-osseous soft-tissue fate.

The safety and efficacy of palovarotene in FOP have been evaluated in:

- Study PVO-1A-201 (complete): a randomised, double-blind, placebo-controlled, multicentre phase II study evaluating the efficacy (percentage of responders, defined by no or minimal new HO at flare-up site, compared with Baseline as assessed by plain radiographs) and safety of palovarotene. Participants experiencing a flare-up were enrolled in two cohorts for which the cohort data were pooled:

- patients ≥15 years were randomized 3:1 to palovarotene 10/5 mg (Weeks 1-2/3-6) or placebo;
- patients ≥6 years were randomized 3:3:2 to palovarotene 10/5 mg, palovarotene 5/2.5 mg (Weeks 1–2/3–6), or placebo.

• Study PVO-1A-202: an open-label extension of Study 201 collecting additional flare-up outcome data and evaluating the long-term efficacy (annualised change in new HO volume as assessed by low-dose whole body computed tomography (WBCT), excluding head, in Part C) and safety of palovarotene in participants with FOP, consisting of three parts:
  - Part A (complete): participants experiencing another flare-up received palovarotene 10/5 mg (2/4 weeks) (or the weight-based equivalent for participants with <90% skeletal maturity);
  - Part B (complete): participants ≥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 palovarotene 20/10 mg (4/8 weeks) flare-up treatment or the weight-based equivalent;
  - Part C (complete): the dosing regimens in Part B will continue for up to an additional 48 months with the exception that participants with <90% skeletal maturity will receive palovarotene 5 mg (or the weight-based equivalent) daily in addition to 20/10 mg palovarotene or the weight- based equivalent for flare-ups;
  - Part D (complete): a 2-year safety follow-up for skeletally immature children who stopped palovarotene for any reason.
• Study PVO-1A-301 (MOVE): a 24-month (Part A) with 24-month extension (Part B), multicentre, single treatment arm, open-label phase III study currently evaluating the efficacy (annualised change in new HO volume as assessed by low-dose WBCT, excluding head) and safety of palovarotene in participants with FOP aged 4 years and older:
  - Participants received palovarotene 5 mg daily with increased dosing at the time of a 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 (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 a substantial high-risk traumatic event;
  - Doses were weight-adjusted for skeletally immature participants; <90% skeletal maturity (assessed by knee/wrist radiography every 6 months, or every 3 months in participants who received flare-up treatment since last assessment and/or had not achieved 100% skeletal maturity at last assessment);
  - In interim analyses (data cut-off of 28 February 2020 for final interim analysis), data were compared with untreated participants enrolled in a 3-year, longitudinal, non-interventional natural history study (NHS) (complete) conducted to further evaluate the disease characteristics, natural progression of FOP and the impact of flare-ups;
  - Part C (complete): a 2-year safety follow-up for skeletally immature children who

stopped palovarotene for any reason.

The safety summary that follows is based on the Core Company Datasheet.

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; the target population for this registry study) 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 of 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* (97.8%), *Gastrointestinal disorders* (75.5%) and *Infections and infestations* (48.9%) System Organ Classes (SOC).

Serious adverse reactions reported in palovarotene-treated participants aged ≥8/10 years included premature physeal closure (PPC) (preferred term (PT); epiphysis premature fusion) and cellulitis (1.4%). All others were reported in single participants and included the following: ankle fracture, epiphyseal disorder, anaemia and seizure, each in 0.7% of subjects.

Adverse events leading to permanent discontinuation occurred in 10 participants (7.0%) of palovarotene treated participants aged ≥8/10 years with dry skin being the most common in 2 participants (1.4%). 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 (35%) than during chronic treatment (3%).

Participants <18 years with open epiphyses were assessed for growth during the clinical studies. PPC was identified in 24 of 102 participants (24%) <18 years of age and was more common in younger (<8/10 years: 14 of 25 participants, 56%) compared with older (≥8/10 to <18 years: 10 of 77 participants, 13%; ≥8/10 to <14 years: 10 of 39 participants, 26%) participants. In participants who received only chronic dosing, PPC, when observed, typically occurred between 12 and 18 months. The higher proportion of younger participants with PPC is not unexpected 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 are predisposed to developing PPC or are more sensitive to the effects of palovarotene cannot be excluded.

Palovarotene treatment is currently proposed for children aged 8 years and above for females and 10 years and above for males (or as per the approved indication in locally approved label). However, children between the ages of 4 years and 8/10 years were included in the clinical studies and exposed to palovarotene. The safety profile for palovarotene in participants with FOP was consistent across adult (≥18 years) and paediatric (≥8/10 to <18 years) age subgroups except for epiphyses premature fusion, which was more common in younger (<8/10 years, 56.0%) than older (≥8/10 to <18 years, 13%) paediatric participants. Some mucocutaneous effects such as decubitus ulcers had a higher incidence in adult participants, which was consistent with disease burden, increasing disability, and prolonged exposure to corticosteroids. A total of 8 participants experienced severe cases of epiphyses premature fusion, of these 5 were in the <8 age group. Palovarotene must not be used in children under

8 years of age for females and 10 years of age for males.

Radiological vertebral fractures (PT: Spinal fracture) were identified as a risk associated with palovarotene based on retrospective analyses performed on WBCT data in participants with FOP in the Phase 3 (MOVE) study.

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 and after the 28 February 2020 safety data cut-off.

Ipsen will implement a registry study, defined as an observational, prospective, post-authorisation safety study (PASS), which is intended primarily to collect and assess real-world safety data on paediatric and adult patients with FOP treated with palovarotene and secondly, to describe the effectiveness of this treatment, including its effect on physical function.

Research Question and Objectives

The aim of this registry study is primarily to collect and assess real-world safety data on paediatric and adult patients with FOP treated with palovarotene and secondly, to describe the effectiveness of this treatment, including its effect on physical function.

Primary objective:

To collect and assess real-world safety data in patients with FOP treated with palovarotene.

Secondary objectives:

- To describe the effect of palovarotene on range of motion (ROM) as assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP;
- To describe the use of assistive devices and adaptations for daily living by FOP participants;
- To describe the effect of palovarotene on physical function using age-appropriate forms of the Fibrodysplasia Ossificans Progressiva-Physical Function Questionnaire (FOP-PFQ);
- 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 Baseline and over time under palovarotene treatment;
- To describe the effect of palovarotene on physical and mental health (participants ≥15 years old) and overall quality of life (QoL) (participants <15 years old) using age-appropriate forms of the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale;
- To describe the flare-up frequency
- To describe any movement mobility change by key body location and annually;
- To describe the number of locations impacted per patient annually;
- To describe the movement mobility outcomes (change in extra bone growth and change in movement), causes, associated symptoms with flare-up events by body location
- To describe the use (dose, frequency) of palovarotene in the real-world setting.

For women:

- Incidence of pregnancy;
- Description of pregnancy outcomes.

For growing children:

- To describe height velocity;
- To describe the difference between chronological age and bone age;
- To describe the frequency, severity and descriptive details of premature physeal closure.

For fractures (including vertebral fractures):

- To describe the frequency, severity, outcome and descriptive details of any fractures.

Registry Study Design

International, multicentre, observational, prospective PASS.

This is an observational registry study designed to collect safety and effectiveness data on the use of palovarotene in patients with FOP.

The decision to prescribe palovarotene will be made prior to and independently of the decision to enrol the patient in this observational registry study.

Participants will be receiving palovarotene as prescribed by their treating physician and according to the Summary of Product Characteristics (SmPC)/prescribing information (PI) and/or according to the Marketing Authorisation.

There will be a Study Steering Committee and a Publications Steering Committee. The Study Steering Committee will be composed of investigators, external clinical experts not directly involved in the registry and staff from the sponsor with the primary objective of assessing the study quality and conduct, as well as for the scientific quality of the final study report. The Publications Steering Committee will be composed of external experts (clinicians and scientists), patients and representatives of patient associations with the primary objective of driving publications.

Population

Adults and children with FOP who have been prescribed palovarotene, as per local label, by their treating physician.

Inclusion criteria:

To be included in the registry study, the participant should fulfil all the following inclusion criteria:

(1) Adult or child with FOP who have been prescribed palovarotene (prior to and independently of the decision to enrol the patient in this registry study and as per local label) by their treating physician according to the locally approved product information;

(2) Signed informed consent as per local regulations must be obtained and maintained. Consent/assent from the participant should be obtained as appropriate before any registry study data collection is conducted. If applicable, parents or legally authorised representatives must give signed informed consent.

Exclusion criteria:

Participants will not be included in the study if:

(1) Currently participating in a palovarotene clinical trial;

(2) Currently participating in any interventional clinical trial for FOP;

(3) Have any contraindication to palovarotene as per the locally approved label (except for pregnant women who have previously received and discontinued palovarotene at any time during the pregnancy and who will be included for safety follow-up).

Sample size: Target of approximately 80% of patients treated with palovarotene in participating countries where palovarotene is marketed and where the registry study will be implemented.

Variables

Participants will be treated in accordance with usual medical practice during their participation in this registry study. No additional assessments or tests will be required by this protocol. This registry study is observational, thus if some assessments are not routinely performed by the Investigator, he/she will not complete the corresponding sections in the electronic Case Report Form (eCRF).

Relevant data collected as part of routine medical care will be captured in the eCRF by the Investigator. These data will be transmitted to the Sponsor for analysis. Data transmitted will be pseudonymised and will be identified by a participant number.

Data will be collected at the Baseline Visit and at each Follow-up Visit (scheduled as per routine clinical practice*).

**Follow-up Visits are recommended every 6 months, or as per local label.*

The Baseline Visit should ideally be a clinic visit but all visits can be performed by either telephone/video contact or by clinic visit as per the Investigator's judgement.

If AEs or their sequelae (any AE, based on the Investigator's opinion, not only those assessed as related) persist after the date of palovarotene discontinuation, the Investigator must ensure that the participant receives appropriate medical follow-up and this should be properly documented in the participant's medical records.

Primary safety endpoints are:

- Incidence and description of all treatment-emergent adverse events (TEAEs), whether or not they are considered as related to palovarotene;
- 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 palovarotene;
- Incidence and description of all non serious TEAEs whether or not they are considered as related to palovarotene.

Secondary endpoints are:

- Raw values and change from Baseline in CAJIS total score at each Follow-up Visit;
- Raw values and shift from Baseline in use of assistive devices and adaptations for daily living at each Follow-up Visit;
- Raw values and change from Baseline in % of worst score for total score, upper extremities subscore and mobility subscore using age-appropriate forms of the FOP-PFQ at each Follow-up Visit;

- Raw values and change from Baseline in observed and % predicted FVC at each Follow-up Visit;
- Raw values and change from Baseline in observed and % predicted FEV_1 at each Follow-up Visit;
- Raw values and change from Baseline in absolute and % predicted FEV_1/FVC ratio at each Follow-up Visit;
- Raw values and change from Baseline in observed and % predicted DLCO at each Follow-up Visit;
- Raw values and change from Baseline in physical and mental function (mean global physical and mental health score converted into T-scores) for participants ≥15 years old and overall QoL (mean total score converted into T-scores) for participants <15 years old using age-appropriate forms of PROMIS Global Health Scale at each Follow-up Visit;
- Number of flare-ups over the past 12 months before inclusion and since the last visit;
- Any movement mobility change (better movement/the same movement/slightly worse movement/moderately worse movement/severely worse movement) by key body location and annually;
- Number of locations impacted per participant annually and change from Baseline;
- Evolution of impacted location (how many times a location is impacted) per location;
- Movement mobility outcomes (change in extra bone growth and change in movement), causes, associated symptoms with flare-up events by body location;
- Mean dose/year for chronic treatment;
- Mean dose/cycle for flare-up treatment.

For women:

- Incidence of pregnancy;
- Description of pregnancy outcomes.

For growing children:

- Raw values and change from Baseline in height velocity at each Follow-up Visit;
- Mean difference between chronological age and bone age at each Follow-up Visit;
- Frequency, severity and descriptive details of premature physeal closure overall and at each Follow-up Visit.

For fractures (including vertebral fractures):

- Frequency, severity, outcome and descriptive details of any fractures overall and at each Follow-up Visit.

Data Sources

Source data includes any data collected as part of routine medical care which will be captured in an eCRF by the Investigator and transmitted to the Sponsor for analysis. The patient-reported questionnaires (FOP-PFQ, PROMIS Global Health Scale and FOP assistive devices assessment) will be completed directly by the participant on paper.

Registry Study Size

Sample size: Target of approximately 80% of patients treated with palovarotene in participating countries where palovarotene is marketed and where the registry study will be implemented.

Data Analysis

Statistical Analyses:

Analyses will be primarily descriptive.

Descriptive summary statistics will include number of documented data, mean, standard deviation, 95% confidence intervals (CI) of the mean/median, median, minimum, maximum, or frequency counts of the data collected. Percentages will be based on the number of non-missing observations.

Missing data will also be presented.

Subgroup analyses will be performed by age group, gender.

Interim effectiveness and safety descriptive analyses are planned to be performed every 2 years. For the first interim analysis, a minimum of 30 participants will have to be enrolled.

Milestones

Approximately 10 years (from first participant, first visit) with a minimum of 1-year data collected for participants who are enrolled within that period.

Participant enrolment will start from the date of palovarotene commercial availability in the given country and once the investigational site has been activated.

Planned start of data collection: Q1 2024.

Planned end of data collection: Q1 2035.

CCI

[redacted]

6 MILESTONES

Milestone	Planned date
Start of data collection	Once palovarotene is commercially available and first site approved to enrol Planned Q1 2024
End of data collection	11 years following start of data collection Planned Q1 2035
Registration in the EU PAS register	Following protocol approval by PRAC
Final report of registry study results	Planned Q3 2035

7 RATIONALE AND BACKGROUND

7.1 Disease Background

Fibrodysplasia ossificans progressive (FOP; Online Mendelian Inheritance in Man (OMIM) #135100) is an ultra-rare genetic disorder, with an estimated prevalence of 1.36 per million individuals [1]; however, the number of confirmed cases varies by country [2, 3]. FOP affects all races, and there is no ethnic, sex-linked or geographic predisposition [4, 5]. Median patient age at time of FOP diagnosis is 6.4 years [1].

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 [4, 5]. Bone morphogenetic proteins are extracellular ligands belonging to the TGF-β superfamily [6, 7]. 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 [6, 7].

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 [6, 7]; this is regulated by the inhibitory factor FKBP12, which binds to the BMP type I receptor and stabilises the inactive form [6, 7].

Most patients with FOP have classic FOP (~97%), but a minority are affected by atypical FOP (~3%) [5]. In classic FOP, approximately 90% of patients carry the same specific *ACVR1/ALK2* gene mutation (c.617G>A; p.R206H) in the glycine and serine activation domain of the gene [8-15]. In the presence of the mutated *ACVR1/ALK2* gene, FKBP12 binding is reduced, leading to enhanced BMP signalling [7]. FOP diagnosis is clinical but requires genetic confirmation [4, 16].

Patients with FOP experience sporadic and unpredictable episodes of soft-tissue swelling, pain, reduced movement, stiffness and fever, referred to as “flare-ups” [4, 16–18]. Flare-ups appear spontaneously or after muscle fatigue, minor trauma, intramuscular injections or influenza-like viral illnesses, and develop rapidly over several hours [17]; these inciting events induce local inflammation, which is followed by recruitment of bone progenitor cells that differentiate into chondrocytes [19]. Although some flare-ups regress spontaneously, many appear to lead to heterotopic ossification (HO), which transforms soft and connective tissues (including aponeuroses, fascia, ligaments, tendons and skeletal muscles) into heterotopic bone [4, 17]. Of patients with FOP, 95% manifest HO before reaching 15 years of age [20].

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 [1, 18]. Other clinical features observed in patients with FOP are shortened thumbs, cervical spine malformations, short broad femoral necks and proximal medial tibial osteochondromas [4, 9]. 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) [8]. Heterotopic ossifications develop into ribbons, sheets and plates of extra bone throughout the body and across joints, thereby progressively restricting movement [1]. 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 [1, 4, 21–23].

FOP is not only an extremely disabling disease but also a condition of considerably shortened lifespan [24]. 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 [25] and pain [26]. Patients with FOP reach a median survival of

56 (95% 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 [1, 4, 16, 24].

Misdiagnosis and delayed diagnosis contribute to the accumulation of disability in patients with FOP. There is often a delay in the diagnosis of FOP because of lack of physician awareness and inadequate description in most medical textbooks [4, 27]. The median delay from onset of symptoms to the correct diagnosis is 1.1 years (range: <1 month to 49 years), after consultation with a median of six different healthcare professionals [27]. FOP is misdiagnosed in up to 87% of individuals, with the most common incorrect diagnoses including cancer, aggressive juvenile fibromatosis, ankylosing spondylitis and bunions [4, 27].

Until recently, there were no effective treatments to reduce the formation of heterotopic bone in FOP, with therapeutic approaches being limited to symptom management and flare-up prevention [17, 28]; consequently, as well as an imperative to improve early diagnosis and to reduce iatrogenic harm, there is a critical unmet need for definitive therapies for patients with FOP [27, 29].

7.2 Treatment Background

Palovarotene is being developed by Ipsen for the treatment of FOP. Palovarotene was first approved by Health Canada for the treatment of patients with FOP for both chronic uses, and for flare-ups, in adults and children aged 8 years and above for females and 10 years and above for males with FOP. Palovarotene is an orally bioavailable retinoic acid receptor gamma (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 [30], where it operates as a transcriptional repressor [31]. Activation of the retinoid signalling pathway and RARγ has been demonstrated to inhibit both chondrogenesis and HO [29]. Given that chondrogenesis requires a decrease in retinoid signalling concurrent with upregulation of pro-chondrogenic pathways, including BMP signalling [32, 33], RARγ agonists are likely to elicit anti-chondrogenic and anti-HO effects by maintaining retinoid signalling while reducing BMP signalling [19].

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 non-osseous soft-tissue fate [19, 34].

7.3 Safety and Efficacy of Palovarotene

The safety and efficacy of palovarotene in FOP have been evaluated in:

- Study PVO-1A-201 (complete): a randomised, double-blind, placebo-controlled, multicentre phase II study evaluating the efficacy (percentage of responders, defined by no or minimal new HO at flare-up site, compared with Baseline as assessed by plain radiographs) and safety of palovarotene. Participants experiencing a flare-up were enrolled in two cohorts for which the cohort data were pooled:
  - patients ≥15 years were randomized 3:1 to palovarotene 10/5 mg (Weeks 1-2/3-6) or placebo;
  - patients ≥6 years were randomized 3:3:2 to palovarotene 10/5 mg, palovarotene 5/2.5 mg (Weeks 1–2/3–6), or placebo.
- Study PVO-1A-202: an open-label extension of Study 201 collecting additional flare-up outcome data and evaluating the long-term efficacy (annualised change in new HO volume as assessed by low-dose whole body computed tomography (WBCT), excluding

head, in Part C) and safety of palovarotene in participants with FOP, consisting of three parts:

- Part A (complete): participants experiencing another flare-up received palovarotene 10/5 mg (2/4 weeks) (or the weight-based equivalent for participants with <90% skeletal maturity);
- Part B (complete): participants ≥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 palovarotene 20/10 mg (4/8 weeks) flare-up treatment or the weight-based equivalent;
- Part C (complete): the dosing regimens in Part B will continue for up to an additional 48 months with the exception that participants with <90% skeletal maturity will receive palovarotene 5 mg (or the weight-based equivalent) daily in addition to 20/10 mg palovarotene or the weight- based equivalent for flare-ups;
- Part D (complete): a 2-year safety follow-up for skeletally immature children who stopped palovarotene for any reason.

• Study PVO-1A-301 (MOVE): a 24-month (Part A) with 24-month extension (Part B), multicentre, single treatment arm, open-label phase III study currently evaluating the efficacy (annualised change in new HO volume as assessed by low-dose WBCT, excluding head) and safety of palovarotene in participants with FOP aged 4 years and older:

- Participants received palovarotene 5 mg daily with increased dosing at the time of a 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 (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 a substantial high-risk traumatic event;
- Doses were weight-adjusted for skeletally immature participants; <90% skeletal maturity (assessed by knee/wrist radiography every 6 months, or every 3 months in participants who received flare-up treatment since last assessment and/or had not achieved 100% skeletal maturity at last assessment);
- In interim analyses (data cut-off of 28 February 2020 for final interim analysis), data were compared with untreated participants enrolled in a 3-year, longitudinal, non-interventional natural history study (NHS) (complete) conducted to further evaluate the disease characteristics, natural progression of FOP and the impact of flare-ups;
- Part C (complete): a 2-year safety follow-up for skeletally immature children who stopped palovarotene for any reason.

The below safety and efficacy summary is based on the Core Company Datasheet.

7.3.1 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; the target population for this registry study) 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 of 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* (97.8%), *Gastrointestinal disorders* (75.5%) and *Infections and infestations* (48.9%) System Organ Classes (SOC).

Serious adverse reactions reported in palovarotene-treated participants aged ≥8/10 years included premature physeal closure (PPC) (preferred term (PT); epiphysis premature fusion) and cellulitis (1.4%). All others were reported in single participants and included the following: ankle fracture, epiphyseal disorder, anaemia and seizure, each in 0.7% of subjects.

Adverse events leading to permanent discontinuation occurred in 10 participants (7.0%) of palovarotene-treated participants aged ≥8/10 years with dry skin being the most common in 2 participants (1.4%). 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 (35%) than during chronic treatment (3%).

Participants <18 years with open epiphyses were assessed for growth during the clinical studies. PPC was identified in 24 of 102 participants (24%) <18 years of age and was more common in younger (<8/10 years: 14 of 25 participants, 56%) compared with older (≥8/10 to <18 years: 10 of 77 participants, 13%; ≥8/10 to <14 years: 10 of 39 participants, 26%) participants. In participants who received only chronic dosing, PPC, when observed, typically occurred between 12 and 18 months. The higher proportion of younger participants with PPC is not unexpected given that pre-adolescent individuals are not expected to have physiological 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 are predisposed to developing PPC or are more sensitive to the effects of palovarotene cannot be excluded.

Palovarotene treatment is currently proposed for children aged 8 years and above for females and 10 years and above for males (or as per the approved indication in locally approved label). However, children between the ages of 4 years and 8/10 years were included in the clinical studies and exposed to palovarotene. The safety profile for palovarotene in participants with FOP was consistent across adult (≥18 years) and paediatric (≥8/10 to <18 years) age subgroups except for epiphyses premature fusion, which was more common in younger (<8/10 years, 56.0%) than older (≥8/10 to <18 years, 13%) paediatric participants. Some mucocutaneous effects such as decubitus ulcers had a higher incidence in adult participants, which was consistent with disease burden, increasing disability, and prolonged exposure to corticosteroids. A total of 8 participants experienced severe cases of epiphyses premature fusion, of these 5 were in the <8 age group. Palovarotene must not be used in children under 8 years of age for females and 10 years of age for males.

Radiological vertebral fractures (PT: Spinal fracture) were identified as a risk associated with palovarotene based on retrospective analyses performed on WBCT data in participants with FOP in the Phase 3 (MOVE) study.

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 and after the 28 February 2020 safety data cut-off.

7.3.2 Efficacy of Palovarotene

7.3.2.1 Phase II Studies

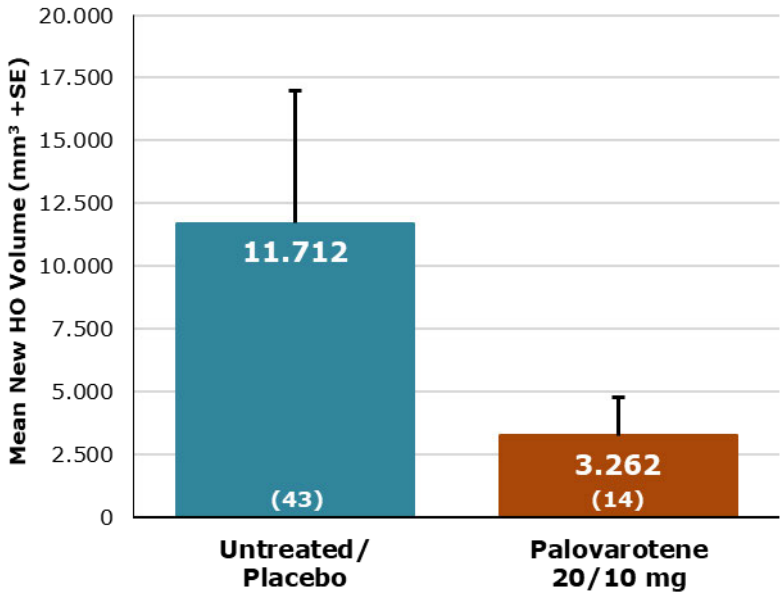
The flare-up only regimen was assessed in the phase II programme, including the double-blind, placebo-controlled Study PVO-1A-201 and, the open-label extension, Study PVO-1A-202.

The median (range) age of participants in the overall population in the palovarotene 20/10 mg flare-up only treatment group (N=12) and in the untreated group (N=42) was 11 (7, 34) and 15 (4, 53) years, respectively. The median (range) age of participants in the target population (≥8/10 years) in the palovarotene group (N=12) and in the untreated group (N=38) was 11 (7, 34) and 15 (7, 53) years, respectively. The percentage of male participants was 33.3% and 50.0% in the respective groups in both the overall and target population. As the number of participants in the palovarotene treatment group was the same in the overall and target population, efficacy data for target population is presented below.

The clinical endpoints for the flare-up only treatment included the proportion of flare-ups with any new HO at Week 12, and the mean volume of new HO following a flare-up at Week 12 in evaluable flare-ups as shown in Figure 1. The comparator group included flare-ups imaged in untreated participants from the NHS 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.

Phase II studies in the target ≥8/10 years population demonstrated a reduction of 72% (approximated p-value of 0.04) in new HO volume in the 14 flare-ups treated with the 20/10 mg flare-up only dose (3262 mm^3) compared to 43 untreated (from NHS)/placebo flare-ups (11 712 mm^3) (see Figure 1).

Figure 1 Mean Volume of New HO at Week 12 in Palovarotene vs. Placebo/untreated Flare-ups (≥8/10 years)



HO=heterotopic ossification; SE=standard error.

Note: Numbers in parentheses are the number of flare-ups.

The mean results in the target ≥8/10 years population were similar for the 44 flare-ups administered the 10/5 mg flare-up only treatment (2807 mm^3; 76% reduction) (approximate p-value of 0.10).

7.3.2.2 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 with data from the NHS, Study PVO-1A-001. The NHS was an international, 3-year, longitudinal, non-interventional study in 114 participants with FOP with R206H mutation; 98 participants provided at least one post-baseline assessment. All WBCT images from treated participants in Study PVO-1A-301 and untreated participants in the NHS were read in a manner blinded to study origination. Of the 107 participants enrolled in Study PVO-1A-301, 99 had the R206H mutation and 8 had other FOP mutations. Of the 99 with the R206H mutation, 97 had at least one post-baseline HO volume measurement and were included in the Full Analysis Set. The treatment groups assessed in the chronic/flare-up regimen were well matched for baseline demographics.

The median age (range) of participants in the overall population in the palovarotene group (N=99) and in the untreated group (N=111) was 13 (4, 61) and 15 (4, 56) years, respectively. There were more male than female participants in both the palovarotene (53.5% and 46.5%, respectively) and untreated (54.1% and 45.9%, respectively) groups.

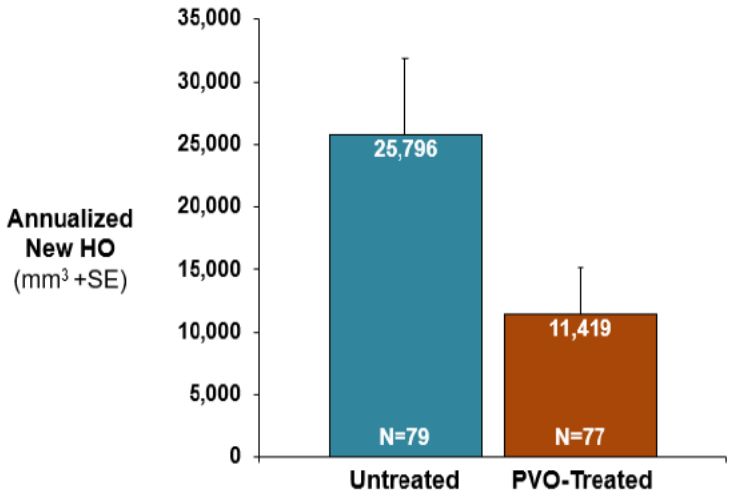
Post-hoc analyses showed that mean annualised new HO volume in the overall population was 60% lower in participants receiving the chronic/flare-up palovarotene regimen (9427 mm^3) versus untreated participants from the NHS (23 720 mm^3).

The weighted linear mixed effects (wLME) analysis showed 54% lower fitted mean annualised new HO volume in palovarotene-treated participants (9367 mm^3) versus untreated participants in the NHS (20 273 mm^3) yielding 2-sided nominal p-value p=0.0392.

The median age (range) of participants in the target ≥8/10 years population in the palovarotene group (N=79) and in the untreated group (N=88) was 14 (8, 61) and 18 (9, 56) years, respectively. There were more male than female participants in both the palovarotene (54.4% and 45.6%, respectively) and untreated (51.1% and 48.9%, respectively) groups.

The mean annualised new HO volume in the target ≥8/10 years population in palovarotene-treated and untreated participants is shown in Figure 2. Results were similar to the overall population, with the mean annualised new HO volume in palovarotene-treated participants (11 419 mm^3) 56% lower than that observed in untreated participants (25 796 mm^3). The wLME analysis showed 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.

Figure 2 Mean Annualised New HO Volume in Study PVO-1A-301 (≥8/10 years)



HO=heterotopic ossification; SE=standard error.

Note: Figure summarises mean observed annualised new HO.

7.4 Registry Study Rationale

Ipsen will implement a registry study, defined as an observational, prospective post-authorisation safety study (PASS), which is intended primarily to assess real-world safety data on paediatric and adult patients with FOP treated with palovarotene and secondly, to describe the effectiveness of this treatment, including its effect on physical function.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

The aim of this registry study is primarily to assess real-world safety data on paediatric and adult patients with FOP treated with palovarotene and secondly, to describe the effectiveness of this treatment, including its effect on physical function.

8.2 Objectives

8.2.1 Primary Objective

To collect and assess real-world safety data in patients with FOP treated with palovarotene.

8.2.2 Secondary Objectives

- To describe the effect of palovarotene on range of motion (ROM) as assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP;
- To describe the use of assistive devices and adaptations for daily living by FOP participants;
- To describe the effect of palovarotene on physical function using age-appropriate forms of the Fibrodysplasia Ossificans Progressiva-Physical Function Questionnaire (FOP-PFQ);
- 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 Baseline and over time under palovarotene treatment;
- To describe the effect of palovarotene on physical and mental health (participants ≥15 years old) and overall quality of life (QoL) (participants <15 years old) using age-appropriate forms of the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale;
- To describe the flare-up frequency;
- To describe any movement mobility change by key body location and annually;
- To describe the number of locations impacted per participant annually;
- To describe the movement mobility outcomes (change in extra bone growth and change in movement), causes, associated symptoms with flare-up events by body location;
- To describe the use (dose, frequency) of palovarotene in the real-world setting.

For women:

- To describe incidence of pregnancy;
- To describe pregnancy outcomes.

For growing children:

- To describe height velocity;
- To describe the difference between chronological age and bone age;
- To describe the frequency, severity and descriptive details of premature physeal closure.

For fractures (including vertebral fractures):

- To describe the frequency, severity, outcome, and descriptive details of any fractures.

9 RESEARCH METHODS

9.1 Registry Study Design

This is an international, multicentre, observational, prospective PASS designed primarily to collect and assess real-world safety data on paediatric and adult patients with FOP treated with palovarotene and secondly, to describe the effectiveness of this treatment including its effect on physical function, over a period of approximately 10 years.

This registry study will be implemented in participating countries where palovarotene is marketed.

Adults and children with FOP who have been prescribed palovarotene, as per local label, by their treating physician will be enrolled. The decision to prescribe palovarotene will be made prior to and independently of the decision to enrol the patient in this observational registry study. Participants who started palovarotene treatment before the implementation of the registry study in their country may also be enrolled.

As this is a non-interventional, observational registry study designed to collect and assess real-world data, participants will receive palovarotene as prescribed by their treating physician and according to the Summary of Product Characteristics (SmPC)/ prescribing information (PI) and/or according to the Marketing Authorisation. Palovarotene will be supplied to the participant according to usual practice, not by the Sponsor.

In addition, participants will be treated in accordance with usual medical practice during their participation in this registry study. No additional assessments or tests will be required by this protocol. All relevant data collected as part of routine medical care will be captured using the electronic Case Report Form (eCRF) by the Investigator (patient-reported questionnaires will be completed directly by the participant on paper and returned to the site for data entry into the eCRF) and transmitted to the Sponsor. If some assessments are not routinely performed by the Investigator, he/she will not complete the corresponding sections in the eCRF.

This registry study will collect data at Baseline and at each Follow-up Visit. Follow-up Visits are scheduled as per routine clinical practice (recommended every 6 months).

The duration of the registry study is approximately 10 years from first participant, first visit, with a minimum of 1-year of data collected for participants who are enrolled within that period.

The primary objective of this registry study is to collect and assess real-world safety data in patients with FOP treated with palovarotene, to permit the description and incidence of all treatment-emergent adverse events (TEAEs), serious TEAEs and nonserious TEAEs, whether or not they are considered related to palovarotene, and all serious and nonserious treatment-related TEAEs.

Secondary objectives include collecting real-world data to describe the effectiveness of palovarotene on ROM, use of assistive devices and adaptions for daily living, physical function, lung function and physical and mental health (or overall QoL in participants <15 years old). The flare-up frequency, any movement mobility change, the number of impacted locations and the movement mobility outcomes will also be described as will the use of palovarotene (dose, frequency) in the real-world setting. Incidence of pregnancy and outcomes of pregnancies will be described for women. Height velocity, the difference between chronological age and bone age and the frequency of PPC will be described for growing children. The frequency, severity and descriptive details of any fractures will be described as part of the AEs monitoring in all participants.

There will be a Study Steering Committee and a Publications Steering Committee. The Study Steering Committee will be composed of investigators, external clinical experts not directly

involved in the registry and staff from the sponsor with the primary objective of assessing the study quality and conduct, as well as for the scientific quality of the final study report. The Publications Steering Committee will be composed of external experts (clinicians and scientists), patients and representatives of patient associations with the primary objective of driving publications.

9.2 Setting

9.2.1 Inclusion Criteria

To be included in the registry study, the participant should fulfil all the following inclusion criteria:

(1) Adult or child with FOP who have been prescribed palovarotene (prior to and independently of the decision to enrol the patient in this registry study and as per local label) by their treating physician according to the locally approved product information;

(2) Signed informed consent as per local regulations must be obtained and maintained. Consent/assent from the participant should be obtained as appropriate before any registry study data collection is conducted. If applicable, parents or legally authorised representatives must give signed informed consent.

9.2.2 Exclusion Criteria

Participants will not be included in the study if:

(1) Currently participating in a palovarotene clinical trial;

(2) Currently participating in any interventional clinical trial for FOP;

(3) Have any contraindication to palovarotene as per the locally approved label (except for pregnant women who have previously received and discontinued palovarotene at any time during the pregnancy and who will be included for safety follow-up).

Individuals who do not meet the criteria for participation in this study (screen failure) or who withdraw their consent may be rescreened. Rescreened participants should be assigned a new participant number. The informed consent process is described in Section 9.13.

9.2.3 Registry Study Population

Eligible participants will be adults and children with FOP who have been prescribed palovarotene, as per local label, by their treating physician according to the locally approved product information. In order to be enrolled, participants must comply with all the inclusion criteria (Section 9.2.1) and exclusion criteria (Section 9.2.2).

This registry study will aim to enrol approximately 80% of patients treated with palovarotene in participating countries where palovarotene is marketed and where the registry study will be implemented.

9.2.4 Registry Study Duration

The duration of the registry study is approximately 10 years from first participant, first visit, with a minimum of 1-year of data collected for participants who are enrolled within that period.

Participant enrolment will start on the date that palovarotene is commercially available in any given country and once the investigational site has been activated.

If AEs or their sequelae (any AE, based on the Investigator's opinion, not only those assessed as related) persist after the date of palovarotene discontinuation, the Investigator must ensure

that the participant receives appropriate medical follow up and this should be properly documented in the participant's medical records.

9.2.5 Registry Study Place

The registry study will be implemented in participating countries where palovarotene is marketed.

9.2.6 Registry Study Schedule

The schedule of assessments that will be collected during the registry study is summarised in Table 2. As this is a non-interventional, observational registry study designed to collect and assess real-world data, these assessments are not mandated by this protocol. If some assessments are not routinely performed by the Investigator, the data will not be captured in the eCRF.

Table 2 Schedule of Assessments

Assessment/Procedure	Baseline Visit Day 1	Follow-Up Visits (as per routine clinical practice[a])/ End of Treatment Visit
Clinic visit or telephone/video contact visit	X	X
Informed consent [b]	X	
Inclusion/exclusion criteria	X	
Baseline demographics	X	
Physical examination [c]	X [d]	
Medical or surgical history	X	
FOP history	X	
Growth status assessment (bone age, epiphyseal status) [e]	X	X[d]
Tanner staging [e]	X	X
Body height [f], weight	X	X[d]
Vital signs[g]	X	X[d]
Pregnancy testing[h]	X	X [h]
Prior/concomitant medications[i]	X	X
Concomitant surgery	X	X
Palovarotene dose for chronic and flare-up treatment [j]	X	X
Spirometry and DLCO test [k]	X	X[d]
CAJIS	X	X[d]
Movement mobility history	X	
Movement mobility changes		X
Flare-up [l]	X	X
Spinal health assessment [m]	X	X
AEs	X [n]	X
FOP-PFQ assessment [o]	X	X
PROMIS Global Health Scale [o]	X	X
FOP assistive devices assessment [o]	X	X

AE=Adverse event; CAJIS=Cumulative Analogue Joint Involvement Scale for FOP; DLCO=Diffusion capacity of the lung for carbon monoxide; FOP=Fibrodysplasia ossificans progressiva; FOP-PFQ=FOP-Physical Function Questionnaire; PI=Prescribing Information; PROMIS=Patient Reported Outcomes Measurement Information System; SmPC=Summary of Product Characteristics.

a Follow-up Visits are recommended every 6 months, or as per local label.

b If participant <18 years (or the legal age of consent in the jurisdiction in which the study is taking place), assent and parent or legally authorised representative consent will also be required.

c	This includes a general assessment, dermatologic, lymph nodes, head, eyes, ears, nose and throat (HEENT), chest, cardiac, abdomen, limb/extremities, musculoskeletal, neurologic and other. Performed only if not a telephone/video visit (and if a part of routine clinical care).
d	Performed only if not a telephone/video visit (and if a part of routine clinical care).
e	Collected for growing children. Assessment as per the SmPC/PI
f	Height at 6 to 12 months prior to the Baseline Visit will also be collected.
g	Vital signs to be collected are respiratory rate, blood pressure and heart rate.
h	Participants will be assessed for child-bearing status and pregnancy prevention measures (females only). As per the SmPC/PI, pregnancy testing is carried out with a confirmation of absence of pregnancy monthly as long as the participant receives palovarotene and one month after stopping. These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.
i	This includes prior/current use of palovarotene and start/end date of palovarotene treatment which will be collected at the Baseline Visit if available.
j	Not applicable for pregnant women.
k	Spirometry obtains the lung function parameters of observed and % predicted FVC and FEV1 and the absolute and % predicted FEV1/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	This includes number of flare-ups over the past 12 months before inclusion and since the last visit.
m	Spinal health assessment to be performed using radiological imaging (e.g., Computed Tomography [CT], X-ray, scintigraphy, etc).
n	AE collection begins once the informed consent has been signed.
o	Paper-based patient-reported questionnaires.

9.2.7 Registry Study Visit(s)

Visits will be in accordance with routine clinical practice (Follow-up Visits are recommended every 6 months).

The registry study will collect data at the Baseline Visit, Follow-up Visits and at an End of Treatment Visit.

The Baseline Visit should ideally be a clinic visit but all visits can be performed by either telephone/video contact or by clinic visit as per the Investigator's judgement.

9.2.7.1 Baseline Visit

Investigators at participating sites will identify patients who fulfil the inclusion and exclusion criteria. Written informed consent should be obtained prior to enrolment according to local regulations, and once inclusion and exclusion criteria have been satisfied. If the participant is <18 years old (or the legal age of consent in the jurisdiction in which the study is taking place), assent and parent or legally authorised representative consent will also be required.

The participants will attend a clinic or telephone/video visit and assessments will be performed according to routine clinical care. For this registry study, the following variables will be captured from Baseline Visit records as available:

- Baseline demographics;
- Medical or surgical history;
- FOP history (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);
- Number of flare-ups (over the past 12 months prior to Baseline Visit);
- Movement mobility history (over the past 12 months prior to the Baseline Visit);
- Growth status assessment for growing children (bone age and epiphyseal status, assessment as per the SmPC/PI);
- Tanner staging for growing children;
- Body height and weight (height at 6 to 12 months prior to the Baseline Visit will also be collected);
- Vital signs (respiratory rate, blood pressure and heart rate);
- Physical examination including a general assessment as well as dermatologic, lymph nodes, head, eyes, ears, nose and throat (HEENT), chest, cardiac, abdomen, limb/extremities, musculoskeletal, neurologic and other assessments (as per routine clinical care);
- Pregnancy test (as per the SmPC/PI, female participants are assessed for child-bearing status and pregnancy prevention measures. These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy);
- Prior and concomitant medications (includes prior/current use of palovarotene and start/end date of palovarotene treatment, which will be collected if available);
- Concomitant surgery;
- Palovarotene dose;
- Spirometry and DLCO test;
- CAJIS for FOP;
- Spinal health assessment using radiological imaging (e.g., CT, X-ray, scintigraphy, etc);

- AEs (following provision of signed informed consent);
- FOP-PFQ (the adult form should be used for participants 15 years and older and for participants under 15 years old, there is a self-completed paediatric form (developed for participants 8 to 14 years old) and a proxy completed paediatric form (developed for participants 5 to 14 years old;
- PROMIS Global Health Scale (the adult form should be used for participants 15 years and older and for participants under 15 years old, there is a self-completed paediatric form (developed for participants 8 to 14 years old) and a proxy completed paediatric form (developed for participants <15 years old);
- FOP assistive devices assessment.

9.2.7.2 Follow-up Visits/End of Treatment Visit

The participants will attend a clinic or telephone/video visit and assessments will be performed according to routine clinical care. For this registry study, the following variables will be captured from medical records as available:

- Growth status assessment for growing children (bone age and epiphyseal status, assessment as per the SmPC/PI);
- Tanner staging for growing children;
- Body height and weight;
- Vital signs;
- Pregnancy test (in accordance with the SmPC/PI, pregnancy tests should be performed monthly while treatment with palovarotene is ongoing and one month after treatment is stopped) and change in fertility status;
- Concomitant medications;
- Concomitant surgery;
- Palovarotene dose;
- Spirometry and DLCO test;
- CAJIS for FOP;
- Number of flare-ups since last visit;
- Movement mobility changes;
- Spinal health assessment using radiological imaging;
- AEs;
- FOP-PFQ;
- PROMIS Global Health Scale;
- FOP assistive devices assessment.

9.2.8 Registry Study Discontinuation/Withdrawal

The participant can withdraw (or be withdrawn if the subject is a child upon legal representative's decision) from the registry study at any time. The date and primary reason for withdrawal should be recorded in the eCRF as well as if the participant stopped palovarotene or not.

For study results to remain unbiased, it is important that no data are modified, as a result, the data collected in clinical studies need to remain untouched for results to be trusted. Should the participant withdraw from the study, no further data will be collected, nevertheless, data

collected up to the time of the withdrawal will be kept for analysis, safety and integrity of study results.

The participant will be withdrawn from the registry study if:

- they enrol in any interventional clinical trial for FOP, or,
- the participant is no longer receiving palovarotene (except if palovarotene is discontinued due to a safety concern, in such cases the participant will be monitored for safety, see Section 11.4 for follow-up of AEs and Section 11.1.3.1 for follow-up of pregnancies).

Investigators may decide to stop their patient's participation in the registry study at any time without consequences on the normal participant follow-up.

9.2.9 Treatment Discontinuation

Palovarotene treatment may be discontinued in the event of any serious adverse events (SAEs), AEs or special situations (see Section 11.1.3 for definition of special situations) deemed by the Investigator to warrant treatment discontinuation. In the event of pregnancy, palovarotene treatment must be discontinued (See Section 11.1.3.1).

Discontinuation of treatment due to AEs should be distinguished from discontinuation/withdrawal from the registry study due to participant/parent decision or end of follow-up.

If AEs or their sequelae (any AE, based on the Investigator's opinion, not only those assessed as related) persist after the date of palovarotene discontinuation, the Investigator must ensure that the participant receives appropriate medical follow up and this should be properly documented in the participant's medical records.

All participants discontinuing palovarotene treatment will be followed up to 30 days after last palovarotene intake (unless consent is withdrawn).

9.2.10 Early Registry Study Termination

The Sponsor can decide at any time to discontinue the registry study for any reason. Investigators will be informed of the decision. Ethics committees and Competent Authorities (Cas) will also be informed if required by local regulations.

9.3 Endpoints and Variables

9.3.1 Endpoints

9.3.1.1 Primary Endpoints

- Incidence and description of all TEAEs, whether or not they are considered as related to palovarotene;
- 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 palovarotene;
- Incidence and description of all nonserious TEAEs whether or not they are considered as related to palovarotene.

9.3.1.2 Secondary Endpoints

- Raw values and change from Baseline in CAJIS total score at each Follow-up Visit;
- Raw values and shift from Baseline in use of assistive devices and adaptations for daily living at each Follow-up Visit;

- Raw values and change from Baseline in % of worst score for total score, upper extremities subscore and mobility subscore using age-appropriate forms of the FOP-PFQ at each Follow-up Visit;
- Raw values and change from Baseline in observed and % predicted FVC at each Follow-up Visit;
- Raw values and change from Baseline in observed and % predicted FEV_1 at each Follow-up Visit;
- Raw values and change from Baseline in absolute and % predicted FEV_1/FVC ratio at each Follow-up Visit;
- Raw values and change from Baseline in observed and % predicted DLCO at each Follow-up Visit;
- Raw values and change from Baseline in physical and mental function (mean global physical and mental health score converted into T-scores) for participants ≥15 years old and overall QoL (mean total score converted into T-scores) for participants <15 years old using age-appropriate forms of PROMIS Global Health Scale at each Follow-up Visit;
- Number of flare-ups over the past 12 months before inclusion and since the last visit
- Any movement mobility change (better movement/the same movement/slightly worse movement/moderately worse movement/severely worse movement) by key body location and annually
- Number of locations impacted per participant annually and change from Baseline
- Evolution of impacted location (how many times a location is impacted) per location
- Movement mobility outcomes (change in extra bone growth and change in movement), causes, associated symptoms with flare-up events by body location
- Mean dose/year for chronic treatment;
- Mean dose/cycle for flare-up treatment.

For women:

- Incidence of pregnancy;
- Description of pregnancy outcomes.

For growing children:

- Raw values and change from Baseline in height velocity at each Follow-up Visit;
- Mean difference between chronological age and bone age at each Follow-up Visit;
- Frequency, severity and descriptive details of premature physeal closure overall and at each Follow-up Visit.

For fractures (including vertebral fractures):

- Frequency, severity, outcome and descriptive details of any fractures overall and at each Follow-up Visit.

9.3.2 Variables

Only the data collected as part of routine medical care will be captured using the eCRF by the Investigator (patient-reported questionnaires will be completed directly by the participant on paper and returned to the site for data entry into the eCRF). If some assessments are not routinely performed by the Investigator, he/she will not complete the corresponding sections in the eCRF.

9.3.2.1 Demographic and Baseline Characteristics

The registry study will collect the following data at the Baseline Visit if available:

- Baseline demographics including date of birth, gender and race, where permitted;
- All medical or surgical history within the past year, excluding FOP related history;
- History of FOP 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;
- Number of flare-ups over the past 12 months prior to Baseline;
- Movement mobility history over the past 12 months prior to Baseline including: locations, mobility impact start date, change in movement, change in extra bone growth, flare-up event, causes;
- Physical examination (only if clinic visit) including a general assessment as well as dermatologic, lymph nodes, head, eyes, ears, nose and throat (HEENT), chest, cardiac, abdomen, limb/extremities, musculoskeletal, neurologic and other assessments (as per routine clinical care);

9.3.2.2 Prior and Concomitant Medication

The registry study will collect the use of prior and concomitant medication including dose, frequency, start/end dates and reason for prescription at the Baseline Visit and at the Follow-up/End of Treatment Visits if available.

This includes prior/current use of palovarotene and start/end date of palovarotene treatment will be collected at the Baseline Visit if available.

9.3.2.3 Concomitant Surgery

The registry study will collect the following data on concomitant surgery at the Baseline Visit and at the Follow-up/End of Treatment Visits if available:

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

9.3.2.4 Body Height and Weight

The registry study will collect body height and weight for all participants at the Baseline Visit and at the Follow-up/End of Treatment Visits (only if clinic visit) if available. Height at 6 to 12 months prior to the Baseline Visit will also be collected if available.

9.3.2.5 Safety Variables

Adverse Events and Special Situations

The registry study will collect the following AE data from the signing of the ICF until last palovarotene intake + 30 days:

- All AEs, TEAEs, irrespective of causality, including serious TEAEs, start/end date, time to onset, nature, severity, seriousness, causality assessment, any treatment administered for the AE, action taken and outcome (definitions, management and reporting of AEs are described in Section 11);
- Deaths, irrespective of causality, including date and cause of death;

- Special situations (defined in Section 11.1.3), irrespective of causality, including start/end date, category, description, whether the special situation led to an AE and outcome.

If AEs or their sequelae (any AE, based on the Investigator's opinion, not only those assessed as related) persist after the date of palovarotene discontinuation, the Investigator must ensure that the participant receives appropriate medical follow up and this should be properly documented in the participant's medical records.

All participants discontinuing palovarotene treatment will be followed up in the registry up to 30 days after last palovarotene intake (unless consent is withdrawn).

Vital Signs

The registry study will collect respiratory rate, blood pressure and heart rate at the Baseline Visit and at the Follow-up/End of Treatment Visits (only if clinic visit) if available.

Growth Status

The registry study will collect bone age and epiphyseal status ("open" or "closed") (assessment as per the SmPC/PI) for growing children at the Baseline Visit and at the Follow-up/End of Treatment Visits if available.

Growing children are children in whom their growth plates have not fused. Whether the participant is a growing child is based on the Investigator's assessment.

Tanner Staging

The registry study will collect Tanner stage (rating of development of secondary sex characteristics; pubic hair, testicular volume, breast development, where Stage 1 corresponds to the pre-pubertal form and Stage 5, the final adult form [35]) for growing children at the Baseline Visit and at the Follow-up/End of Treatment Visits if available.

Pregnancy Testing

In accordance with the SmPC/PI, female participants are assessed for child-bearing status and pregnancy prevention measures prior to receiving palovarotene. Pregnancy testing is carried out with a confirmation of absence of pregnancy monthly for as long as the female participant receives palovarotene and for one month after stopping. These conditions also apply to females who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Pregnancy is contraindicated to the use of palovarotene, therefore if a participant is pregnant or has a positive pregnancy test at any time during the registry study, this will result in immediate discontinuation of palovarotene. A pregnant participant will be followed throughout her pregnancy and the health status of the baby will be verified (see Section 11.1.3.1).

Spinal Health Assessment

The registry study will collect the outcome/results of radiological imaging and the type of imaging used to assess the participants' spinal health status in clinical practice, as recommended by the product label. The radiological imaging techniques for which outcomes/results will be collected include, but are not limited to, CT, X-ray and scintigraphy.

Fractures (including vertebral fractures)

The registry study will collect the severity and descriptive details of any fractures (including vertebral fractures) in the SAE eCRF page.

9.3.2.6 Effectiveness Variables

CAJIS

The CAJIS for FOP will be collected at the Baseline Visit and at the Follow-up/End of Treatment Visits (only if a clinic visit) if available.

The CAJIS is an objective measure of joint movement completed by the Investigator to document total joint involvement [36]. This scale, which was developed by the Investigators from the Center for Research in FOP and Related Disorders, assesses functional disability by categorising ROM 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 activities of daily living;
- Needs complete help with activities of daily living.

Use of Assistive Devices and Adaptations for Daily Living

The use of assistive devices and adaptations for daily living will be collected at the Baseline Visit and at the Follow-up/End of Treatment Visits if available.

The questionnaire will be filled in by the participant or the proxy as per below table:

Questionnaire	If participant is an Adult (15 years and +)	If participant is a Child (under 15 years)	
	Filled by	Filled by	
	Participant	Participant	Proxy
FOP assistive devices assessment (Version 1.0)	X*		X

* If participants are unable to answer on their own, an individual can be involved and reports only the patient's response on their behalf.

In case of PRO completion by an individual (if participants are unable to answer on their own), the recommendations for such administration are detailed below:

- The individual should be different from a healthcare professional and should be the same across multiple assessments.
- The individual must only report the participant's response without any amendments or interpretation.

Assistive devices and adaptations for daily living (including Healthcare utilization) include:

- Mobility aids (e.g. cane/crutch, walker, manual wheelchair, motorised scooter, customised motorised wheelchair, adapted vehicle for driving or for motorised wheelchair);

- Eating tools (e.g. 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 (e.g. 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 (ICE) Taggisar with annual membership and label for emergency care, customised dental care tools);
- Bathroom aids and devices (e.g. 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 (e.g. 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 (e.g. 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 (CO) detectors and alert);
- Work environment adaptions (e.g. customised desk/office chair/workstation/office tools, use of handicapped bathroom facilities);
- Technology adaptions (e.g. 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 (e.g. protective helmet/body gear, adapted bicycle, other adapted recreational gear);
- School adaptions (e.g. adapted desk, adapted chair, reaching tools, special electronics for learning, adapted curriculum);
- Medical therapies for daily living (e.g. supplemental oxygen, physical therapy, hydrotherapy, energy medicine therapy, occupational therapy, lymphoedema massage treatments and wraps, wound care specialist, positive expiratory pressure (PEP) mask or spirometer for breathing exercises);
- Healthcare utilization (e.g. general practitioner (GP), including primary care doctor/family doctor/paediatrician, homeopathic/naturopathic provider, podiatrist, dentist – orthodontist, occupational therapist, physiotherapist (physical therapy), speech therapist, ear, nose and throat doctor including audiology for hearing, psychologist/psychiatrist/counsellor, orthopaedic specialist, gastroenterologist, obstetrician-gynecologist, dermatologist, pulmonologist (lung doctor), pain specialist, cardiologist (heart doctor), urologist (kidney doctor), rheumatologist, neurologist, wound care specialist.

Physical and Mental Function

Physical function as assessed by the age-appropriate forms of the FOP-PFQ and physical and mental function (overall QoL for participants <15 years old) as assessed by the age-appropriate forms of the PROMIS Global Health Scale will be collected at the Baseline Visit and at the Follow-up/End of Treatment Visits if available.

Questionnaires will be filled in by the participant or the proxy as per below table:

Questionnaires	If participant is an Adult (15 years and +)	If participant is a Child (under 15 years)	
	Filled by	Filled by	
	Participant	Participant	Proxy
FOP-PFQ assessment – [8-14] years – proxy questionnaire (Version 1.0)			X
FOP-PFQ assessment – [8-14] years - self questionnaire (Version 1.0)		X*	
FOP-PFQ assessment – adult questionnaire (Version 1.0)	X*		
PROMIS Global Health Scale – [8-14] years - proxy questionnaire (Version 1.0)			X
PROMIS Global Health Scale – [8-14] years - self questionnaire (Version 1.0)		X*	
PROMIS Global Health Scale – adult questionnaire (Version 1.2)	X*		

* If participants are unable to answer on their own, an individual can be involved and reports only the patient's response on their behalf.

In case of PRO completion by an individual (if participants are unable to answer on their own), the recommendations for such administration are detailed below:

- The individual should be different from a healthcare professional and should be the same across multiple assessments.
- The individual must only report the participant's response without any amendments or interpretation.

The FOP-PFQ is a disease-specific patient-reported outcome measure of physical impairment which includes questions related to activities of daily living and physical performance. There are adult and paediatric versions of the FOP-PFQ; the adult form should be used for participants 15 years and older and for participants under 15 years old, there is a self-completed paediatric form (developed for participants 8 to 14 years old) and a proxy-completed paediatric form (developed for participants 5 to 14 years old).

The FOP-PFQ consists of 28 questions in the adult version and 26 questions in the paediatric version which are scored on a scale of 1 to 5, with lower scores indicating that the participant has more difficulty completing those tasks. Score calculations are described in Section 9.7.3.8.

PROMIS Global Health Scale is a patient-reported outcome measure of physical and mental function in participants ≥15 years old and overall QoL for participants <15 years old. There are

adult and paediatric versions of the PROMIS Global Health Scale; the adult form should be used for participants 15 years and older and for participants under 15 years old, there is a self-completed paediatric form (developed for participants 8 to 14 years old) and a proxy completed paediatric form (developed for participants <15 years old).

The PROMIS Global Health Scale consists of 10 questions in the adult version and 9 questions in the paediatric version. For the adult form, 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). For the paediatric form, only a total score is calculated, ranging from 7 (worse health) to 35 (better health). All 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 9.7.3.8.

Lung Function Parameters

Lung function parameters will be collected at the Baseline Visit and at the Follow-up/End of Treatment Visits (only if clinic visit) if available.

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 SI unit of mmol/min/kPa) [37] 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 (CO) has a high affinity for haemoglobin, and it follows the same pathway as that of oxygen to finally bind with haemoglobin. Inhaled CO is used for this test due to its high affinity for haemoglobin which is 200-250 times that of oxygen [38].

At Baseline, the Investigator will ask the participant how many flare-ups they experienced over the past 12 months. At each follow-up visit, the Investigator will ask the participant how many flare-ups they experienced since the last visit.

Movement mobility change

For each movement mobility change, the impacted location, start date, causes, the outcome (change in extra bone growth, change in movement and associated flare-up event, if any) at the Baseline Visit and Follow-up/End of Treatment associated Visits if available. Movement mobility history over the past 12 months prior to the Baseline Visit will also be collected at the Baseline Visit.

Associated symptoms to flare-up include, but are not limited to, pain, swelling, stiffness, redness, warmth, fever, lethargy, loss of appetite, decreased range of motion, and change in mood or behavior.

At each visit, the Investigator will ask the participant if they experienced any movement mobility change since their last visit.

9.3.2.7 Treatment Variables

The registry study will collect the following data on chronic and flare-up palovarotene treatment at the Baseline Visit and at the Follow-up/End of Treatment Visits if available:

- Dose and frequency of palovarotene for chronic and flare-up treatment;
- Dose modifications, interruptions, start date, end date.

9.4 Data Sources

Source data includes any data collected as part of routine medical care which will be captured in an eCRF by the Investigator and transmitted to the Sponsor for analysis. The patient reported questionnaires (FOP-PFQ, PROMIS Global Health Scale and FOP assistive devices

assessment) will be completed directly by the participant or proxy on paper (see Section 9.3.2.6).

Definitions of source data and source documents are provided in Section 9.8.3.

9.5 Registry Study Size

No formal sample size calculations have been performed for this registry study.

This registry study will aim to enrol approximately 80% of patients treated with palovarotene in participating countries where palovarotene is marketed and where the registry study will be implemented.

9.6 Data Management

Data management will be conducted by a Service Provider (SP) directed by the Sponsor's Global Medical Affairs Biometry Department. All data management procedures will be completed in accordance with the Standard Operating Procedures (SOPs) of Ipsen and the contracted SP.

9.6.1 Data Collection

The specific data to be collected at each visit, if available, are summarised in the Schedule of Assessments (Table 2).

All relevant data collected as part of routine medical care will be captured using the eCRF by the Investigator (patient-reported questionnaires will be completed directly by the participant or proxy on paper and returned to the site for data entry into the eCRF) and transmitted to the Sponsor. If some assessments are not routinely performed by the Investigator, he/she will not complete the corresponding sections in the eCRF.

Data will be collected in an eCRF via the internet utilising a secured website. The Sponsor and the SP will ensure that the eCRF developed is appropriate to capture the data required by the protocol. The Sponsor will ensure that the entrusted SP uses adequate technology to ensure data security transfer and backup.

Each site is required to have a computer and internet connection available for site entry of clinical data. Data entry in the eCRF will be performed by the Investigator or by the designated person from his/her team and in order to ensure confidentiality and security of the data, all entries into the eCRF will be made under the electronic signature (e-signature) of the person performing the action (username and password). Only Sponsor-authorised users will be given access to the eCRF as appropriate for their study responsibilities. All users must have successfully undergone software application training prior to entering data into the eCRF.

Once written informed consent (and assent, if applicable) has been obtained, the eCRF will provide a numeric participant identifier to pseudonymise the data from each participant. Data for each participant must be entered into the eCRF within 5 days of the participant's enrolment, each Follow-Up Visit and the End of Treatment Visit. Data transmitted will be pseudonymised and will be identified only by the participant number. Only investigating sites will be able to link the numeric identifier to each participant's identity.

In compliance with Good Pharmacoepidemiology Practices (GPP), the participant's medical records should be clearly marked and permit easy identification of their participation in this study.

Medical and surgical history, non drug therapies, concomitant surgeries, special situations and AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and prior/concomitant medication will be coded using the World Health Organization Drug Dictionary (WHODD) by the contracted SP and reviewed by the Sponsor.

Queries will be edited in English and addressed to the investigational site using the eCRF.

Investigators or authorised registry study staff members will answer the queries directly into the eCRF.

The eCRF will be signed electronically by the Investigator to certify that all the data recorded in it are consistent with the source documents and reflect the status of the participant during the corresponding part of the registry study.

9.6.2 Data Archiving and Retention

During the site initiation visits, the monitor must ensure that the archiving facilities are adequate and archiving/retention responsibilities of the Investigator have been discussed.

Registry study documents should be retained for at least 15 years after registry study completion. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing-out the site. The Sponsor will inform the Investigator, in writing, as to when these documents no longer need to be retained.

If the Investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of registry study documents, the Sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

9.7 Data Analysis

9.7.1 Analyses Population Definitions

Safety Population: all participants who have taken at least one dose of palovarotene following enrolment.

9.7.2 Sample Size Determination

No formal sample size calculations have been performed for this registry study.

This registry study will aim to enrol approximately 80% of patients treated with palovarotene in participating countries where palovarotene is marketed and where the registry study will be implemented.

9.7.3 Statistical and Analytical Methods

9.7.3.1 Statistical Analyses

The statistical analyses will be performed by an external SP, managed by the Sponsor's Medical Affairs Biometry Department.

A Statistical Analysis Plan (SAP) describing the planned statistical analysis in detail with table, figure and listing templates will be developed as a separate document.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (Version 9.2 or higher).

No formal statistical testing will be performed, and all the analyses will be primarily descriptive in nature. When appropriate and unless otherwise specified, 2-sided 95% CIs will be displayed and if p-values are presented, they will be for exploratory purposes only.

Descriptive summary statistics will include the number of documented data, number of missing data and the following:

- Mean, standard deviation, 95% CIs of the mean/median when appropriate, median, minimum and maximum for continuous variables;
- Frequency count and percentages for categorical nominal variables.

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

Percentages will be based on the number of non-missing observations.

9.7.3.2 Demographic and Baseline Characteristics

Demographic and Baseline data will be included in the participant data listings using the Safety Population.

Descriptive statistics of demographic and Baseline data will be presented for the Safety Population.

Medical and surgical history will be coded using MedDRA and summarised.

9.7.3.3 Prior and Concomitant Medication

Prior and concomitant medication will be included in the participant data listings using the Safety Population.

Descriptive statistics of prior and concomitant medication will be presented for the Safety Population.

Prior and concomitant medication will be coded using the WHODD and summarised by drug categories.

9.7.3.4 Concomitant Surgery

Concomitant surgery data will be included in the participant data listings using the Safety Population.

Descriptive statistics of concomitant surgery will be presented for the Safety Population.

9.7.3.5 Participant Disposition and Withdrawals

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

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

9.7.3.6 Body Height and Weight

Body height and weight will be included in the participant data listings using the Safety Population.

Actual values and mean changes from the Baseline Visit in body height and weight will be presented at each visit for the Safety Population.

Abnormal findings considered clinically significant by the Investigator will be reported as an AE.

9.7.3.7 Safety Evaluations

Adverse Events and Special Situations

All AEs and special situations will be included in the participant data listings using the Safety Population. Analyses and summary tables will be presented overall for the Safety Population.

Adverse events will be coded according to MedDRA and will be classified by 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, all serious TEAEs, all nonserious TEAEs, AEs leading to death, AEs leading to treatment discontinuation and special situations will be tabulated separately. In addition, summary tables for TEAEs will be presented by maximum intensity and drug relationship (Investigator-reported causality assessment).

A TEAE is defined as any AE that occurs during the administration of palovarotene + 30 days after discontinuation if:

- It was not present prior to receiving the first dose of palovarotene; or
- It was present prior to receiving the first dose of palovarotene but the intensity increased during treatment with palovarotene.

All TEAEs will be flagged in the AE listings.

Vital Signs

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

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

Abnormal findings considered clinically significant by the Investigator will be reported as an AE.

Growth Status

Bone age and epiphyseal status will be included in the participant data listings for growing children using the Safety Population.

Height velocity and chronological age will be derived for growing children.

Mean raw values, mean changes from the Baseline Visit in height velocity and the mean difference between chronological age and bone age will be presented at each visit for the Safety Population. The frequency of PPC in growing children will also be presented overall and at each Follow-up Visit.

Tanner Staging

Tanner stage will be included in the participant data listings for growing children using the Safety Population.

Actual values as well as the shift from the Baseline Visit in Tanner stage will be presented for each visit.

Pregnancy

Confirmation of an absence of pregnancy will be included in the participant data listings using the Safety Population.

Spinal Health Assessment

Spinal health status, assessed by radiological imaging, will be included in the participant data listings using the Safety Population.

Fractures (including vertebral fractures)

All fractures will be included in the participant data listings using the Safety Population. Analyses and summary tables will be presented overall for the Safety Population.

Fractures will be coded according to MedDRA and will be classified by PT and system organ class (SOC). Fracture listings will be presented by participant, SOC and PT.

The incidence of all reported fractures will be tabulated separately. In addition, summary tables will be presented by maximum intensity and drug relationship (Investigator-reported causality assessment).

9.7.3.8 Effectiveness Evaluation

Effectiveness data will be included in the participant data listings using the Safety Population. Analyses and summary tables will be presented overall for the Safety Population.

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

CAJIS

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

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

Use of Assistive Devices and Adaptations for Daily Living

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

FOP-PFQ

The FOP-PFQ consists of 28 questions in the adult version and 26 questions in the paediatric version which are scored on a scale of 1 to 5.

The total score will be calculated as follows:

- Adult version: the sum of the scores from each question which will range from $28 \times 1 = 28$ to $28 \times 5 = 140$;
- Paediatric version: the sum of the scores from each question which will range from $26 \times 1 = 26$ to $26 \times 5 = 130$.

The upper extremities subscore will be calculated as follows:

- Adult version: the sum of the scores from 15 questions (Questions 1-12, 14, 25 and 26) which will range from $15 \times 1 = 15$ to $15 \times 5 = 75$;
- Paediatric version: the sum of the scores from 18 questions (Questions 1, 2, 6-11, 16-19 and 21-26) which will range from $18 \times 1 = 18$ to $18 \times 5 = 90$.

The mobility subscore will be calculated as follows:

- Adult version: the sum of the scores from 13 questions (Questions 13, 15-24, 27 and 28) which will range from $13 \times 1 = 13$ to $13 \times 5 = 65$;
- Paediatric version: the sum of the scores from 8 questions (Questions 3, 4, 5, 12-15 and 20) which will range from $8 \times 1 = 8$ to $8 \times 5 = 40$.

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 for the adult version and × 26 for the paediatric form).

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

As the analysis for FOP-PFQ will be performed across all participants (adult and paediatric) and the number of contributing questions differs, 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 Baseline Visit will be presented for each visit overall and by age group.

PROMIS Global Health Scale

For the adult version, the global physical health and global mental health scores will be calculated as follows:

- Global physical health scores will be calculated as 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 scores will be calculated as 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 3.

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 3 Rescaled Global Physical and Mental Health Scores for the Adult Version of PROMIS

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

For the paediatric version, the total score will be calculated as the sum of scores from the first 7 questions and will range from 7 (worse health) to 35 (better health).

If more than 3 questions contributing to the total score are missing, the total score will not be calculated. It will be considered as missing.

If not more than 3 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. × 7).

The global physical health score, the global mental health score and the total score will also be converted into T-scores. 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

standard deviation 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 standard deviation better (healthier) than the general population. Conversion tables are provided in Appendix 2.

Actual values as well as the change from the Baseline Visit in mean global physical and mental health score converted into T-scores (for participants ≥15 years old) and mean total score converted into T-scores (for participants <15 years) will be presented for each visit overall and by age group.

Lung Function Parameters

Actual values as well as the change from the Baseline Visit in observed and % predicted FVC, observed and % predicted FEV1, absolute and % predicted FEV1/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 [37].

Flare-ups

The number of flare-ups over the past 12 months prior to baseline and since the last visit will be presented for each visit.

Mobility change

Any movement mobility change (better/the same/slightly worse/moderately worse/severely worse movement) will be summarised by key body locations annually.

Actual values as well as the change from the Baseline Visit in number of impacted locations per patient will be presented annually.

The evolution of impacted location will be presented annually by summarising for each location (some grouping might be done) the number of times the location is impacted.

Movement mobility outcomes (change in extra bone growth, change in movement and flare-up event), causes, associated symptoms to flare-up will be summarised by location.

9.7.3.9 Treatment Evaluation

The treatment duration as well as the dose of palovarotene at each visit will be described. The mean dose/year will be calculated for chronic treatment and the mean dose/cycle will be calculated for flare-up treatment.

Dose modifications, interruptions, start date and end date will be summarised.

9.7.4 Subgroup Analyses

Subgroup analyses will be performed by age group and gender.

9.7.5 Interim Analyses

The Sponsor will review safety data on an ongoing basis. There will be regular updates in the Periodic Benefit-Risk Evaluation Reports (PBRERs) and Periodic Safety Update Reports (PSURs).

Interim effectiveness and safety descriptive analyses are planned to be performed every 2 years. For the first interim analysis, a minimum of 30 participants will have to be enrolled.

9.8 Quality Control

9.8.1 Routine Monitoring and Monitoring Procedures

The monitoring procedures of the study may be conducted by an external SP directed by the Sponsor's Global Medical Affairs, Clinical Operations Department. All monitoring activities will be completed in accordance with Ipsen and the SP's SOPs and as per the monitoring plan. The monitoring of the study should ensure that the rights and wellbeing of the participants are protected, that the registry study data are accurate (complete and verifiable to source data) and that the registry study is conducted in compliance with the protocol, Good Pharmacoepidemiology Practices (GPP) [39] and regulatory requirements.

The Investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information and the results of any other assessments. All information in the eCRF must be traceable to these source documents in the participant's file. Data not requiring a separate written record will be defined before study start and will be recorded directly in the eCRF. The Investigator must also keep the original Informed Consent Form (ICF) signed by the participant (or assent, if applicable) or their parent/legally authorised representative and a signed copy is given to them.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry.

Ipsen monitoring standards require full verification for the presence of informed consent/assent, adherence to the inclusion/exclusion criteria, documentation of SAEs and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

The frequency of the monitoring may be adapted according to participant recruitment rate or any other suitable reason. The Investigator will allow direct access to all relevant files (for all participants) for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.

The site Investigator or authorised registry study staff members must complete the eCRF in a timely manner and on an ongoing basis to allow regular review by the registry study monitor.

Whenever a participant's name is revealed on a document required by the Sponsor (e.g. laboratory print-outs), the name must be blacked out permanently by the site personnel and annotated with the participant number as identification.

Before study initiation, at a site initiation visit or remote site initiation visit, an Ipsen/delegated SP representative will review the protocol and data capture requirements (i.e. eCRFs) with the Investigators and their staff. During the study, Ipsen (or designee) employs several methods of ensuring protocol, GPP and Good Pharmacovigilance Practices (GVP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture/data entry, the adherence to the protocol and to GPP and GVP and the progress of enrolment. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralised Ipsen/delegated SP. In addition to on-site monitoring visits, the sites will receive regular monitoring phone calls from monitors, in order to:

- Allow for early identification and direct solving of any issue with the site;

- Follow the enrolment of the participants listed in the patient screening log, and in particular, to remind the sites to propose the registry study to all eligible patients presenting for a consultation, and to identify any issue related to recruitment (e.g. to identify a site with specific difficulties in collecting informed consents, etc.);
- Follow the included participants and avoid/limit the drop out of participants;
- Answer any questions related to the completion of the eCRF.

9.8.2 Inspections and Auditing Procedures

Authorised personnel from external CA and Sponsor-authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the Sponsor.

Auditors and inspectors must have direct access to registry study documents and site facilities, and to any other locations used for the purpose of the registry study in question (e.g. laboratories).

In the event of the site being notified directly of a regulatory inspection, the Investigator must notify the Sponsor representative as soon as possible, to assist with preparations for the inspection.

9.8.3 Source Data Verification

According to the study monitoring plan, during monitoring visits, the monitor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported in the eCRF. However, this verification will only address key data of the eCRF and only be based on available Investigator's participant notes.

The source documents must, as a minimum, contain the following; a statement that the participant is included in a registry study, the date on which informed consent (and assent, if applicable) was obtained prior to participation in the registry study, the identity of the registry study, diagnosis and eligibility criteria, visit dates and any AEs and associated concomitant medication.

Definitions for source data and source documents are given below:

- **Source data:** all original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the registry study. Source data are contained in source documents (original records or certified copies);
- **Source documents:** original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the registry study).

The participant (if adult) or their parent/legally authorised representative (if participant is not an adult) must have consented to their medical records being viewed by Sponsor authorised personnel, and by local, and possibly foreign, CA. This information is included in the ICF.

9.8.4 Data Quality

The Investigator is responsible for the validity of all data collected and must provide an e-signature, consisting of an individual and confidential username and password combination,

to each eCRF to attest to the accuracy and completeness of all the data. This e-signature is declared to be the legally binding equivalent of the handwritten signature.

The eCRF is a validated system with restricted access to study staff only with a personal username and password. The eCRF data transferred from the investigational site to the assigned Data Management group will be reviewed for completeness, consistency and protocol compliance. Inadequate data can be queried for clarification and any queries generated during the data management process will be tracked by the contracted data management SP according to the Data Handling Manual. Of note, due to the nature of this registry study, missing data is expected.

Data consistency and accuracy will be ensured by running real-time checks at the time of data entry in the eCRF. All corrections to the eCRF data are recorded in the system audit trail which automatically tracks the data changes, the user, the time and the reason. The audit trail function will also allow the changes and clarifications made to be viewed.

9.9 Limitations of the Research Methods

This is an observational, prospective PASS designed to collect and assess real-world data on patients with FOP treated with palovarotene. Participants will be treated in accordance with usual medical practice during their participation in this registry study. Only relevant data collected as part of routine medical care will be captured using an eCRF by the Investigator (patient-reported questionnaires will be completed directly by the participant on paper). If some assessments are not routinely performed by the Investigator, he/she will not complete the corresponding sections in the eCRF. Therefore, some key data may be missing and the assessments performed and the data provided from different study sites may vary depending on local medical practice. This, however, is an inherent limitation to the observational design of this study, crucial in gathering real-world data on patients with FOP treated with palovarotene.

No formal statistical testing will be performed, and all the analyses will be primarily descriptive in nature.

9.10 Other Aspects

None.

9.11 Regulatory and Ethics Approval

The SP will ensure that all legal and regulatory aspects are covered, including submitting the protocol to the national CA in accordance with local regulatory requirements and obtaining any necessary approvals from the appropriate regulatory authorities prior to registry study initiation.

Before initiating the registry study, the Investigator/institution should have written and dated approval/favourable opinion from the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) for the registry study protocol/amendment(s), inform consent form, any ICF updates, participant recruitment procedures (e.g. advertisements), any written information to be provided to participants such as the Participant Information Sheet and a statement from the IEC/IRB that they comply with local requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

Any changes to the protocol after IEC/IRB approval will require a formal protocol amendment. Changes that do not affect participant safety or data integrity are classified as administrative changes and generally do not require ethics approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethics approval of administrative changes will be obtained if required by local/site IEC/IRB.

Any protocol amendments will be submitted to CA and IEC/IRBs according to local regulatory requirements.

9.12 Compliance with Good Pharmacoepidemiology Practice and Ethical Considerations

This study will be conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (Helsinki, 1964, and all subsequent amendments) [40], International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) – Good Clinical Practice (GCP) guidelines and the International Ethical Guidelines for Epidemiological Studies, Council for International Organizations of Medical Sciences (CIOMs) [41].

This study is non-interventional and falls outside the scope of European Commission European Union (EU) Directive 2001/20/EC [42] and EU Directive 2005/28/EC [43].

This study complies with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data [44].

This study will also follow the recommendations of the International Epidemiological Association Guidelines for the Proper Conduct in Epidemiologic Research (GEP) [45], the International Society for Pharmacoepidemiology (ISPE) Guidelines for GPP [39], the European Medicines Agency (EMA) Guideline on GVP [46, 47] (unless safety data collection and reporting is dictated by relevant local legislation in which case that must be followed instead) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [48]. The completed ENCePP Checklist for Study Protocols is provided in Appendix 1.

This study will also be conducted in compliance with the ENCePP Code of Conduct for Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies [49], Ipsen's Code of Ethical Conduct and any other applicable local regulations.

9.13 Informed Consent

Prior to the registry study entry, the Investigator (or a person designated by the Investigator) will explain the nature, purpose, benefits and risks of participation in the registry study to each participant, the participant's parents or the participant's legally authorised representative. Participants (if adult) or parents/legally authorised representatives (if not an adult) will be provided with a Participant Information Sheet containing information in readily understood language on the benefits and risks associated with participating in the registry study and will be given sufficient time to discuss any concerns and to consider their decision to participate. Signed written informed consent (and assent, if applicable) must be obtained prior to the participant entering the registry study and maintained during the registry study. The Sponsor will provide a template of the ICF.

The ICF and any participant recruitment materials will follow ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The final versions of the forms must be approved by the Sponsor and the IEC/IRB and must contain all the elements included in the template form, in language readily understood by the participant. Each participant's original ICF, personally signed and dated by the participant, the participant's parents or by the participant's legally authorised representative, and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled participants with a copy of their signed ICF.

The ICF may need to be revised during the course of the registry study if new information becomes available that may be relevant to the safety of the participant or as a result of protocol amendments. In this instance, approval should always be given by the IEC/IRB. It is the Investigator's responsibility to ensure that all participants subsequently entered into the registry study, as well as those currently in the registry study, sign the amended form. This is documented as previously described. Parents of participants (or participants' legally authorised representatives) and participants having completed the registry study should be informed of any new information that may impact on their welfare/wellbeing.

The Investigator should, with the consent/assent of the participant, the consent of the participant's parents or the participant's legally authorised representative, inform the participant's primary General Practitioner about their participation in the registry study.

For participants already enrolled in the registry study, eligibility must be reconfirmed and a new written informed consent must be obtained as per local regulations for any substantial protocol amendments before implementing them.

Participants already enrolled in the registry study that reach the legal age of consent as per the jurisdiction in which the study is taking place must provide a new written informed consent to remain in the study.

10 PROTECTION OF HUMAN PARTICIPANTS

10.1 Data Collection, Privacy and Confidentiality

After recruitment, each site will be assigned a unique identification number. At enrolment, each participant will be assigned a unique identification number by the Sponsor.

Data will be collected in an eCRF via the internet utilising a secured website. Data entry in the eCRF will be performed by the Investigator or by the designated person from his/her team in order to ensure confidentiality and security of the data.

Any data transmitted will be pseudonymised and will be identified only by the participant number. Only investigating sites will be able to link the numeric identifier to each participant's identity.

The participant must be informed that his/her personal registry study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent/assent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by the Sponsor's auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

In case of public data presentation or publication, personal identifiers of participants will not be used.

10.2 Data Protection

As the data controller (study Sponsor) is located in France, this study will be conducted in compliance with EU data protection requirements and in particular the EU General Data Protection Regulation 2016/679 [44].

In addition, the Sponsor will ensure that all applicable local regulatory requirements for data protection are met.

10.3 Insurance

Insurance may be contracted according to local regulatory requirements.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event

AE Definition
An AE is any untoward medical occurrence in a patient/participant, administered a medicinal product [palovarotene] and which does not necessarily have a causal relationship with this treatment. NOTE: An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not related to the medicinal product.

Events Meeting the AE Definition
Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. electrocardiograms, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e. not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. For studies involving marketed products in established indications: The signs, symptoms and/or clinical sequelae resulting from lack of effectiveness will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. The disease/disorder being studied or expected progression (e.g. flare-up), signs, or symptoms of the disease/disorder being studied, unless judged by the Investigator to be more severe than expected for the participant's condition. Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.1.2 Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalisation for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other important medical event Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Any radiological or clinical fracture must be reported as serious (seriousness criteria should be "important medical event" if no other seriousness criteria are present (e.g. hospitalisation)).
Is a suspected transmission of any infectious agent via an authorised medicinal product

11.1.3 Special Situations

A special situation (SS) is any incidence of drug exposure during pregnancy (i.e. drug exposure to a fetus in utero (whether the fetus is exposed via the mother taking the product)) or breastfeeding, overdose, off-label use, misuse, abuse, occupational exposure, medication errors or lack of therapeutic effectiveness whilst using the medicinal product. A "special situation" should be collected by the Investigator and reported to Ipsen whether or not these "special situations" are associated with an AE.

11.1.3.1 Pregnancy or Breastfeeding

Pregnancy

Palovarotene is highly teratogenic and must not be used by female participants who are or may become pregnant.

In accordance with the SmPC/PI, if pregnancy occurs in a female treated with palovarotene, treatment must be stopped and the participant should be referred to a physician for evaluation and advice. Females of child-bearing potential must use at least one highly effective method of contraception (e.g. intrauterine device (IUD)) or two effective methods (e.g. combined hormonal contraception in combination with another method of contraception such as a barrier method) during the course of the study.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the product has interfered with a contraceptive method. If pregnancy occurs whilst using the medicinal product, the outcome of the pregnancy will then need to be collected. This applies irrespective of whether the pregnancy is considered to be related to interference by the product with a contraceptive method.

Details of all pregnancies in female participants will be collected from the signing of the informed consent form (ICF) and the participant will be followed throughout her pregnancy and the health status of the baby will be verified up until one year of age.

Information regarding any pregnancies must be collected on the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable, including those with normal progress and through the Drug Exposure for Pregnancy Form (080479-FOR).

Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital abnormalities, ectopic pregnancy) are considered SAEs. If there is an abnormal pregnancy outcome or an AE is reported in the foetus/neonate/child following exposure to a marketed Ipsen product, attempt to follow-up until one year after delivery.

The Investigator must instruct all female participants to inform them immediately should they become pregnant whilst using palovarotene.

Reports of pregnancy must be reported to Ipsen within 24 hours of the Investigator's knowledge.

Breastfeeding

Breastfeeding is contraindicated to palovarotene use. No data are available on the presence of palovarotene in human milk, or the effects of palovarotene on the breastfed child, or on milk production. Because of the potential for serious adverse reactions from palovarotene in a breastfed child, lactating women should not breastfeed during treatment with palovarotene.

Any use of an Ipsen product during lactation/ breastfeeding must be collected on the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable.

11.1.3.2 Overdose, Off-label Use, Misuse, Abuse, Occupational Exposure, Medication Error and Lack of Effectiveness

Overdose

Any dose higher than the maximum recommended dose in local label/SmPC. For products which require gradual titration, any dose (initial or maintenance) which is higher than the recommended regime or labeling text will be assessed as 'overdose'. Overdose should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the SS is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in SS eCRF page. All overdoses should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable.

Off-label Use

Off-label use relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation.

Off-label use should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the SS is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in SS eCRF page. All off-label use should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable.

Misuse

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the Marketing Authorisation.

Misuse should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the SS is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in SS eCRF page. All misuse should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable.

Abuse

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Abuse should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the SS is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in SS eCRF page. All abuse should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and

Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable.

Occupational Exposure

Occupational exposure refers to the exposure to a medicinal product, as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release as finished product.

Occupational exposure should be reported in the Special Situations eCRF. All occupational exposure should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable.

Medication Error

Medication error is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the participant.

Medication error should be reported in the Special Situations eCRF whether or not it was associated with an AE. If the SS is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in SS eCRF page. All medication error should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable.

Lack of Effectiveness

Lack of effectiveness can be defined as the extent to which a drug does not achieve its intended effect in the usual clinical setting.

Lack of therapeutic effectiveness should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the SS is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in SS eCRF page. All lack of therapeutic effectiveness should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Special Situations Reporting Form for Non-Interventional Studies" (134232-FOR) if the electronic data collection tool is unavailable.

11.1.4 Adverse Events of Special Interest

Not applicable.

11.2 Time Period and Frequency for Collecting and Reporting of AE, SS and SAE Information

11.2.1 Collection of AEs/SAEs/Special Situations in the eCRF

The collection and reporting of AEs will follow regulations related to non-interventional studies.

All AEs, whether they are serious/nonserious or related/unrelated, and all special situations should be collected in the eCRF during the course of the registry study. Adverse events will be assessed according to incidence, intensity, causality, outcome, action taken and seriousness.

All AEs will be collected in the eCRF from the signing of the ICF until last palovarotene intake + 30 days.

11.2.2 Reporting of SAEs, Nonserious Adverse Drug Reactions and Special Situations to Sponsor Pharmacovigilance

Investigators must report to Ipsen Pharmacovigilance all the following events using the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable:

- All SAEs: related and non-related;
- All related nonserious AEs (adverse drug reactions);
- Any special situations (see definitions in Section 11.1.3).

Primary Data Collection Noninterventional Studies (NIS)		
Safety Event	**Collected on the eCRF**	**Reported on the « AE and SS NIS Form » (134232-FOR) to Ipsen Global Pharmacovigilance (if the electronic data collection tool is unavailable)**
Nonserious AE	All AEs related or not	Only the related AEs — within 7 calendar days of awareness
SAE	All SAEs related or not	All — within 24 hours of awareness
Pregnancy	All pregnancies	All — within 24 hours of awareness*
Special situations	All special situations related or not (regardless of whether associated with an AE)	All (regardless of whether associated with an AE) — within 7 calendar days of awareness

* Drug Exposure for Pregnancy Form (080479-FOR) should also be completed

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours (once known), as indicated below. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

All nonserious related AEs and special situations will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 7 calendar days (once known), as indicated below.

AE (related), SAE and Special Situation Reporting to the sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an AE (related), SAE or Special Situation to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper NIS AE form (134232-FOR) to report the SAE and pregnancy within 24 hours of awareness of the event and to report nonserious related AE and special situation (excluding pregnancy and special situations associated with an SAE) within 7 calendar days. The site will enter the AE (related), SAE and Special Situation data into the electronic system as soon as it becomes available again.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new AE (related), SAE or Special Situation from a study participant or receives updated data on a previously reported AE (related), SAE or Special Situation after the electronic data collection tool has been taken off-line, then the site can report this information on a paper NIS AE form (134232-FOR) (see next section).

• Contacts for AE (related), SAE or Special Situation reporting can be found on the NIS AE form (134232-FOR).

AE (related), SAE or Special Situation Reporting to sponsor via paper NIS AE form
• The site will email the NIS AE form (134232-FOR) to the sponsor if the electronic data collection tool is unavailable (**Email:** PPD). It must be retrospectively recorded as soon as the electronic data collection tool becomes available. • Contacts for AE (related), SAE or Special Situation reporting can be found on the NIS AE form (134232-FOR).

All AEs will be processed by Ipsen according to their relevant SOPs. This includes the follow up of AE reports with the Investigator, as required.

If an AE occurs with a "non-Ipsen product", the Investigator should consider informing the CA in the Member State where the event occurred or to the Marketing Authorisation Holder (MAH) of the suspected medicinal product, but not to both (to avoid duplicate reporting).

Mandatory Information for reporting an Adverse Event

The following information is the minimum that must be provided to Ipsen's Pharmacovigilance contact within 24 hours for a SAE and within 7 days for a nonserious related AE of awareness for each AE:

- Participant identifier;
- Product name;
- AE description including assessment of causal relationship and seriousness;
- Investigator name and contact details.

The additional information included in the AE report form must be provided to Ipsen as soon as it is available.

The Investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The Investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications. The Investigator should also provide the batch number and expiry date of the concerned product wherever possible.

11.3 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE/related AE reports are provided below.

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

AE/SAE/SS Recording

- When an AE/SAE/SS occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/SS information in the eCRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to sponsor pharmacovigilance in lieu of completion of the AE/SAE/SS CRF page.
- There may be instances when copies of medical records for certain cases are requested by sponsor pharmacovigilance. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor pharmacovigilance.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE/SS.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Other measures to evaluate AEs and SAEs may be utilized (e.g. National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor pharmacovigilance. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor pharmacovigilance.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

11.4 Follow-up of AEs and SAEs

After the initial AE/SAE/special situation report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs including SAEs (defined in Section 11.1) and special situations (defined in Section 11.1.3) will be followed until resolution, the event is otherwise explained, the participant is lost to follow-up or up to 30 days after last palovarotene intake. Further information on follow-up procedures is provided below.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the registry study or during a recognised follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

11.5 Regulatory Reporting Requirements for SAEs and Related AEs

- Prompt notification by the Investigator to the Sponsor of a SAE/related AE is essential so that legal obligations and ethical responsibilities towards the safety of participants are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of any medicinal product. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs and Investigators.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs) from the Sponsor will

review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

11.6 Expectedness of Events

The expectedness of an AE shall be determined by the Sponsor according to the SmPC or package insert for an authorised medicinal product that is being used according to the terms and conditions of the Marketing Authorisation. If the product has Marketing Authorisation in several countries with different SmPCs or package inserts, one will be selected by the study team as the reference document for assessing expectedness and agreed by the pharmacovigilance Ipsen representative.

The reference document for assessing expectedness of AEs/events in this study will be the current approved EU SmPC/PI for palovarotene.

11.7 Safety Review

The Sponsor will review safety data on an ongoing basis. There will be regular updates in the PBRERs and PSURs.

12 PLANS FOR DISSEMINATING AND COMMUNICATING REGISTRY STUDY RESULTS

12.1 Registry Study Reports

A final registry study report will be prepared once the registry study is complete.

Interim effectiveness and safety descriptive analyses are planned to be performed every 2 years. For the first interim analysis, a minimum of 30 participants will have to be enrolled.

12.2 Publication Policy

12.2.1 Ethical Obligation to Publish

Ipsen is committed to disclosing information about the studies it sponsors. Results may be communicated at scientific meetings and all reasonable efforts must be made to seek publication of key data in a peer-reviewed scientific journal.

As a minimum, summary results of the final data should be posted in an associated publicly available database.

12.2.2 Publications Steering Committee

There will be a Publications Steering Committee composed of external experts (clinicians and scientists) as well as patients and representatives of patient associations with the main objective of driving publications. The committee will meet annually. A charter has been developed to describe the roles and responsibilities of the committee.

The Steering Committee should discuss and agree the publication plan and appropriate authors to be invited for planned publications in advance. Where possible, all contributing Investigators should be acknowledged, together with any others who may have contributed, but not sufficiently to qualify for authorship.

The Steering Committee will also involve the Global Medical Publications and Communications (GMPC) Manager and other Ipsen personnel (e.g. Medical Director, Biometry lead), to plan publications and review data sharing requests.

12.2.3 Company-sponsored Publications

Specific publication concepts, including data to be covered, target congress/journal and proposed authors, should be discussed with the appropriate GMPC Manager, reviewed by the Publications Strategy Group, and incorporated in the relevant publication plan before initiation.

All company-sponsored publications arising from this registry study will be reviewed by relevant functions at Ipsen, coordinated by GMPC as per the applicable SOP. Requests and suggestions for changes will be discussed with all authors (and medical writer, if applicable). Resolution of scientific differences in the presentation or interpretation of the registry study findings will be conducted along principles of honest scientific debate and mediated by the lead author. Review comments must be answered before a final version for submission can be approved by the authors. All company-sponsored manuscripts should be published as immediate open access.

12.2.4 Non-company-sponsored Publications

For publications not sponsored by Ipsen, the Sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or manuscript before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. Ipsen will undertake to comment on the draft documents within the time period agreed in the contractual arrangements (different time periods are allowed according to the types of publication),

including registry study agreements, governing the relationship between Ipsen and authors (or the author's institution). Requested amendments should be carefully considered by the author(s), provided they do not alter the scientific value of the material. Where possible, non-company-sponsored manuscripts should be published as immediate open access.

12.2.5 Authorship

Selection of authors for scientific publications will follow the International Committee of Medical Journal Editors guidelines (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). Those named as authors, whether employed by Ipsen or an Ipsen affiliate, or external investigators, 'should have participated sufficiently in the work to take public responsibility for the content'. Time spent on authorship activities should not be reimbursed.

Authorship should be based on:

- Substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data; AND
- Drafting the article or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects for the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

All authors of a publication should meet all four criteria. Every author must agree to their inclusion in the list of authors. Professional medical writing support may be used.

12.2.6 Intellectual Property

If patentability would be adversely affected by data publication, publication will be delayed until (i) a patent application has been filed for the content of the publication in accordance with applicable provisions of the registry study agreement concerned, (ii) Ipsen consents to the publication, or (iii) after such a time as may be agreed in the contractual arrangements, including registry study agreements, governing the relationship between Ipsen and authors (or authors' institution) after receipt of the proposed publication by Ipsen, whichever of these provisos (i), (ii) or (iii) is satisfied first.

The author(s) undertake(s) to reasonably consider Ipsen's request for delay to the proposed publication should the sponsor reasonably deem it premature to publish the results obtained at the stage of the registry study concerned.

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LIST OF APPENDICES

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Appendix 1 EUROPEAN NETWORK OF CENTRES FOR PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE (ENCEPP) CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer "N/A" (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: An International Observational Registry Study to Further Describe Long-term Safety and Effectiveness of Palovarotene in Patients with Fibrodysplasia Ossificans Progressiva (FOP)

EU PAS Register® number: Pending **Study reference number:** CLIN-60120-453

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	N/A
1.1.4 Interim report(s)	☐	☒	☐	6
1.1.5 Registration in the EU PAS Register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6
Comments:				

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.4, 8.1
2.1.2 The objective(s) of the study?	☒	☐	☐	8.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.3
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	N/A
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	N/A
Comments: Analyses in this study are primarily descriptive in nature, no formal statistical testing will be performed, therefore hypotheses are not applicable.				

1 Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
2 Date from which the analytical dataset is completely available.

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g. rate, risk, prevalence)	☐	☐	☒	N/A
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	N/A
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11
Comments: Analyses in this study are primarily descriptive in nature, no formal statistical testing will be performed.				

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.2.3
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2.4
4.2.2 Age and sex	☒	☐	☐	9.2.1, 9.2.3
4.2.3 Country of origin	☐	☒	☐	9.2.1, 9.2.3
4.2.4 Disease/indication	☒	☐	☐	9.2.3
4.2.5 Duration of follow-up	☒	☐	☐	9.2.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1, 9.2.2
Comments: The registry study will be implemented in participating countries where palovarotene is marketed.				

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2.7
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	N/A
5.3 Is exposure classified according to time windows?	☐	☐	☒	N/A
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.2.7
5.5 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	N/A
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	N/A
Comments: This study will report the use of palovarotene in a real-world setting and is primarily descriptive in nature.				

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3, 9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	N/A
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	9.3
Comments:				

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	N/A
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	N/A
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	N/A
Comments:				

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.4
Comments:				

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4, 9.8.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4, 9.8.3
9.1.3 Covariates and other characteristics?	☐	☐	☒	N/A
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.2, 9.8.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2, 9.8.3
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle, etc.)	☐	☐	☒	N/A
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.7.3.3

Section 9: Data sources	Yes	No	N/A	Section Number
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7.3.7.1
9.3.3 Covariates and other characteristics?	☐	☐	☒	N/A
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.6.1
Comments:				

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.3
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.3
10.4 Are stratified analyses included?	☐	☐	☒	N/A
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.4
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	N/A
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.3.1
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	N/A
Comments:				

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☐	N/A
Comments:				

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				

Section 12: Limitations	Yes	No	N/A	Section Number
12.1.1 Selection bias?	☐	☐	☒	N/A
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	N/A
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.2.4, 9.5,
Comments:				

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.11
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	N/A
13.3 Have data protection requirements been described?	☒	☐	☐	10.1, 10.2
Comments:				

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5
Comments:				

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12
Comments:				

Name of the main author of the protocol:

Date: / /

Signature: _____

Appendix 2 CONVERSION TABLES OF PROMIS RAW SCORE INTO T-SCORES

Table 4 PROMIS T-Score Conversions for Adult Global Physical and Mental Health

Adult Global Physical Health			Adult 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

Table 5 PROMIS T-Score Conversions for Paediatric Global Health

Paediatric Self-Completed Total			Paediatric Proxy-Completed Total		
Raw Score	**T-Score**	**Standard Error**	**Raw Score**	**T-Score**	**Standard Error**
7	16	3.4	7	14.7	2.9
8	17.1	3.6	8	15.3	3.1
9	18.3	3.7	9	16	3.2
10	19.7	3.8	10	16.9	3.4
11	21.2	3.8	11	18.1	3.6
12	22.8	3.7	12	19.4	3.7
13	24.4	3.6	13	21	3.8
14	26.1	3.6	14	22.7	3.8
15	27.6	3.5	15	24.4	3.7
16	29.2	3.5	16	26.1	3.7
17	30.8	3.5	17	27.7	3.7
18	32.4	3.6	18	29.4	3.8
19	34	3.6	19	31.2	3.8
20	35.6	3.6	20	32.9	3.8
21	37.2	3.6	21	34.6	3.8
22	38.8	3.6	22	36.2	3.8
23	40.4	3.6	23	37.9	3.9
24	42.1	3.7	24	39.7	4
25	43.9	3.7	25	41.7	4
26	45.7	3.6	26	43.6	3.9
27	47.5	3.6	27	45.4	3.8
28	49.2	3.6	28	47.3	3.9
29	51.1	3.7	29	49.3	4.1
30	53.3	3.9	30	51.8	4.4
31	55.7	4.2	31	54.5	4.7
32	58.3	4.5	32	57.3	5
33	61.1	4.9	33	60.2	5.4
34	64.2	5.4	34	63.2	6
35	67.5	6.1	35	66.1	6.5

PROMIS=Patient-Reported Outcomes Measurement Information System

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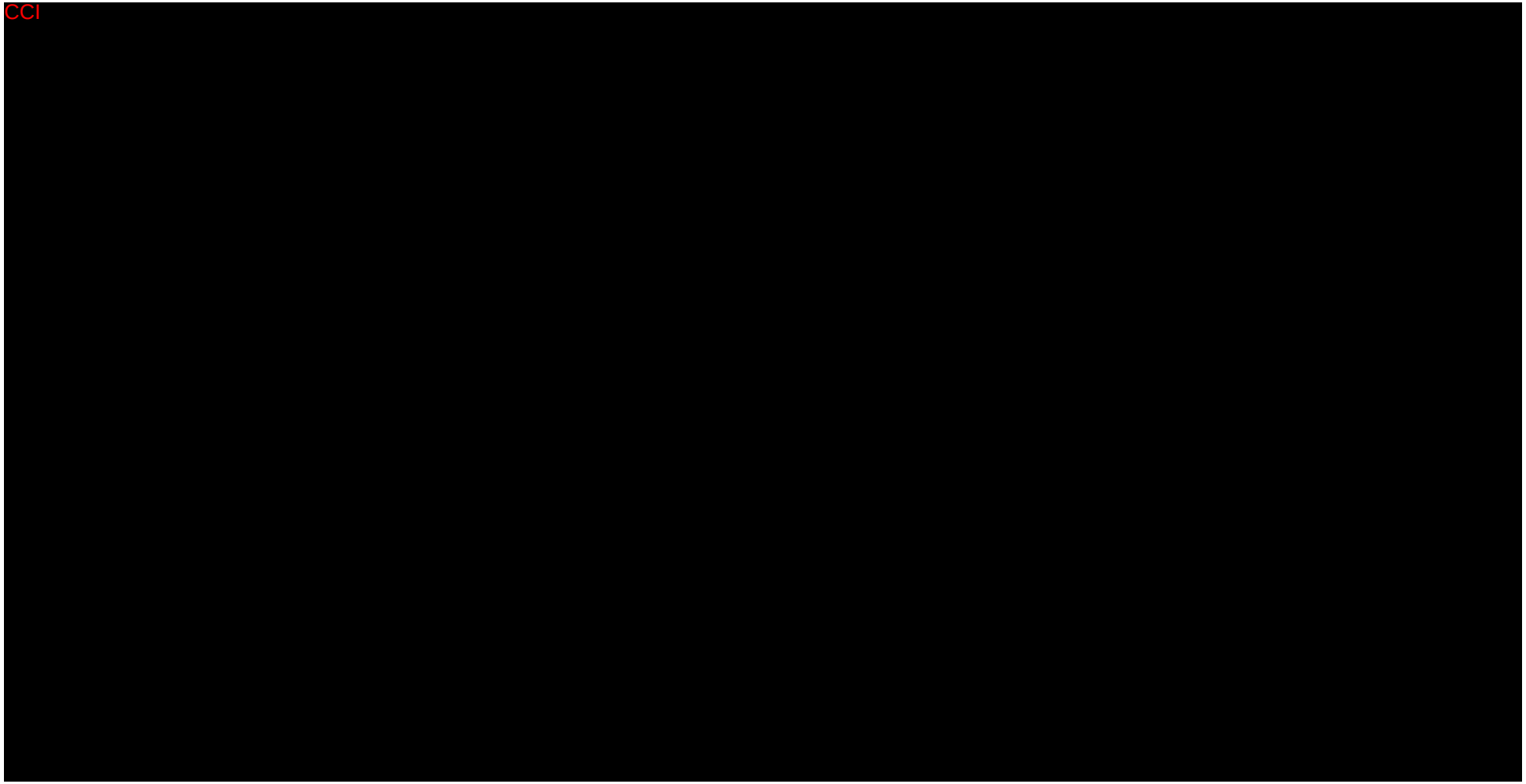

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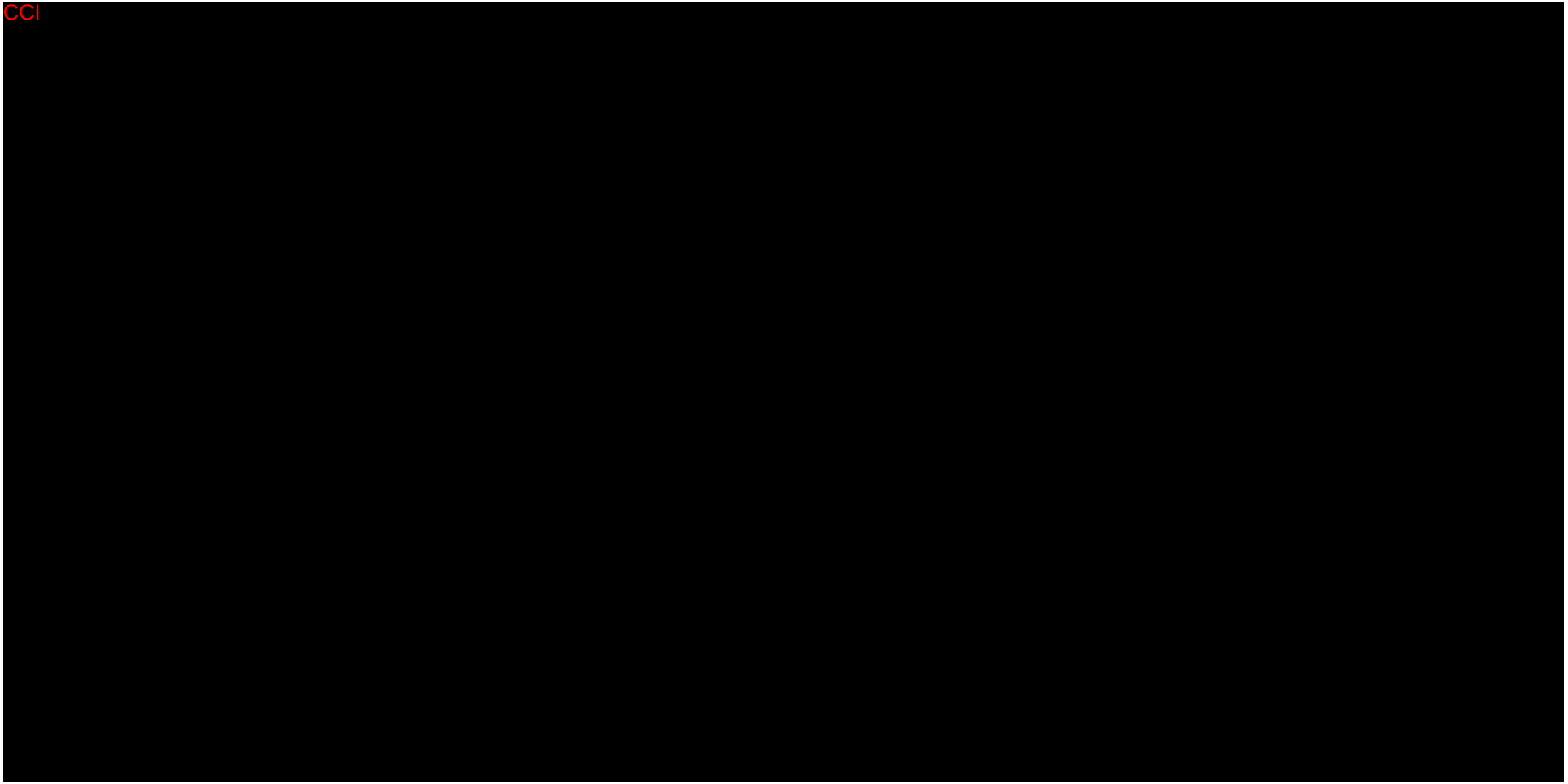

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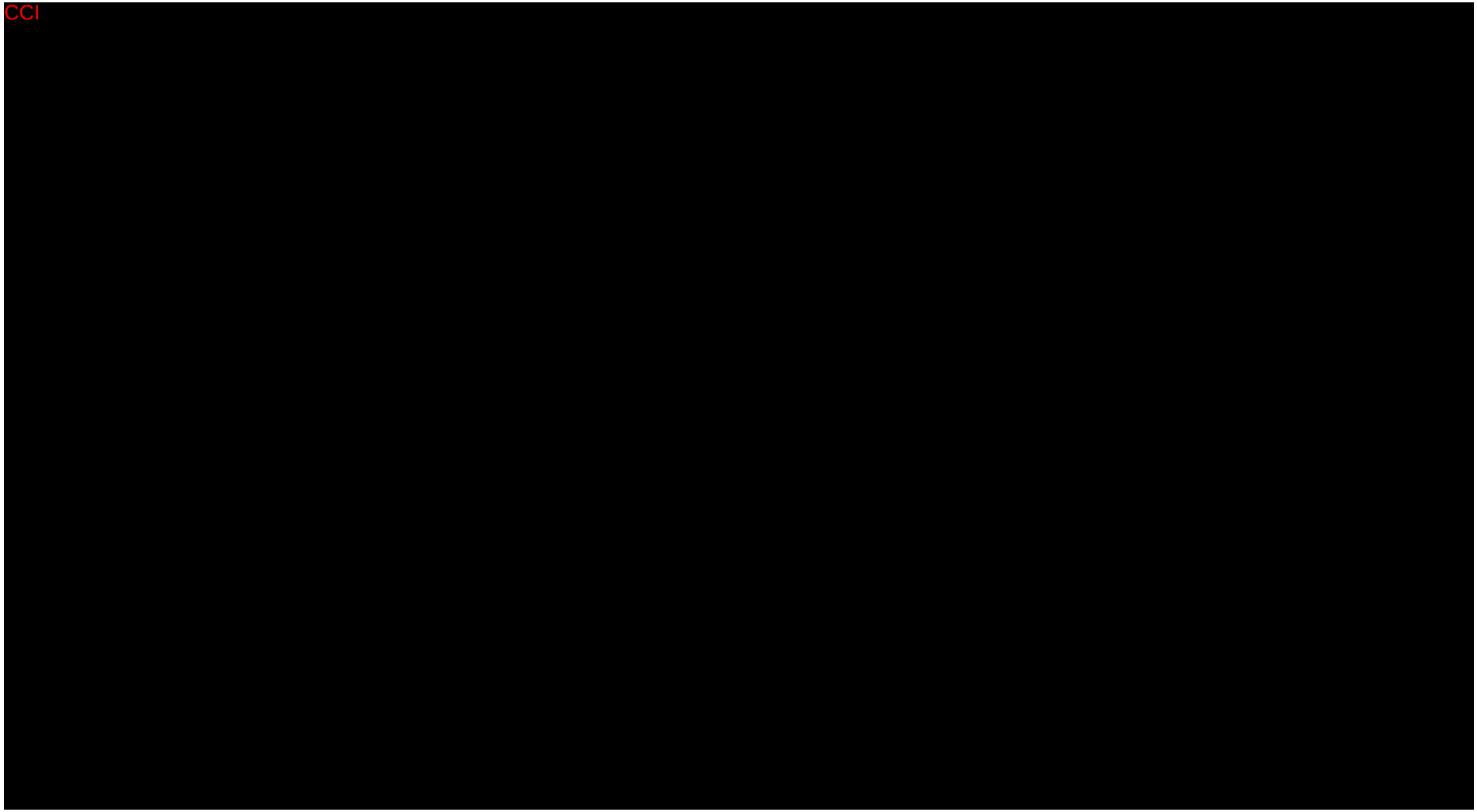

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