Clinical trial results:
A Phase 3, Efficacy and Safety Study of Oral Palovarotene for the Treatment of Fibrodysplasia Ossificans Progressiva (FOP)

Summary

EudraCT number	2017-002541-29
Trial protocol	GB SE ES DE FR NL IT Outside EU/EEA
Global end of trial date	07 September 2022

Results information

Result version number	v1
This version publication date	20 March 2023
First version publication date	20 March 2023

Trial information

Trial identification

Sponsor protocol code	PVO-1A-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03312634
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Clementia Pharmaceuticals Inc.
Sponsor organisation address	1000 De La Gauchetière West, Suite 1200 Montreal, Quebec, Canada, H3B 4W5
Public contact	Medical Director, Ipsen, clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen, clinical.trials@ipsen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001662-PIP01-14
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of palovarotene in decreasing heterotopic ossification (HO) in adult and pediatric participants with fibrodysplasia ossificans progressiva (FOP) as assessed by low-dose, whole body computed tomography (WBCT), excluding head, as compared to untreated participants from Clementia's FOP natural history study (Study PVO-1A-001).
To evaluate the safety of palovarotene in adult and pediatric participants with FOP.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, inclusive of any subsequent amendment(s), and that are consistent with the International Council for Harmonisation Good Clinical Practice (E6), EU Directive 2001/20/EC, United States Food and Drug Administration Code of Federal Regulations, and other applicable local regulatory requirements, which ever affords the greater participant protection.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Japan: 4
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 42
Worldwide total number of subjects	107
EEA total number of subjects	30

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	45
Adolescents (12-17 years)	35
Adults (18-64 years)	27
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase 3, open-label study was conducted in adult and pediatric participants with FOP at 16 centers in 11 countries (Argentina, Australia, Brazil, Canada, France, Italy, Japan, Spain, Sweden, the United Kingdom, and the US). Two other sites in Germany and Netherland were envisaged as participating countries but did not recruit any participants.

Pre-assignment

Screening details:

This study included 2 parts: Part A, the main part, and Part B, the 24-month extension. A total of 107 participants were enrolled and treated in this study. Data from participants in PVO-1A-001 were used as an external control for only primary endpoint of this study.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Palovarotene

Arm description:

Participants were administered 5 milligram (mg) palovarotene orally once daily up to 24 months. Participants with flare-up symptoms or traumatic events received palovarotene 20 mg once daily for 4 weeks after the flare-up confirmation by the Investigator. Followed by palovarotene 10 mg once daily for 8 weeks.

Arm type	Experimental
Investigational medicinal product name	Palovarotene
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Palovarotene 5 mg once daily up to 24 months. Palovarotene 20 mg once daily for 4 weeks then followed by 10 mg once daily for 8 weeks for participants with flare-up or traumatic symptoms. Flare-up dose was weight-adjusted for skeletally immature participants.

Number of subjects in period 1	Palovarotene
Started	107
Completed	48
Not completed	59
Consent withdrawn by subject	32
Physician decision	1
Adverse event, non-fatal	12
Roll over to other protocol	1
Sponsor request	2
Ended as per protocol amendment 5	11

Baseline characteristics

Reporting groups

Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	107	107	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	45	45	
Adolescents (12-17 years)	35	35	
Adults (18-64 years)	27	27	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	49	49	
Male	58	58	
Race Units: Subjects			
White	78	78	
Black or African American	1	1	
Asian	9	9	
American Indian or Alaska Native	0	0	
Native Hawaiian or other Pacific Islander	1	1	
Multiple	6	6	
Other	1	1	
Unknown	11	11	
Ethnicity Units: Subjects			
Hispanic Or Latino	19	19	
Not Hispanic Or Latino	77	77	
Not Reported	11	11	

End points

End points reporting groups

Reporting group title	Palovarotene

Reporting group description:

Participants were administered 5 milligram (mg) palovarotene orally once daily up to 24 months. Participants with flare-up symptoms or traumatic events received palovarotene 20 mg once daily for 4 weeks after the flare-up confirmation by the Investigator. Followed by palovarotene 10 mg once daily for 8 weeks.

Subject analysis set title	Palovarotene
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants were administered 5 mg palovarotene orally once daily up to 24 months. Participants with flare-up symptoms or traumatic events received palovarotene 20 mg once daily for 4 weeks after the flare-up confirmation by the Investigator. Followed by palovarotene 10 mg once daily for 8 weeks.

Subject analysis set title	Untreated (PVO-1A-001)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants from study PVO-1A-001 (NCT02322255) were included with FOP caused by the R206H mutation and with baseline data. Participants were not administered palovarotene and compared as external control.

Primary: Annualized New Heterotopic Ossification (HO)

End point title	Annualized New Heterotopic Ossification (HO)[1]

End point description:

The annualized new HO was assessed by low-dose, whole body computed tomography (WBCT), excluding head. The weighted linear mixed effect method without square-root transformation and negatives included was used for annualized new HO analysis. The Principal Full Analysis Set (FAS) included all enrolled participants in the Principal EP who had a baseline HO volume measurement and at least 1 post-baseline HO volume measurement in PVO-1A-301.For study PVO-1A-001, the Principal FAS included participants enrolled with available baseline and at least 1 post-baseline HO volume measurement. Study PVO-1A-001 was used as an external control. Only data from the participants analyzed were reported.

End point type	Primary

End point timeframe:

Baseline (within one month of screening/Day 1) and up to 24 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analysis was prespecified for this endpoint.

End point values	Palovarotene	Untreated (PVO-1A-001)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	101		
Units: cubic millimeters (mm^3)				
arithmetic mean (standard deviation)	9427.1 (± 3084.0)	23720.2 (± 4850.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Any New HO

End point title	Percentage of Participants With Any New HO

End point description:

The new HO was assessed by WBCT scan. The percentage of participants with any new HO (volume > 0 mm^3) were analyzed using the Bayesian distribution. The Principal FAS included all enrolled participants in the Principal EP who had a baseline HO volume measurement and at least 1 post-baseline HO volume measurement in study PVO-1A-301. Only data from the participants analyzed at Month 12 were reported.

End point type	Secondary

End point timeframe:

Month 12

End point values	Palovarotene			
Subject group type	Subject analysis set			
Number of subjects analysed	92			
Units: percentage of participants				
number (not applicable)	64.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Body Regions With New HO

End point title	Number of Participants With Body Regions With New HO

End point description:

The number of participants with any new HO (new HO > 0 mm^3) by number of body regions are reported. The presence of HO across various body regions was analyzed using WBCT scan. The Principal FAS included all enrolled participants in the Principal EP who had a baseline HO volume measurement and at least 1 post-baseline HO volume measurement in the study PVO-1A-301. Only data from the participants analyzed at Month 12 reported.

End point type	Secondary

End point timeframe:

Month 12

End point values	Palovarotene			
Subject group type	Subject analysis set			
Number of subjects analysed	92			
Units: percentage of participants				
number (not applicable)				
0 body region with new HO	33			
1 body region with new HO	28			
2 body regions with new HO	16			
3 body regions with new HO	9			
4 body regions with new HO	1			
5 body regions with new HO	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Flare-Ups

End point title	Percentage of Participants With Flare-Ups

End point description:

Flare-up as an event with one or more flare-up symptoms, and regardless of flare-up symptom onset. Flare-up was evaluated remotely, or by telephone or video-conferencing, unless the Investigator deemed that a site visit was necessary. The Principal SS included all enrolled participants in the Principal EP set (ie, participants with the R206H ACVR1 mutation) receiving at least 1 dose of palovarotene in study PVO-1A-301.

End point type	Secondary

End point timeframe:

Month 12

End point values	Palovarotene			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: percentage of participants				
number (not applicable)	64.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio of Flare-Up Per Participant-Month of Exposure Through Month 24

End point title	Ratio of Flare-Up Per Participant-Month of Exposure Through Month 24

End point description:

Flare-up as an event with one or more flare-up symptoms, and regardless of flare-up symptom onset. Flare-up was evaluated remotely, or by telephone or video-conferencing, unless the Investigator deemed that a site visit was necessary. The flare-up rate per participant-month exposure was analyzed using a negative binomial regression. The Principal SS included all enrolled participants in the Principal EP set (ie, participants with the R206H ACVR1 mutation) receiving at least 1 dose of palovarotene in the study PVO-1A-301.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to Month 24

End point values	Palovarotene			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: ratio of flare-up				
number (confidence interval 95%)	0.13 (0.09 to 0.17)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were collected from first date of palovarotene intake up to last dose of palovarotene, a maximum of approximately 49 months

Adverse event reporting additional description:

The Safety analysis set included all enrolled participants who received at least 1 dose of palovarotene in study PVO-1A-301.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Palovarotene

Reporting group description:

Participants were administered 5 mg palovarotene orally once daily up to 48 months. Participants with flare-up symptoms or traumatic events received palovarotene 20 mg once daily for 4 weeks after the flare-up confirmation by the Investigator. Followed by palovarotene 10 mg once daily for 8 weeks.

Serious adverse events	Palovarotene		
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 107 (51.40%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Coronavirus test positive			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic fracture			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Exposure to communicable disease			
subjects affected / exposed	3 / 107 (2.80%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Post procedural haematoma			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			

subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sensory loss			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superior mesenteric artery syndrome			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Anuria			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epiphyseal disorder			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Epiphyses premature fusion			
subjects affected / exposed	24 / 107 (22.43%)		
occurrences causally related to treatment / all	24 / 24		
deaths causally related to treatment / all	0 / 0		
Mobility decreased			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aneurysmal bone cyst			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial sepsis			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Cellulitis			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Klebsiella bacteraemia			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Mycoplasma infection			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 107 (2.80%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Corona virus infection			
subjects affected / exposed	15 / 107 (14.02%)		
occurrences causally related to treatment / all	0 / 15		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Malnutrition			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Palovarotene		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 107 (99.07%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Peripheral swelling			
subjects affected / exposed	9 / 107 (8.41%)		
occurrences (all)	10		
Oedema peripheral			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	11		
Pyrexia			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	9		
Swelling			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	8		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	8 / 107 (7.48%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	13 / 107 (12.15%) 14		
Epistaxis subjects affected / exposed occurrences (all)	9 / 107 (8.41%) 17		
Oropharyngeal pain subjects affected / exposed occurrences (all)	8 / 107 (7.48%) 8		
Psychiatric disorders Depressed mood subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 7		
Anxiety subjects affected / exposed occurrences (all)	7 / 107 (6.54%) 7		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 6		
Bone density decreased subjects affected / exposed occurrences (all)	16 / 107 (14.95%) 16		
Injury, poisoning and procedural complications Back injury subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 6		
Contusion subjects affected / exposed occurrences (all)	16 / 107 (14.95%) 20		
Fall subjects affected / exposed occurrences (all)	17 / 107 (15.89%) 27		
Skin abrasion subjects affected / exposed occurrences (all)	15 / 107 (14.02%) 24		

Head injury subjects affected / exposed occurrences (all) Joint injury subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 6 7 / 107 (6.54%) 9		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	21 / 107 (19.63%) 25		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) Hypoacusis subjects affected / exposed occurrences (all)	7 / 107 (6.54%) 8 9 / 107 (8.41%) 9		
Eye disorders Dry eye subjects affected / exposed occurrences (all)	18 / 107 (16.82%) 22		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Chapped lips subjects affected / exposed occurrences (all) Cheilitis subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Lip dry subjects affected / exposed occurrences (all)	10 / 107 (9.35%) 10 15 / 107 (14.02%) 18 10 / 107 (9.35%) 16 8 / 107 (7.48%) 10 52 / 107 (48.60%) 55		

Nausea			
subjects affected / exposed	16 / 107 (14.95%)		
occurrences (all)	18		
Vomiting			
subjects affected / exposed	16 / 107 (14.95%)		
occurrences (all)	23		
Constipation			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	38 / 107 (35.51%)		
occurrences (all)	51		
Dermatitis			
subjects affected / exposed	10 / 107 (9.35%)		
occurrences (all)	11		
Drug eruption			
subjects affected / exposed	34 / 107 (31.78%)		
occurrences (all)	64		
Dry skin			
subjects affected / exposed	76 / 107 (71.03%)		
occurrences (all)	175		
Eczema			
subjects affected / exposed	7 / 107 (6.54%)		
occurrences (all)	13		
Erythema			
subjects affected / exposed	26 / 107 (24.30%)		
occurrences (all)	36		
Pruritus			
subjects affected / exposed	31 / 107 (28.97%)		
occurrences (all)	45		
Pruritus generalised			
subjects affected / exposed	24 / 107 (22.43%)		
occurrences (all)	40		
Rash			

subjects affected / exposed	30 / 107 (28.04%)		
occurrences (all)	64		
Rash generalised			
subjects affected / exposed	9 / 107 (8.41%)		
occurrences (all)	14		
Rash maculo-papular			
subjects affected / exposed	7 / 107 (6.54%)		
occurrences (all)	11		
Skin exfoliation			
subjects affected / exposed	21 / 107 (19.63%)		
occurrences (all)	37		
Skin irritation			
subjects affected / exposed	11 / 107 (10.28%)		
occurrences (all)	15		
Acne			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Ingrowing nail			
subjects affected / exposed	8 / 107 (7.48%)		
occurrences (all)	13		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	45 / 107 (42.06%)		
occurrences (all)	84		
Back pain			
subjects affected / exposed	12 / 107 (11.21%)		
occurrences (all)	19		
Groin pain			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	9		
Musculoskeletal pain			
subjects affected / exposed	12 / 107 (11.21%)		
occurrences (all)	18		
Neck pain			

subjects affected / exposed	10 / 107 (9.35%)		
occurrences (all)	15		
Pain in extremity			
subjects affected / exposed	32 / 107 (29.91%)		
occurrences (all)	53		
Pain in jaw			
subjects affected / exposed	8 / 107 (7.48%)		
occurrences (all)	11		
Joint range of motion decreased			
subjects affected / exposed	8 / 107 (7.48%)		
occurrences (all)	13		
Joint swelling			
subjects affected / exposed	10 / 107 (9.35%)		
occurrences (all)	11		
Musculoskeletal chest pain			
subjects affected / exposed	7 / 107 (6.54%)		
occurrences (all)	9		
Myalgia			
subjects affected / exposed	7 / 107 (6.54%)		
occurrences (all)	9		
Infections and infestations			
Ear infection			
subjects affected / exposed	12 / 107 (11.21%)		
occurrences (all)	14		
Gastroenteritis			
subjects affected / exposed	8 / 107 (7.48%)		
occurrences (all)	10		
Nasopharyngitis			
subjects affected / exposed	20 / 107 (18.69%)		
occurrences (all)	42		
Paronychia			
subjects affected / exposed	17 / 107 (15.89%)		
occurrences (all)	28		
Upper respiratory tract infection			
subjects affected / exposed	28 / 107 (26.17%)		
occurrences (all)	41		

Urinary tract infection subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Otitis externa subjects affected / exposed occurrences (all) Otitis media subjects affected / exposed occurrences (all)	7 / 107 (6.54%) 9 13 / 107 (12.15%) 13 7 / 107 (6.54%) 7 10 / 107 (9.35%) 11		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	10 / 107 (9.35%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2018	Participants with other FOP variants associated with progressive HO were provided optimal treatment. Enrollment criteria for participants from Study PVO-1A-202 and PVO-1A-204 were specified. Inclusion criterion 6 was modified. Eligibility criterion for enrollment was specified. Primary efficacy analysis for participants with R206H mutation who were not treated with palovarotene were restricted. Primary efficacy endpoint and safety analyses summarization were specified. Baseline assessment of WBCT scan for participants who were enrolled from Phase 2 were specified. Additional clarifications were specified in-order to reduce participant burden. Schedule for linear growth measurements were specified. Blood pressure cuff measurement procedures were added. Pregnancy prevention measures and re-assessments were added to avoid risk of pregnancy. Criterion for serious adverse events follow-up was updated. Participants bone age assessment schedule specified. Additional high-level descriptions included for participant safety monitoring. Hearing tests added at Baseline and months 12 and 24. Daily assessment regarding onset of flare-up symptoms were included participant diary. Safety monitoring procedures clarified on termination of study. Sample determination for primary and secondary endpoints were updated.
19 February 2019	Schedule for clinical laboratory assessments during chronic treatment were changed. Schedule for clinical laboratory assessment, Columbia-Suicide Severity Rating scale, vital signs and body weight determination during flare-up cycle were changed. Specification for flare-up dosing added. Visit window for flare-up safety visit and final flare-up safety visit changed. Criteria for discontinuation of palovarotene added. Planned enrollment number was increased. Timings of the second and third interim analyses were changed. The frequency of pregnancy testing was emphasized.
29 October 2019	Extension period for Part B was added. Radiographic assessment of the knee and hand-wrist added in Part A and B. All scheduled assessments during chronic dosing to continue in Part B. Safety assessments schedule updated for Part A and B. Secondary objective for Part B was added. Statistical analyses modified for Part B. Dose modification details revised for partial or complete premature growth plate closure. Updated palovarotene, pharmacokinetics, efficacy, and safety findings from the FOP interventional trials.
04 February 2020	Additional columns for monthly remote pregnancy testing in Part B were updated. Specified that study continued despite crossing the futility boundary.
30 October 2020	Part C was added to ensure continued collection of safety data off treatment for participants <14 years of age and any participants who were skeletally immature at the time of their end-of-study visit. Assessments for spinal health carried out on low-dose WBCT scans collected in the study were added. Additional clarification updated for safety measures. Part C added for skeletally immature participants who had stopped taking medications for any reasons before completion of Part A/B. Assessment and duration for Part C were added. Secondary objective added and safety data were summarized for Part C. Editorial changes updated for clarification and consistent presentation. Vendor contact information revised.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported