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	v4 (current)
This version publication date	27 January 2024
First version publication date	20 March 2023
Version creation reason	• Correction of full data set Correction of full data set

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: 24
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Italy: 20
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: 27
Country: Number of subjects enrolled	United States: 84
Worldwide total number of subjects	221
EEA total number of subjects	59

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)	81
Adolescents (12-17 years)	65
Adults (18-64 years)	75
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 3 parts: Part A, the main part of the study, Part B, the 24-month extension and Part C, up to 2 year post last dose of study treatment follow-up. 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

Are arms mutually exclusive?	Yes
Arm title	Palovarotene

Arm description:

Participants were administered 5 milligram (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.

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 48 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.

Arm title	Untreated (PVO-1A-001)

Arm 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 in this study and only compared as external control.

Arm type	External control

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Palovarotene	Untreated (PVO-1A-001)
Started	107	114
Completed	49	33
Not completed	58	81
Physician decision	1	-
Enrolled in study at time of a flare-up	-	9
Enrolled into noninterventional study	-	5
Consent withdrawn by subject	31	9
Adverse event, non-fatal	11	-
Death	-	1
Sponsor request	2	-
Worsening clinical condition	-	1
Non-compliance	-	2
Participant did not want to travel	-	1
Unspecified	13	-
Enrolled in an interventional study	-	52
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Palovarotene
Reporting group description:	
Participants were administered 5 milligram (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.	
Reporting group title	Untreated (PVO-1A-001)
Reporting group 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 in this study and only compared as external control.	

Reporting group values	Palovarotene	Untreated (PVO-1A-001)	Total
Number of subjects	107	114	221
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	45	36	81
Adolescents (12-17 years)	35	30	65
Adults (18-64 years)	27	48	75
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	49	52	101
Male	58	62	120
Race Units: Subjects			
White	78	84	162
Black or African American	1	0	1
Asian	9	8	17
American Indian or Alaska Native	0	1	1
Native Hawaiian or other Pacific Islander	1	0	1
Multiple	6	2	8
Other	1	4	5
Unknown	11	15	26
Ethnicity Units: Subjects			
Hispanic Or Latino	19	23	42
Not Hispanic Or Latino	77	73	150
Not Reported	11	18	29

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 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.

Reporting group title	Untreated (PVO-1A-001)

Reporting group 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 in this study and only compared as external control.

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 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.

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.

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	Reporting group	Reporting group		
Number of subjects analysed	97	101		
Units: cubic millimeters (mm^3)				
arithmetic mean (standard error)	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. Results are presented for overall ITT period.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to end of 4-year follow-up period (approximately 57 months)

End point values	Palovarotene			
Subject group type	Subject analysis set			
Number of subjects analysed	97			
Units: percentage of participants				
number (not applicable)	83.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Body Regions With New HO

End point title	Number of Body Regions With New HO

End point description:

All participants were analyzed for number of body regions with any new HO (new HO > 0 mm^3). 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. Results are presented for overall ITT period. Only data from the participants analyzed were reported.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to end of 4-year follow-up period (approximately 57 months)

End point values	Palovarotene			
Subject group type	Subject analysis set			
Number of subjects analysed	81			
Units: body regions				
arithmetic mean (standard deviation)	3.0 (± 1.68)			

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. 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	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

End point title	Ratio of Flare-Up Per Participant-Month of Exposure[2]

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 Safety analysis set included all enrolled participants who received at least 1 dose of palovarotene in study PVO-1A-301. Results are presented for overall ITT period.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to end of 4-year follow-up period (approximately 57 months)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants treated with palovarotene were analyzed for this endpoint.

End point values	Palovarotene			
Subject group type	Reporting group			
Number of subjects analysed	107			
Units: ratio of flare-up				
arithmetic mean (standard deviation)	0.2 (± 0.40)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are collected from first date of palovarotene intake up to 4-year follow-up (approximately 57 months) for study PVO-1A-301. Adverse events (AEs) were collected from study day 1 up to approximately 37 months (PVO-1A-001).

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. The FAS included all participants in the Enrolled Analysis Set with FOP caused by the R206H mutation and who had baseline data in study PVO-1A-001. MedDRA version 21.0 for PVO-1A-001 study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Palovarotene 20/10 mg

Reporting group description:

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.

Reporting group title	Untreated (PVO-1A-001)

Reporting group 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 in this study and only compared as external control. While no pharmacological intervention was applied in this observational study, safety issues resulting only from any study-related procedure were recorded as AEs.

Reporting group title	Palovarotene 5 mg

Reporting group description:

Participants were administered 5 mg palovarotene orally once daily up to 48 months.

Serious adverse events	Palovarotene 20/10 mg	Untreated (PVO-1A-001)	Palovarotene 5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 81 (23.46%)	0 / 114 (0.00%)	34 / 107 (31.78%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Radius fracture			

subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic fracture			
subjects affected / exposed	1 / 81 (1.23%)	0 / 114 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exposure to communicable disease			
subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	3 / 107 (2.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			
subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 114 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Condition aggravated			

subjects affected / exposed	3 / 81 (3.70%)	0 / 114 (0.00%)	2 / 107 (1.87%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 81 (1.23%)	0 / 114 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiphyseal disorder			
subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiphyses premature fusion			
subjects affected / exposed	10 / 81 (12.35%)	0 / 114 (0.00%)	11 / 107 (10.28%)
occurrences causally related to treatment / all	10 / 10	0 / 0	11 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mobility decreased			

subjects affected / exposed	1 / 81 (1.23%)	0 / 114 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aneurysmal bone cyst			
subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 114 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 114 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mycoplasma infection			

subjects affected / exposed	1 / 81 (1.23%)	0 / 114 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 114 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corona virus infection			
subjects affected / exposed	2 / 81 (2.47%)	0 / 114 (0.00%)	10 / 107 (9.35%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	1 / 81 (1.23%)	0 / 114 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Palovarotene 20/10 mg	Untreated (PVO-1A-001)	Palovarotene 5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 81 (95.06%)	0 / 114 (0.00%)	105 / 107 (98.13%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 81 (6.17%)	0 / 114 (0.00%)	1 / 107 (0.93%)
occurrences (all)	5	0	1
Bone density decreased			
subjects affected / exposed	5 / 81 (6.17%)	0 / 114 (0.00%)	8 / 107 (7.48%)
occurrences (all)	5	0	8
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	6 / 81 (7.41%)	0 / 114 (0.00%)	9 / 107 (8.41%)
occurrences (all)	6	0	12
Fall			
subjects affected / exposed	7 / 81 (8.64%)	0 / 114 (0.00%)	10 / 107 (9.35%)
occurrences (all)	12	0	12
Skin abrasion			
subjects affected / exposed	9 / 81 (11.11%)	0 / 114 (0.00%)	8 / 107 (7.48%)
occurrences (all)	13	0	11
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 81 (8.64%)	0 / 114 (0.00%)	10 / 107 (9.35%)
occurrences (all)	7	0	13
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	6 / 81 (7.41%)	0 / 114 (0.00%)	3 / 107 (2.80%)
occurrences (all)	7	0	3
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 81 (1.23%)	0 / 114 (0.00%)	6 / 107 (5.61%)
occurrences (all)	1	0	7
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 81 (0.00%)	0 / 114 (0.00%)	7 / 107 (6.54%)
occurrences (all)	0	0	8
Eye disorders			
Dry eye			
subjects affected / exposed	11 / 81 (13.58%)	0 / 114 (0.00%)	8 / 107 (7.48%)
occurrences (all)	14	0	8
Gastrointestinal disorders			
Chapped lips			
subjects affected / exposed	10 / 81 (12.35%)	0 / 114 (0.00%)	6 / 107 (5.61%)
occurrences (all)	11	0	7
Cheilitis			
subjects affected / exposed	8 / 81 (9.88%)	0 / 114 (0.00%)	3 / 107 (2.80%)
occurrences (all)	13	0	3
Diarrhoea			

subjects affected / exposed	2 / 81 (2.47%)	0 / 114 (0.00%)	6 / 107 (5.61%)
occurrences (all)	2	0	6
Lip dry			
subjects affected / exposed	17 / 81 (20.99%)	0 / 114 (0.00%)	37 / 107 (34.58%)
occurrences (all)	17	0	38
Nausea			
subjects affected / exposed	3 / 81 (3.70%)	0 / 114 (0.00%)	9 / 107 (8.41%)
occurrences (all)	3	0	9
Vomiting			
subjects affected / exposed	5 / 81 (6.17%)	0 / 114 (0.00%)	11 / 107 (10.28%)
occurrences (all)	5	0	14
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 81 (6.17%)	0 / 114 (0.00%)	7 / 107 (6.54%)
occurrences (all)	5	0	7
Epistaxis			
subjects affected / exposed	3 / 81 (3.70%)	0 / 114 (0.00%)	6 / 107 (5.61%)
occurrences (all)	3	0	14
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	21 / 81 (25.93%)	0 / 114 (0.00%)	19 / 107 (17.76%)
occurrences (all)	28	0	23
Dermatitis			
subjects affected / exposed	7 / 81 (8.64%)	0 / 114 (0.00%)	3 / 107 (2.80%)
occurrences (all)	8	0	3
Drug eruption			
subjects affected / exposed	26 / 81 (32.10%)	0 / 114 (0.00%)	15 / 107 (14.02%)
occurrences (all)	40	0	24
Dry skin			
subjects affected / exposed	37 / 81 (45.68%)	0 / 114 (0.00%)	60 / 107 (56.07%)
occurrences (all)	77	0	95
Erythema			
subjects affected / exposed	16 / 81 (19.75%)	0 / 114 (0.00%)	11 / 107 (10.28%)
occurrences (all)	21	0	15
Pruritus			

subjects affected / exposed	14 / 81 (17.28%)	0 / 114 (0.00%)	19 / 107 (17.76%)
occurrences (all)	16	0	29
Pruritus generalised			
subjects affected / exposed	11 / 81 (13.58%)	0 / 114 (0.00%)	16 / 107 (14.95%)
occurrences (all)	19	0	21
Rash			
subjects affected / exposed	11 / 81 (13.58%)	0 / 114 (0.00%)	25 / 107 (23.36%)
occurrences (all)	22	0	40
Rash generalised			
subjects affected / exposed	4 / 81 (4.94%)	0 / 114 (0.00%)	6 / 107 (5.61%)
occurrences (all)	5	0	9
Skin exfoliation			
subjects affected / exposed	11 / 81 (13.58%)	0 / 114 (0.00%)	11 / 107 (10.28%)
occurrences (all)	23	0	14
Skin irritation			
subjects affected / exposed	5 / 81 (6.17%)	0 / 114 (0.00%)	6 / 107 (5.61%)
occurrences (all)	6	0	9
Ingrowing nail			
subjects affected / exposed	4 / 81 (4.94%)	0 / 114 (0.00%)	6 / 107 (5.61%)
occurrences (all)	5	0	8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 81 (18.52%)	0 / 114 (0.00%)	32 / 107 (29.91%)
occurrences (all)	24	0	49
Back pain			
subjects affected / exposed	3 / 81 (3.70%)	0 / 114 (0.00%)	8 / 107 (7.48%)
occurrences (all)	4	0	13
Musculoskeletal pain			
subjects affected / exposed	5 / 81 (6.17%)	0 / 114 (0.00%)	7 / 107 (6.54%)
occurrences (all)	5	0	9
Neck pain			
subjects affected / exposed	6 / 81 (7.41%)	0 / 114 (0.00%)	6 / 107 (5.61%)
occurrences (all)	9	0	6
Pain in extremity			

subjects affected / exposed	9 / 81 (11.11%)	0 / 114 (0.00%)	21 / 107 (19.63%)
occurrences (all)	13	0	33
Pain in jaw			
subjects affected / exposed	2 / 81 (2.47%)	0 / 114 (0.00%)	6 / 107 (5.61%)
occurrences (all)	2	0	7
Joint range of motion decreased			
subjects affected / exposed	3 / 81 (3.70%)	0 / 114 (0.00%)	6 / 107 (5.61%)
occurrences (all)	3	0	9
Myalgia			
subjects affected / exposed	2 / 81 (2.47%)	0 / 114 (0.00%)	6 / 107 (5.61%)
occurrences (all)	2	0	6
Infections and infestations			
Ear infection			
subjects affected / exposed	6 / 81 (7.41%)	0 / 114 (0.00%)	5 / 107 (4.67%)
occurrences (all)	7	0	5
Gastroenteritis			
subjects affected / exposed	2 / 81 (2.47%)	0 / 114 (0.00%)	6 / 107 (5.61%)
occurrences (all)	2	0	8
Nasopharyngitis			
subjects affected / exposed	9 / 81 (11.11%)	0 / 114 (0.00%)	14 / 107 (13.08%)
occurrences (all)	12	0	26
Paronychia			
subjects affected / exposed	10 / 81 (12.35%)	0 / 114 (0.00%)	9 / 107 (8.41%)
occurrences (all)	15	0	13
Upper respiratory tract infection			
subjects affected / exposed	6 / 81 (7.41%)	0 / 114 (0.00%)	23 / 107 (21.50%)
occurrences (all)	7	0	30
Urinary tract infection			
subjects affected / exposed	1 / 81 (1.23%)	0 / 114 (0.00%)	6 / 107 (5.61%)
occurrences (all)	2	0	6
Influenza			
subjects affected / exposed	4 / 81 (4.94%)	0 / 114 (0.00%)	7 / 107 (6.54%)
occurrences (all)	4	0	7
Otitis media			
subjects affected / exposed	3 / 81 (3.70%)	0 / 114 (0.00%)	6 / 107 (5.61%)
occurrences (all)	3	0	7

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? Yes

Date	Interruption	Restart date
04 December 2019	As of 04 December 2019, all participants <14 years of age were required to interrupt study drug due to a partial clinical hold placed on the palovarotene clinical development program by the FDA. On 24-Jan-2020, treatment was temporarily halted in all participants equal to and over the age of 14 years in the palovarotene FOP trials when the futility boundary was crossed at an interim analysis in the Phase 3 PVO-1A-301 study. After post-hoc analyses showed that the pre-specified analyses may have skewed and negatively affected the results, dosing was re-initiated only in participants 14 years and above that were able and willing to re-start treatment (in the context of COVID-19 conditions, starting 30 April 2020).	30 April 2020

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A valid comparison of AEs from observational study (PVO-1A-001) was not made since AEs were only captured as related to study procedures.

Notes: