Clinical trial results:
A Phase 2, Open-Label Extension, Efficacy and Safety Study of a RAR-Specific Agonist (Palovarotene) in the Treatment of Preosseous Flare-ups in Subjects with Fibrodysplasia Ossificans Progressiva (FOP)

Summary

EudraCT number	2014-002496-28
Trial protocol	GB Outside EU/EEA
Global end of trial date	20 September 2022

Results information

Result version number	v3 (current)
This version publication date	27 June 2024
First version publication date	05 April 2023
Version creation reason	• New data added to full data set New data entry

Trial information

Trial identification

Sponsor protocol code	PVO-1A-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02279095
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Clementia Pharmaceuticals Inc.
Sponsor organisation address	1000 De La Gauchetière, 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	20 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A: To evaluate the long-term safety and efficacy of prior palovarotene treatment in fibrodysplasia ossificans progressiva (FOP) participants who completed study PVO-1A-201. To evaluate the safety and efficacy of palovarotene in FOP participants who experienced up to 2, new, distinct flare-ups.

Parts B and C: To evaluate the safety and efficacy of different palovarotene dosing regimens in participants with FOP.

Part D: To implement safety measures based on data monitoring committee recommendations in order to ensure that assessments of safety continue for up to 2 years post last dose of study treatment for skeletally immature participants.

Protection of trial subjects:

The clinical 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), European Union Directive 2001/20/EC, United States Food and Drug Administration (FDA) 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	09 October 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 38
Worldwide total number of subjects	58
EEA total number of subjects	11

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)	7
Adolescents (12-17 years)	15
Adults (18-64 years)	36
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase 2, open-label extension of study PVO1A201 was conducted in participants with FOP at 8 investigational sites in 5 countries. Participants enrolled in France were followed under a country-specific study PVO-1A-204 (as Part B of the study) as requested by French regulatory authorities. Overall, 58 participants were enrolled in this study.

Pre-assignment

Screening details:

Study divided into 4 parts: Part A (participants who completed PVO-1A-201 study were enrolled and followed for 3 years), Part B (participants from Part A and 18 new adult participants were followed for 2 years), Part C (participants from Part B were followed for 2 years) and Part D (treatment discontinued participants were followed for 2 years).

Period 1

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

Arms

Arm title	All Participants

Arm description:

Participants who completed PVO-1A-201 study were followed for up to 36 months in Part A. Eligible participants with a flare-up received palovarotene 10 milligram (mg) capsule orally daily for 2 weeks followed by 5 mg daily for 4 weeks during the flare-up component of Part A.
In Part B, eligible participants from Part A and participants from the new Adult Cohort received chronic treatment with palovarotene 5 mg daily for up to 24 months. Participants with flare-ups received palovarotene 20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks.
In Part C, eligible participants received chronic treatment of palovarotene 5mg daily for up to 36 months. Participants with flare-ups received palovarotene 20mg daily for 4 weeks followed by 10mg daily for 8 weeks. For skeletal immature participants, the exposure-equivalent dose was determined based on weight.
In Part D, no study drug was administered.
Participants in Part C/D were followed for up to an additional 48 months.

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:

Participants received palovarotene 10 mg daily for 2 weeks followed by 5 mg daily for 4 weeks (or exposure-equivalent doses based on weight) during flare-ups, totaling 6 weeks of treatment in Part A of the study.
Participants received palovarotene 20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks (or exposure-equivalent doses based on weight) during flare-ups, totaling 12 weeks of treatment in Part B of the study.
Participants received palovarotene 20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks (or exposure-equivalent doses based on weight) during flare-ups, totaling 12 weeks of treatment in Part C of the study.
Participants in new Adult Cohort received 5 mg daily for 24 months during Parts B and C.
No study drug was administered in Part D of the study.
Palovarotene was to be taken orally with food at approximately the same time each day.

Number of subjects in period 1	All Participants
Started	40
Entered Part A	40
Completed Part A	13 [1]
Entered Part B	54
Completed Part B	16 [2]
Entered Part C	48
Completed Part C	29
Entered Part D	2 [3]
Completed	39
Not completed	19
Consent withdrawn by subject	8
Non-Compliance	1
Adverse event, non-fatal	2
Unspecified	7
Lost to follow-up	1
Joined	18
New Adult Cohort into Part B	18

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only 13 participants completed Part A of the study.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only 16 participants completed Part B of the study.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only 2 participants entered Part D of the study.

Baseline characteristics

Reporting groups	
Reporting group title	All Participants

Reporting group description:

Participants who completed PVO-1A-201 study were followed for up to 36 months in Part A. Eligible participants with a flare-up received palovarotene 10 milligram (mg) capsule orally daily for 2 weeks followed by 5 mg daily for 4 weeks during the flare-up component of Part A.
In Part B, eligible participants from Part A and participants from the new Adult Cohort received chronic treatment with palovarotene 5 mg daily for up to 24 months. Participants with flare-ups received palovarotene 20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks.
In Part C, eligible participants received chronic treatment of palovarotene 5mg daily for up to 36 months. Participants with flare-ups received palovarotene 20mg daily for 4 weeks followed by 10mg daily for 8 weeks. For skeletal immature participants, the exposure-equivalent dose was determined based on weight.
In Part D, no study drug was administered.
Participants in Part C/D were followed for up to an additional 48 months.

Reporting group values	All Participants	Total	
Number of subjects	58	58	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	21.0		
standard deviation	± 9.27	-	
Gender categorical Units: Subjects			
Female	32	32	
Male	26	26	

End points

End points reporting groups

Reporting group title	All Participants

Reporting group description:

Participants who completed PVO-1A-201 study were followed for up to 36 months in Part A. Eligible participants with a flare-up received palovarotene 10 milligram (mg) capsule orally daily for 2 weeks followed by 5 mg daily for 4 weeks during the flare-up component of Part A.
In Part B, eligible participants from Part A and participants from the new Adult Cohort received chronic treatment with palovarotene 5 mg daily for up to 24 months. Participants with flare-ups received palovarotene 20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks.
In Part C, eligible participants received chronic treatment of palovarotene 5mg daily for up to 36 months. Participants with flare-ups received palovarotene 20mg daily for 4 weeks followed by 10mg daily for 8 weeks. For skeletal immature participants, the exposure-equivalent dose was determined based on weight.
In Part D, no study drug was administered.
Participants in Part C/D were followed for up to an additional 48 months.

Subject analysis set title	Part A: Palovarotene 10/5 mg - Flare-up
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received palovarotene 10 mg for 14 days followed by 5 mg for 28 days during flare-ups (10/5-mg regimen). The participants were followed for an additional 42 days without treatment.

Subject analysis set title	Part B: Flare-up Combined
Subject analysis set type	Per protocol

Subject analysis set description:

Skeletally mature participants received palovarotene 20 mg for 28 days followed by 10 mg for 56 days during flare-ups (20/10-mg regimen) and 5 mg daily when not taking flare-up dosing. Treatment may have been extended if the flare-up was ongoing and continued until the flare-up resolved. Dosing was extended in 4-week intervals and was based on clinical signs and symptoms as assessed by the Investigator.

Subject analysis set title	Part B: Palovarotene - All Treated Flare-ups
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received palovarotene 20 mg for 28 days followed by 10 mg for 56 days during flare-ups and with 5 mg daily when not taking flare-up dosing for skeletally mature participants. Participants were treated for all flare-ups. The change in new HO total volume was compared to baseline where the baseline value was performed prior to the initiation of non-flare-up based dosing (in Part B).

Subject analysis set title	Part B: Untreated/Undertreated Flare-ups
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received palovarotene 20 mg for 28 days followed by 10 mg for 56 days during flare-ups and with 5 mg daily when not taking flare-up dosing for skeletally mature participants. At least 1 flare-up was untreated/undertreated. The change in new HO total volume was compared to baseline where the baseline value was performed prior to the initiation of non-flare-up based dosing (in Part B).

Subject analysis set title	Part B: No Flare-ups
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received palovarotene 5 mg daily. No flare-ups were reported. The change in new HO total volume was compared to baseline where the baseline value was performed prior to the initiation of non-flare-up based dosing (in Part B).

Subject analysis set title	Part B: All Treated and No Flare-ups Combined
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received palovarotene 20 mg for 28 days followed by 10 mg for 56 days during flare-ups and with 5 mg daily when not taking flare-up dosing for skeletally mature participants. This group pools data from all participants irrespective of treatment. The change in new HO total volume was compared to baseline where the baseline value was performed prior to the initiation of non-flare-up based dosing (in Part B).

Subject analysis set title	Part C: Palovarotene - All Treated Flare-ups
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received palovarotene 5 mg daily and 20 mg for 28 days followed by 10 mg for 56 days during flare-ups. Participants were treated for all flare-ups. The change in new HO total volume was compared to baseline where the baseline value was performed prior to the initiation of non-flare-up based dosing (in Part B
or Part C).

Subject analysis set title	Part C: Untreated/Undertreated Flare-ups
Subject analysis set type	Per protocol

Subject analysis set description:

At least 1 flare-up was untreated/undertreated. The change in new HO total volume was compared to baseline where the baseline value was performed prior to the initiation of non-flare-up based dosing (in Part B or Part C).

Subject analysis set title	Part C: No Flare-ups
Subject analysis set type	Per protocol

Subject analysis set description:

No flare-ups were reported. The change in new HO total volume was compared to baseline where the baseline value was performed prior to the initiation of non-flare-up based dosing (in Part B or Part C).

Subject analysis set title	Part C: All Treated and No Flare-ups Combined
Subject analysis set type	Per protocol

Subject analysis set description:

This group pools data from all participants irrespective of treatment. The change in new HO total volume was compared to baseline where the baseline value was performed prior to the initiation of non-flare-up based dosing (in Part B or Part C).

Subject analysis set title	Part B: Whole Body Computed Tomography (WBCT) Population
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received palovarotene 20 mg for 28 days followed by 10 mg for 56 days during flare-ups (20/10-mg regimen) and with 5 mg daily when not taking flare-up dosing for skeletally mature participants. Treatment may have been extended if the flare-up was ongoing and continued until the flare-up resolved. Dosing was extended in 4-week intervals and was based on clinical signs and symptoms as assessed by the Investigator. The WBCT Population included participants who received chronic dosing and had Baseline and at least 1 post-baseline scan.

Primary: Parts A and B: Percentage of Flare-ups With No New Heterotopic Ossification (HO) at Week 12

End point title	Parts A and B: Percentage of Flare-ups With No New Heterotopic Ossification (HO) at Week 12[1]

End point description:

A responder was defined as a participant with no or minimal new HO at original flare-up site compared with baseline (pre-dose data from PVO-1A-201 study). Minimal new HO was defined as new HO with an HO score <=3 in both the anterior/posterior (AP) and lateral projections (or if 1 view is non-interpretable or non-evaluable, then remaining evaluable view was used). The HO score ranged from 0 to 6 where, 0 = no HO and 6 = single contiguous HO with longest dimension >2 diameters of reference normotopic bone in any projection. Highest HO score from 2 projections was used. Part A: Efficacy population included all participants in the treated population who had an evaluable Week 6 or Week 12 image [computed tomography (CT) scan or plain radiograph]. Part B: Flare-up population included all participants in the treated population who took at least 1 dose of palovarotene during flare-up based treatment in Part B. Here, n = total number of flare-ups at specific timepoint.

End point type	Primary

End point timeframe:

Baseline and Week 12

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: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	Part A: Palovarotene 10/5 mg - Flare-up	Part B: Flare-up Combined		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	35		
Units: percentage of flare-ups				
number (not applicable)				
Week 12 (n= 28, 51)	64.3	72.5		

Statistical analyses

No statistical analyses for this end point

Primary: Parts B and C: Annualized Change in New HO Volume

End point title	Parts B and C: Annualized Change in New HO Volume[2]

End point description:

The annualized change in new HO volume was assessed by low-dose whole body computed tomography (WBCT) scan, excluding head. The Full Analysis Set (FAS) included all enrolled participants having a baseline HO volume measurement and at least 1 post-baseline HO volume measurement in the PVO-1A-202 study. Results are presented for overall intent to treat (ITT) period.

End point type	Primary

End point timeframe:

From Baseline (Day 1) up to end of 2 year follow-up period, approximately a maximum of 96 months

Notes:

[2] - 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: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	Part B: Palovarotene - All Treated Flare-ups	Part B: Untreated/Undertreated Flare-ups	Part B: No Flare-ups	Part B: All Treated and No Flare-ups Combined
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	24	9	13
Units: cubic millimeter (mm^3)/year				
arithmetic mean (standard deviation)	-3464.0 (± 5081.50)	29522.8 (± 89408.15)	25041.1 (± 58529.79)	16270.3 (± 49777.40)

End point values	Part C: Palovarotene - All Treated Flare-ups	Part C: Untreated/Undertreated Flare-ups	Part C: No Flare-ups	Part C: All Treated and No Flare-ups Combined
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	6	7	15
Units: cubic millimeter (mm^3)/year				
arithmetic mean (standard deviation)	-10343.4 (± 18007.89)	52291.4 (± 86019.62)	30530.9 (± 51800.47)	8731.3 (± 41924.30)

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A and B: Percentage of Participants Across the 7 HO Scores at Month 12 of Part A; and Weeks 6 and 12 for Part B

End point title	Parts A and B: Percentage of Participants Across the 7 HO Scores at Month 12 of Part A; and Weeks 6 and 12 for Part B

End point description:

The HO score ranged from 0 to 6 where, 0 = no HO and 6 = single contiguous HO with longest dimension >2 diameters of the reference normotopic bone in any projection. Highest HO score from 2 projections was used. No participants were analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Part A: Baseline (pre-dose data from Study PVO-1A-201 for follow-up component and flare-up screening/Day 1 for flare-up component) and Month 12
Part B: Baseline (flare-up screening/baseline) and Weeks 6 and 12

End point values	Part A: Palovarotene 10/5 mg - Flare-up	Part B: Flare-up Combined		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[3]	0[4]		
Units: percentage of participants				
number (not applicable)				

Notes:

[3] - No participants were analyzed for this endpoint.

[4] - No participants were analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A and B: Volume of New Heterotopic Bone Formed at Month 12

End point title	Parts A and B: Volume of New Heterotopic Bone Formed at Month 12

End point description:

Plain radiographs were utilized in Part A of the study. The interpretation of radiographs was to have documented the absence or presence of new HO at the flare-up site compared with the baseline assessment, and the volume of new HO if present. Low-dose CT scans were utilized in Part B of the study. Low-dose, flare-up site-specific CT scan was used as the primary imaging assessment of HO for flare-ups and low-dose, WBCT scans were used as the primary imaging assessment for total body HO in those participants receiving chronic treatment. Part A: The Efficacy population included all participants in the treated population who had an evaluable Week 6 or Week 12 image (CT scan or plain radiograph). Part B: The Flare-up population included all participants in the treated population who took at least 1 dose of palovarotene during flare-up based treatment in Part B.

End point type	Secondary

End point timeframe:

Month 12

End point values	Part A: Palovarotene 10/5 mg - Flare-up	Part B: Flare-up Combined		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[5]	48[6]		
Units: mm^3				
arithmetic mean (standard deviation)	2310 (± 4739)	4818 (± 17349)		

Notes:

[5] - Total number of flare-ups.

[6] - Total number of flare-ups.

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A and B: Number of Flare-ups With Significant Abnormalities in Cartilage, Bone, Angiogenesis, and Inflammation Biomarkers at Week 12

End point title	Parts A and B: Number of Flare-ups With Significant Abnormalities in Cartilage, Bone, Angiogenesis, and Inflammation Biomarkers at Week 12

End point description:

Blood and urine samples for cartilage, bone, angiogenesis, and inflammation biomarkers were evaluated during Part A and Part B of the study. Bone and cartilage biomarkers included: osteocalcin, bone-specific alkaline phosphatase (ALP), procollagen type 1-N-terminal pro-peptide (PINP), cartilage-derived (CD) retinoic acid protein, procollagen type 1-C-terminal pro-peptide (PICP), and C-terminal telopeptide. Angiogenesis included urinary basic fibroblast growth factor. Inflammation included erythrocyte sedimentation rate, C-reactive protein, Interleukin(IL)-6, IL-1 beta, tumor necrosis factor (TNF)-alpha, creatine phosphokinase, and lactate dehydrogenase. Based on emerging data from studies PVO-1A-001, PVO-1A-201, and Parts A and B of PVO-1A-202, biomarkers were removed from the evaluation during Part C. Part A: The Efficacy population; Part B: Flare-up population. Here, n = total number of flare-ups at specific timepoint and 99999 = not evaluated at specific timepoint.

End point type	Secondary

End point timeframe:

Part A and B: At Week 12

End point values	Part A: Palovarotene 10/5 mg - Flare-up	Part B: Flare-up Combined		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[7]	46[8]		
Units: number of flare-ups				
Parts A and B: Osteocalcin (n= 25, 44)	10	6		
Parts A and B: Bone-specific ALP (n= 26, 45)	2	2		
Parts A and B: P1NP (n= 25, 44)	10	2		

Parts A and B: CD retinoic acid protein (n=26, 45)	4	6		
Parts A and B: P1CP (n= 26, 46)	3	2		
Parts A and B: C-terminal telopeptide (n= 26, 46)	0	1		
Parts A and B: Urinary basic FGF (n= 23, 43)	6	5		
Parts A and B: ESR (n= 26, 43)	4	0		
Parts A and B: C-reactive protein (n= 24, 43)	6	5		
Parts A and B: IL-6 (n= 26, 46)	0	3		
Parts A and B: IL-1 beta (n= 26, 46)	5	5		
Parts A and B: TNF-alpha (n= 26, 46)	3	1		
Parts A and B: Creatine kinase (n= 24, 43)	1	3		
Parts A and B: Lactate dehydrogenase (n= 24, 42)	4	1		

Notes:

[7] - Total number of flare-ups.

[8] - Total number of flare-ups.

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A and B: Change From Baseline in Active Range of Motion (ROM) at Flare-up Site at Week 12

End point title	Parts A and B: Change From Baseline in Active Range of Motion (ROM) at Flare-up Site at Week 12

End point description:

Active range of motion was assessed by goniometer in Part A and B of the study. Measurements were performed by trained and qualified study personnel (eg, physiotherapist) in order to standardize the performance of procedures and minimize variability. Flare-ups at the primary joint was expressed as percent of normal arc of motion. Based on the change in the schedule for flare-up based assessments, active range of motion was not assessed during Part C. Baseline was defined as pre-dose data from Study PVO-1A-201 for follow-up component and flare-up screening/Day 1 for flare-up component for Part A and flare-up screening/baseline for Part B. Part A: Efficacy population included all participants in the treated population who had an evaluable Week 6 or Week 12 image (CT scan or plain radiograph). Part B: Flare-up population included all participants in the treated population who took at least 1 dose of palovarotene during flare-up based treatment in Part B.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Part A: Palovarotene 10/5 mg - Flare-up	Part B: Flare-up Combined		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27[9]	49[10]		
Units: percent of normal total arc of motion				
arithmetic mean (standard deviation)	-6.16 (± 14.362)	-0.49 (± 18.096)		

Notes:

[9] - Total number of flare-ups.

[10] - Total number of flare-ups.

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Baseline in ROM at Week 12

End point title	Part B: Change From Baseline in ROM at Week 12

End point description:

The ROM was assessed by the Investigator using Cumulative Analogue Joint Involvement Scale (CAJIS) for participants in Part B. It includes 12 joints (shoulder, elbow, wrist, hip, knee, and ankle on both the right and left sides), and 3 body regions (jaw, cervical spine [neck], and thoracic/lumbar spine). Each joint/region was assessed as: 0=uninvolved; 1=partially involved; and 2=completely ankylosed. The total score range is 0 (no involvement) to 30 (maximally involved). Baseline was flare-up screening/Baseline. Flare-up population. The data collected for flare-ups used each flare-up as unit of analysis rather than each participant. Additionally, a study participant may have not had any flare-ups whereas another participant may have had multiple flare-ups (note, the number of flare-ups can be larger than the number of participants OR it can be smaller OR it can match, by chance).

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Part B: Flare-up Combined			
Subject group type	Subject analysis set			
Number of subjects analysed	51[11]			
Units: units on a scale				
arithmetic mean (standard deviation)	0.3 (± 1.80)			

Notes:

[11] - Total number of flare-ups.

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: Change From Baseline in ROM at Months 6, 12, 18, 24, 30, 36, 42, and 48

End point title	Part C: Change From Baseline in ROM at Months 6, 12, 18, 24, 30, 36, 42, and 48

End point description:

The ROM was assessed by the Investigator using CAJIS for participants in Part C. It includes 12 joints (shoulder, elbow, wrist, hip, knee, and ankle on both the right and left sides), and 3 body regions (jaw, cervical spine [neck], and thoracic/lumbar spine). Each joint/region was assessed as: 0=uninvolved; 1=partially involved; and 2=completely ankylosed. The total score range is 0 (no involvement) to 30 (maximally involved). Baseline was chronic Day 1. The Safety analysis set included all enrolled participants who received at least 1 dose of palovarotene in the PVO-1A-202 study. Here, n= total number of participants analyzed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline and Months 6, 12, 18, 24, 30, 36, 42, and 48

End point values	Part C: Palovarotene - All Treated Flare-ups			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 6 (n=31)	0.2 (± 1.58)			
Month 12 (n=34)	0.6 (± 1.76)			
Month 18 (n=26)	0.9 (± 1.73)			
Month 24 (n=31)	1.3 (± 2.74)			
Month 30 (n=26)	1.5 (± 2.79)			
Month 36 (n=25)	1.6 (± 3.38)			
Month 42 (n=23)	1.6 (± 3.03)			
Month 48 (n=5)	3.0 (± 2.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Participant and Investigator Global Assessment of Movement at Week 12

End point title	Part B: Participant and Investigator Global Assessment of Movement at Week 12

End point description:

Participants/Investigators assessed how the flare-up was affecting movement (better, same, slightly worse, moderately worse, or severely worse movement) compared with baseline. Based on the change in the schedule for flare-up based assessments. The Flare-up population. The data collected for flare-ups used each flare-up as the unit of analysis rather than each participant. Additionally, a study participant may have not had any flare-ups whereas another participant may have had multiple flare-ups (note, the number of flare-ups can be larger than the number of participants OR it can be smaller OR it can match, by chance). Here, n = total number of flareups at specific timepoint. PA = Participant assessment and IA = Investigator assessment.

End point type	Secondary

End point timeframe:

Week 12

End point values	Part B: Flare-up Combined			
Subject group type	Subject analysis set			
Number of subjects analysed	51[12]			
Units: number of flare-ups				
number (not applicable)				
PA: New HO - Better movement (n= 14)	5			
PA: New HO - Same movement (n= 14)	3			
PA: New HO - Slightly worse movement (n= 14)	2			
PA: New HO - Moderately worse movement (n= 14)	2			
PA: New HO - Severely worse movement (n= 14)	2			
PA: No new HO - Better movement (n= 37)	11			
PA: No new HO - Same movement (n= 37)	20			
PA: No new HO - Slightly worse movement (n= 37)	5			
PA: No new HO - Moderately worse movement (n= 37)	1			
PA: No new HO - Severely worse movement (n= 37)	0			
IA: New HO - Better movement (n= 14)	5			
IA: New HO - Same movement (n= 14)	3			
IA: New HO - Slightly worse movement (n= 14)	2			
IA: New HO - Moderately worse movement (n= 14)	3			
IA: New HO - Severely worse movement (n= 14)	1			
IA: No new HO - Better movement (n= 37)	1			
IA: No new HO - Same movement (n= 37)	29			
IA: No new HO - Slightly worse movement (n= 37)	6			
IA: No new HO - Moderately worse movement (n= 37)	1			
IA: No new HO - Severely worse movement (n= 37)	0			

Notes:

[12] - Total number of flare-ups.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change From Baseline in Numeric Rating Scale (NRS) Pain and Swelling or Faces Pain Scale-Revised (FPS-R) at Weeks 2, 4, 6, 9, and 12

End point title	Part A: Change From Baseline in Numeric Rating Scale (NRS) Pain and Swelling or Faces Pain Scale-Revised (FPS-R) at Weeks 2, 4, 6, 9, and 12

End point description:

The NRSs for pain and swelling were used in Part A of the study to evaluate the effect of palovarotene on pain and swelling at the flare-up site. Flare-up pain was rated on a scale ranging from 0 (no pain or swelling) to 10 (worst pain or swelling ever experienced). For children less than 8 years old, pain was

rated using the FPS-R, which ranges from 0 to 10 in 2-point increments where 0 = no pain and 10 = very much pain. Flare-up swelling was rated on a scale from 0 to 10 where 0 = no swelling and 10 = worst swelling ever experienced. Higher scores indicate worst quality of life for all scales. Baseline was pre-dose data from PVO-1A-201 study/flare-up screening/Day 1. The Efficacy population. The data collected for flare-ups used each flare-up as unit of analysis rather than each participant. Additionally, a study participant may have not had any flare-ups whereas another participant may have had multiple flare-ups. Here, n = total number of flare-ups at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 4, 6, 9, and 12

End point values	Part A: Palovarotene 10/5 mg - Flare-up			
Subject group type	Subject analysis set			
Number of subjects analysed	28[13]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 2: Pain (n= 27)	-1.4 (± 2.22)			
Week 4: Pain (n= 28)	-2.1 (± 2.27)			
Week 6: Pain (n= 28)	-2.6 (± 2.71)			
Week 9: Pain (n= 18)	-2.9 (± 2.97)			
Week 12: Pain (n= 28)	-2.6 (± 2.85)			
Week 2: Swelling (n= 27)	-1.7 (± 1.83)			
Week 4: Swelling (n= 28)	-2.3 (± 2.31)			
Week 6: Swelling (n= 28)	-2.4 (± 2.38)			
Week 9: Swelling (n= 18)	-2.7 (± 2.47)			
Week 12: Swelling (n= 28)	-2.9 (± 2.46)			

Notes:

[13] - Total number of flare-ups.

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A and B: Change From Baseline in Physical Function at Weeks 2, 4, 6, 9, and 12 of Part A; and Weeks 4, 8, and 12 of Part B

End point title	Parts A and B: Change From Baseline in Physical Function at Weeks 2, 4, 6, 9, and 12 of Part A; and Weeks 4, 8, and 12 of Part B

End point description:

Effect of palovarotene on physical function was determined using Fibrodysplasia Ossificans Progressiva-Physical Function Questionnaire (FOP-PFQ). Questionnaire consisted of 28 items ranging from 1 (not able to do) to 5 (with no trouble; without help or assistive device). Total score range from 28 to 140. Lower scores denoted more difficulty with items categorized into upper extremity and mobility sections. Part A: Efficacy population. Part B: Flare-up population. Data collected for flare-ups used each flare-up as unit of analysis rather than each participant. A study participant may have not had any flare-ups whereas another participant may have had multiple flare-ups(number of flare-ups can be larger than number of participants OR it can be smaller OR it can match, by chance). Here, n= total number of flare-ups at specific timepoint and 99999= not evaluated at specific timepoint.

End point type	Secondary

End point timeframe:

Part A: Baseline and Weeks 2, 4, 6, 9, and 12; and Part B: Baseline and Weeks 4, 8, and 12

End point values	Part A: Palovarotene 10/5 mg - Flare-up	Part B: Flare-up Combined		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28[14]	52[15]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Parts A and B: Week 2 (n= 27, 0)	-0.97 (± 4.939)	99999 (± 99999)		
Parts A and B: Week 4 (n= 28, 47)	0.38 (± 4.746)	-1.23 (± 4.453)		
Parts A and B: Week 6 (n= 28, 0)	0.21 (± 6.501)	99999 (± 99999)		
Parts A and B: Week 8 (n= 0, 50)	99999 (± 99999)	0.88 (± 9.357)		
Parts A and B: Week 9 (n= 18, 0)	0.76 (± 6.054)	99999 (± 99999)		
Parts A and B: Week 12 (n= 28, 50)	0.69 (± 6.604)	0.17 (± 6.893)		

Notes:

[14] - Total number of flare-ups.

[15] - Total number of flare-ups.

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: Change From Baseline in Physical Function at Months 6, 12, 18, 24, 30, 36, 42, and 48

End point title	Part C: Change From Baseline in Physical Function at Months 6, 12, 18, 24, 30, 36, 42, and 48

End point description:

The effect of palovarotene on physical function was determined using FOP-PFQ. The questionnaire consisted of 28 items ranging from 1 (not able to do) to 5 (with no trouble; without help or assistive device). Total score range from 28 to 140. Lower scores denoted more difficulty, with items categorized into upper extremity and mobility sections. The Safety analysis set included all enrolled participants who received at least 1 dose of palovarotene in the PVO-1A-202 study. Here, n= number of participants analyzed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline and Months 6, 12, 18, 24, 30, 36, 42, and 48

End point values	Part C: Palovarotene - All Treated Flare-ups			
Subject group type	Subject analysis set			
Number of subjects analysed	36			
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 6 (n= 36)	1.8 (± 6.36)			

Month 12 (n= 36)	1.8 (± 9.81)			
Month 18 (n= 31)	4.0 (± 9.49)			
Month 24 (n= 31)	7.5 (± 14.00)			
Month 30 (n= 27)	8.2 (± 13.45)			
Month 36 (n= 24)	9.8 (± 14.11)			
Month 42 (n= 22)	7.0 (± 13.14)			
Month 48 (n= 7)	8.3 (± 7.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A and B: Change From Baseline in Physical and Mental Health at Weeks 2, 4, 6, 9, and 12 of Part A; and Weeks 4, 8, and 12 of Part B

End point title	Parts A and B: Change From Baseline in Physical and Mental Health at Weeks 2, 4, 6, 9, and 12 of Part A; and Weeks 4, 8, and 12 of Part B

End point description:

The patient reported outcomes measurement information system (PROMIS) global health scale was administered to evaluate the effect of palovarotene on physical and mental health in participants >=15 years of age and mental health in participants <15 years of age, age-appropriate forms of the PROMIS global health scales were administered. A T-score of 50 is normal and increments of 10 are +/- standard deviation away from the norm. A T-score <50 indicates worse health, while a T-score >50 indicates better health. Higher values (positive changes) indicate better health. Part A: The Efficacy population; and Part B: The Flare-up population. Data collected for flare-ups used each flare-up as unit of analysis rather than each participant. Here, n= total number of flare-ups at specific timepoint and 99999 = not evaluated at specific timepoint. AFPH = Adult Form, Physical Health; AFMH = Adult Form, Mental Health; PFH = Pediatric Form, Health.

End point type	Secondary

End point timeframe:

Part A: Baseline and Weeks 2, 4, 6, 9, and 12; and Part B: Baseline and Weeks 4, 8, and 12

End point values	Part A: Palovarotene 10/5 mg - Flare-up	Part B: Flare-up Combined		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28[16]	52[17]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Parts A and B: AFPH - Week 2 (n= 25, 0)	3.26 (± 4.819)	99999 (± 99999)		
Parts A and B: AFPH - Week 4 (n= 26, 32)	2.14 (± 3.976)	0.2 (± 3.17)		
Parts A and B: AFPH - Week 6 (n= 26, 0)	1.78 (± 3.735)	99999 (± 99999)		
Parts A and B: AFPH - Week 8 (n= 0, 33)	99999 (± 99999)	0.3 (± 3.33)		
Parts A and B: AFPH - Week 9 (n= 16, 0)	2.87 (± 5.352)	99999 (± 99999)		
Parts A and B: AFPH - Week 12 (n= 26, 34)	3.22 (± 4.855)	0.6 (± 3.79)		

Parts A and B: AFMH - Week 2 (n= 25, 0)	1.00 (± 4.667)	99999 (± 99999)		
Parts A and B: AFMH - Week 4 (n= 26, 32)	0.39 (± 3.264)	1.0 (± 8.05)		
Parts A and B: AFMH - Week 6 (n= 26, 0)	1.03 (± 3.122)	99999 (± 99999)		
Parts A and B: AFMH - Week 8 (n= 0, 33)	99999 (± 99999)	-0.3 (± 7.47)		
Parts A and B: AFMH - Week 9 (n= 16, 0)	-0.16 (± 4.422)	99999 (± 99999)		
Parts A and B: AFMH - Week 12 (n= 26, 34)	0.99 (± 2.915)	0.2 (± 7.63)		
Parts A and B: PFH - Week 2 (n= 2, 0)	-0.05 (± 2.475)	99999 (± 99999)		
Parts A and B: PFH - Week 4 (n= 2, 16)	1.70 (± 4.950)	0.7 (± 4.77)		
Parts A and B: PFH - Week 6 (n= 2, 0)	5.25 (± 4.596)	99999 (± 99999)		
Parts A and B: PFH - Week 8 (n= 0, 16)	99999 (± 99999)	-2.5 (± 6.32)		
Parts A and B: PFH - Week 9 (n= 2, 0)	0.85 (± 1.202)	99999 (± 99999)		
Parts A and B: PFH - Week 12 (n= 2, 16)	0.85 (± 3.748)	0.4 (± 5.65)		

Notes:

[16] - Total number of flare-ups.

[17] - Total number of flare-ups.

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: Change From Baseline in Physical and Mental Health at Months 6, 12, 18, 24, 30, 36, 42, and 48

End point title	Part C: Change From Baseline in Physical and Mental Health at Months 6, 12, 18, 24, 30, 36, 42, and 48

End point description:

The PROMIS global health scale was administered to evaluate the effect of palovarotene on physical and mental health in participants >=15 years of age and mental health in participants <15 years of age, age-appropriate forms of the PROMIS global health scales were administered. A T-score of 50 is normal and increments of 10 are +/- standard deviation away from the norm. A T-score <50 indicates worse health, while a T-score >50 indicates better health. Higher values (positive changes) indicate better health. The Safety analysis set included all enrolled participants who received at least 1 dose of palovarotene in the PVO-1A-202 study. Here, n= number of participants analyzed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline and Months 6, 12, 18, 24, 30, 36, 42, and 48

End point values	Part C: Palovarotene - All Treated Flare-ups			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: units on a scale				
arithmetic mean (standard deviation)				
AFPH - Month 6 (n= 30)	-0.2 (± 5.59)			

AFPH - Month 12 (n= 30)	0.6 (± 6.04)			
AFPH - Month 18 (n= 24)	-0.1 (± 5.30)			
AFPH - Month 24 (n= 25)	-1.1 (± 7.10)			
AFPH - Month 30 (n= 22)	0.1 (± 4.46)			
AFPH - Month 36 (n= 22)	-1.1 (± 5.97)			
AFPH - Month 42 (n= 21)	-1.8 (± 6.55)			
AFPH - Month 48 (n= 5)	-1.6 (± 3.02)			
AFMH - Month 6 (n= 30)	-2.2 (± 6.49)			
AFMH - Month 12 (n= 30)	-0.0 (± 3.96)			
AFMH - Month 18 (n= 25)	-0.8 (± 5.04)			
AFMH - Month 24 (n= 25)	-2.5 (± 5.96)			
AFMH - Month 30 (n= 22)	-3.0 (± 5.30)			
AFMH - Month 36 (n= 22)	-1.5 (± 4.95)			
AFMH - Month 42 (n= 21)	-2.9 (± 6.24)			
AFMH - Month 48 (n= 6)	-5.2 (± 7.83)			
PFH - Month 6 (n= 4)	3.8 (± 2.91)			
PFH - Month 12 (n= 3)	1.7 (± 1.65)			
PFH - Month 18 (n= 3)	4.7 (± 1.93)			
PFH - Month 24 (n= 3)	3.4 (± 4.63)			
PFH - Month 30 (n= 3)	4.6 (± 2.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A and B: Number of Any Assistive Devices and Adaptations by FOP Participants at Weeks 6 and 12 of Part A; and Week 12 of Part B

End point title	Parts A and B: Number of Any Assistive Devices and Adaptations by FOP Participants at Weeks 6 and 12 of Part A; and Week 12 of Part B

End point description:

The FOP assistive devices and adaptations questionnaire was used in Part A and Part B of the study. Assistive devices and adaptations were grouped into the following categories: mobility aids, care attendants, eating tools, personal care tools/aids, bathroom aids and devices, bedroom aids and devices, home adaptations, work environment adaptations, technology adaptations, sports and recreation adaptations, school, and medical therapies for daily living. When a flare-up did not use an assistive device or adaptation or considered the assistive device or adaptation not applicable, 0 was imputed for analysis. Part A: The Efficacy population; Part B: The Flare-up population. Here, n = total number of flare-ups at specific timepoint and 99999 = not evaluated at specific timepoint.

End point type	Secondary

End point timeframe:

Part A: Weeks 6 and 12; and Part B: Week 12

End point values	Part A: Palovarotene 10/5 mg - Flare-up	Part B: Flare-up Combined		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28[18]	52[19]		
Units: devices adaptations				
arithmetic mean (standard deviation)				
Parts A and B: Week 6 (n= 28, 0)	12.9 (± 11.52)	99999 (± 99999)		
Parts A and B: Week 12 (n= 28, 52)	14.3 (± 12.39)	13.2 (± 10.50)		

Notes:

[18] - Total number of flare-ups.

[19] - Total number of flare-ups.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percentage of Responders at Week 12

End point title	Part A: Percentage of Responders at Week 12

End point description:

A responder was defined as a participant with no or minimal new HO at original flare-up site compared with baseline (flare-up screening/Day 1). Minimal new HO was defined as new HO with an HO score <=3 in both the AP and lateral projections (or if 1 view is non-interpretable or non-evaluable, then remaining evaluable view was used). The HO score ranged from 0 to 6 where, 0 = no HO and 6 = single contiguous HO with longest dimension >2 diameters of the reference normotopic bone in any projection. Highest HO score from 2 projections was used. Results from the Primary Read reviews are presented. The Efficacy population included all participants in the treated population who had an evaluable Week 6 or Week 12 image (CT scan or plain radiograph). Here, n = total number of flare-ups at specific timepoint.

End point type	Secondary

End point timeframe:

Week 12

End point values	Part A: Palovarotene 10/5 mg - Flare-up			
Subject group type	Subject analysis set			
Number of subjects analysed	28[20]			
Units: percentage of participants				
number (not applicable)	64.3			

Notes:

[20] - Total number of flare-ups.

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A and B: Change From Baseline in Amount of Bone Formation Biomarker at Weeks 6 and 12 of Part A; and Week 12 of Part B

End point title	Parts A and B: Change From Baseline in Amount of Bone

	Formation Biomarker at Weeks 6 and 12 of Part A; and Week 12 of Part B

End point description:

The bone formation was measured by PINP biomarker. Baseline was defined as flare-up screening/Day 1. Part A: The Efficacy population included all participants in the treated population who had an evaluable Week 6 or Week 12 image (CT scan or plain radiograph). Part B: The Flare-up population included all participants in the treated population who took at least 1 dose of palovarotene during flare-up based treatment in Part B. Here, n = total number of flare-ups at specific timepoint and 99999 = not evaluated at specific timepoint.

End point type	Secondary

End point timeframe:

Part A: Baseline and Weeks 6 and 12; and Part B: Baseline and Week 12

End point values	Part A: Palovarotene 10/5 mg - Flare-up	Part B: Flare-up Combined		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28[21]	52[22]		
Units: microgram per liter				
arithmetic mean (standard deviation)				
Part A: Week 6 (18, 0)	38.755 (± 50.547)	99999 (± 99999)		
Parts A and B: Week 12 (18, 39)	54.592 (± 140.540)	70.916 (± 130.608)		

Notes:

[21] - Total number of flare-ups.

[22] - Total number of flare-ups.

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A and B: Number of Flare-ups With Soft Tissue Swelling and/or Cartilage Formation at Weeks 6 and 12 of Part A; and Week 12 of Part B

End point title	Parts A and B: Number of Flare-ups With Soft Tissue Swelling and/or Cartilage Formation at Weeks 6 and 12 of Part A; and Week 12 of Part B

End point description:

Magnetic resonance imaging (MRI) was utilized as an imaging modality to evaluate for the presence of soft tissue swelling/edema and cartilage formation for participants who received flare-up based treatment. Ultrasound (US) was utilized to evaluate for the presence of soft tissue swelling in participants unable to undergo MRI. Both MRI and US were interpreted centrally. When US was used, cartilage formation was not assessed. Part A: The Efficacy population included all participants in the treated population who had an evaluable Week 6 or Week 12 image (CT scan or plain radiograph). Part B: The Flare-up population included all participants in the treated population who took at least 1 dose of palovarotene during flare-up based treatment in Part B. Here, n = total number of flare-ups at specific timepoint and 99999 = not evaluated at specific timepoint.

End point type	Secondary

End point timeframe:

Part A: Baseline and Weeks 6 and 12; and Part B: Baseline and Week 12

End point values	Part A: Palovarotene 10/5 mg - Flare-up	Part B: Flare-up Combined		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28[23]	52[24]		
Units: flare-up				
number (not applicable)				
Part A: Edema - Week 6 (n= 18, 0)	7	99999		
Part A: Cartilage Formation - Week 6 (n= 12, 0)	0	99999		
Parts A and B: Edema - Week 12 (n= 17, 49)	9	36		
Parts A and B:Cartilage Formation-Week 12(n=12,22)	0	1		

Notes:

[23] - Total number of flare-ups.

[24] - Total number of flare-ups.

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A and B: Duration of Active Symptomatic Flare-up

End point title	Parts A and B: Duration of Active Symptomatic Flare-up

End point description:

The number of days of active symptomatic flare-up was the number of days the participant reported the presence of symptoms in the diary. Part A: The Efficacy population included all participants in the treated population who had an evaluable Week 6 or Week 12 image (CT scan or plain radiograph). Part B: The Flare-up population included all participants in the treated population who took at least 1 dose of palovarotene during flare-up based treatment in Part B.

End point type	Secondary

End point timeframe:

Part A: From Baseline up to 36 months; and Part B: From Baseline up to 24 months

End point values	Part A: Palovarotene 10/5 mg - Flare-up	Part B: Flare-up Combined		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24[25]	48[26]		
Units: day				
arithmetic mean (standard deviation)	27.1 (± 29.9)	39.5 (± 36.1)		

Notes:

[25] - Total number of flare-ups.

[26] - Total number of flare-ups.

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Baseline in Whole Body Burden of HO at Months 12 and 24

End point title	Part B: Change From Baseline in Whole Body Burden of HO at Months 12 and 24

End point description:

Whole body burden of HO was assessed by low-dose WBCT scan, excluding head. Baseline was Part B Screening. The WBCT Population included participants who received chronic dosing and had baseline and Month 12 WBCT scans. Here, n = number of participants analyzed at specific timepoint and 9999 = Standard deviation could not be determined for one participant.

End point type	Secondary

End point timeframe:

Baseline and Months 12 and 24

End point values	Part B: Whole Body Computed Tomography (WBCT) Population			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: mm^3				
arithmetic mean (standard deviation)				
Month 12 (n= 36) Month 24 (n= 1)	28386 (± 89918) 193150 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Mean Percentage of Flare-ups Per Participant-Month Overall

End point title	Part B: Mean Percentage of Flare-ups Per Participant-Month Overall

End point description:

Flare-ups were counted using the number of participant/Investigator-reported flare-ups. Percentage was calculated by dividing the total number of flare-ups by the total participant months of follow-up. Results are presented for overall ITT period. The Safety analysis set included all enrolled participants who received at least 1 dose of palovarotene in the PVO-1A-202 study.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to end of 2 year follow-up period, approximately a maximum of 96 months

End point values	Part B: Flare-up Combined			
Subject group type	Subject analysis set			
Number of subjects analysed	52[27]			
Units: percentage of flare-up/participant month				
arithmetic mean (standard deviation)	0.12 (± 0.124)			

Notes:

[27] - Total number of flare-ups.

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: Mean Percentage of Flare-ups Per Participant-Month Overall

End point title	Part C: Mean Percentage of Flare-ups Per Participant-Month Overall

End point description:

Flare-ups were counted using the number of participant/Investigator-reported flare-ups. Percentage was calculated by dividing the total number of flare-ups by the total participant months of follow-up. Results are presented for overall ITT period. The Safety analysis set included all enrolled participants who received at least 1 dose of palovarotene in the PVO-1A-202 study.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to end of 2 year follow-up period, approximately a maximum of 96 months

End point values	Part C: Palovarotene - All Treated Flare-ups			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: percentage of flare-up/participant month				
arithmetic mean (standard deviation)	0.14 (± 0.150)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: Percentage of Participants With New HO at Months 12, 24, 36, 60, and 72 (Last Visit)

End point title	Part C: Percentage of Participants With New HO at Months 12, 24, 36, 60, and 72 (Last Visit)

End point description:

New HO was defined as total WBCT new HO volume >0. The FAS included all enrolled participants having a baseline HO volume measurement and at least 1 post-baseline HO volume measurement in the PVO-1A-202 study. Results for Month 72 are presented for overall ITT period. Here, n= number of participants analyzed at specific time point.

End point type	Secondary

End point timeframe:
Months 12, 24, 36, 60, and 72 (last visit)

End point values	Part C: Palovarotene - All Treated Flare-ups			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: percentage of participants				
number (not applicable)				
Month 12 (n= 10)	60.0			
Month 24 (n= 33)	54.5			
Month 36 (n= 26)	61.5			
Month 60 (n= 3)	100.0			
Month 72 (n= 29)	86.2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were recorded from the time informed consent was signed through end of the study (a maximum of 96 months).

Adverse event reporting additional description:

The Safety analysis set included all enrolled participants who received at least 1 dose of palovarotene in the PVO-1A-202 study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Part A

Reporting group description:

Participants who completed PVO-1A-201 study were followed for up to 36 months in Part A. Eligible participants with a flare-up received palovarotene 10 mg capsule orally daily for 2 weeks followed by 5 mg daily for 4 weeks during the flare-up component of Part A.

Reporting group title	Part B

Reporting group description:

Eligible participants from Part A and participants from the new Adult Cohort received chronic treatment with palovarotene 5 mg daily for up to 24 months. Participants with flare-ups received palovarotene 20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks.

Reporting group title	Part C

Reporting group description:

Eligible participants received chronic treatment of palovarotene 5 mg daily for up to 36 months. Participants with flare-ups received palovarotene 20mg daily for 4 weeks followed by 10 mg daily for 8 weeks. For skeletal immature participants, the exposure-equivalent dose was determined based on weight.

Reporting group title	Part D

Reporting group description:

Eligible participants were followed for up to an additional 48 months. No study drug was administered.

Serious adverse events	Part A	Part B	Part C
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	9 / 52 (17.31%)	25 / 46 (54.35%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Condition aggravated			
subjects affected / exposed	1 / 20 (5.00%)	2 / 52 (3.85%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 3	3 / 4	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Local swelling			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
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 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercapnia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia aspiration			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
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 failure			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Drug dependence			
subjects affected / exposed	1 / 20 (5.00%)	0 / 52 (0.00%)	0 / 46 (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
Investigations			
Coronavirus test positive			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	5 / 46 (10.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Exposure to communicable disease			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	4 / 46 (8.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extraskeletal ossification			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			

subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-traumatic pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
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			
Epilepsy			

subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myoclonus			
subjects affected / exposed	1 / 20 (5.00%)	1 / 52 (1.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal convulsion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Tooth impacted			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			

subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
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			
Pain in extremity			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	3 / 46 (6.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiphyses premature fusion			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle tightness			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Corona virus infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	6 / 46 (13.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 52 (1.92%)	4 / 46 (8.70%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			

subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part D		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Local swelling			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspiration				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypercapnia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Drug dependence				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				

Coronavirus test positive				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Exposure to communicable disease				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ankle fracture				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Extraskeletal ossification				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fracture				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Humerus fracture				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post-traumatic pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skull fracture				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haemorrhage				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Epilepsy				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myoclonus				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Convulsion				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Grand mal convulsion				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Tooth impacted				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal stenosis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Decubitus ulcer				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erythema				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Haematuria				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Adrenal insufficiency				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arthralgia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epiphyses premature fusion			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscle tightness			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Corona virus infection			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastroenteritis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Parainfluenzae virus infection			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Staphylococcal sepsis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part A	Part B	Part C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)	52 / 52 (100.00%)	46 / 46 (100.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 20 (0.00%)	6 / 52 (11.54%)	0 / 46 (0.00%)
occurrences (all)	0	6	0
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Chills			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Condition aggravated			
subjects affected / exposed	9 / 20 (45.00%)	29 / 52 (55.77%)	6 / 46 (13.04%)
occurrences (all)	29	65	9
Fatigue			
subjects affected / exposed	0 / 20 (0.00%)	7 / 52 (13.46%)	5 / 46 (10.87%)
occurrences (all)	0	8	5
Feeling cold			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Gait disturbance			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Influenza like illness			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	0 / 46 (0.00%)
occurrences (all)	0	4	0
Local swelling			
subjects affected / exposed	3 / 20 (15.00%)	16 / 52 (30.77%)	16 / 46 (34.78%)
occurrences (all)	8	31	25
Oedema peripheral			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Pyrexia			
subjects affected / exposed	2 / 20 (10.00%)	12 / 52 (23.08%)	10 / 46 (21.74%)
occurrences (all)	3	17	15
Vessel puncture site bruise			
subjects affected / exposed	0 / 20 (0.00%)	6 / 52 (11.54%)	0 / 46 (0.00%)
occurrences (all)	0	10	0
Reproductive system and breast disorders			

Dysmenorrhoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	5 / 46 (10.87%)
occurrences (all)	0	0	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 20 (0.00%)	14 / 52 (26.92%)	10 / 46 (21.74%)
occurrences (all)	0	17	11
Dyspnoea			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	4 / 46 (8.70%)
occurrences (all)	0	5	8
Epistaxis			
subjects affected / exposed	2 / 20 (10.00%)	10 / 52 (19.23%)	5 / 46 (10.87%)
occurrences (all)	3	16	9
Nasal congestion			
subjects affected / exposed	2 / 20 (10.00%)	7 / 52 (13.46%)	0 / 46 (0.00%)
occurrences (all)	2	14	0
Nasal dryness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Oropharyngeal pain			
subjects affected / exposed	2 / 20 (10.00%)	9 / 52 (17.31%)	5 / 46 (10.87%)
occurrences (all)	2	15	9
Rhinorrhoea			
subjects affected / exposed	0 / 20 (0.00%)	6 / 52 (11.54%)	3 / 46 (6.52%)
occurrences (all)	0	7	3
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 20 (10.00%)	5 / 52 (9.62%)	5 / 46 (10.87%)
occurrences (all)	2	8	8
Depressed mood			
subjects affected / exposed	2 / 20 (10.00%)	7 / 52 (13.46%)	4 / 46 (8.70%)
occurrences (all)	2	9	4
Depression			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	4 / 46 (8.70%)
occurrences (all)	0	0	4
Insomnia			

subjects affected / exposed	0 / 20 (0.00%)	5 / 52 (9.62%)	4 / 46 (8.70%)
occurrences (all)	0	5	4
Irritability			
subjects affected / exposed	3 / 20 (15.00%)	5 / 52 (9.62%)	0 / 46 (0.00%)
occurrences (all)	3	5	0
Sleep disorder			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	4 / 46 (8.70%)
occurrences (all)	0	0	5
Investigations			
Amylase increased			
subjects affected / exposed	2 / 20 (10.00%)	0 / 52 (0.00%)	0 / 46 (0.00%)
occurrences (all)	2	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 20 (10.00%)	8 / 52 (15.38%)	0 / 46 (0.00%)
occurrences (all)	2	10	0
Blood bilirubin increased			
subjects affected / exposed	2 / 20 (10.00%)	0 / 52 (0.00%)	0 / 46 (0.00%)
occurrences (all)	2	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	2 / 20 (10.00%)	0 / 52 (0.00%)	0 / 46 (0.00%)
occurrences (all)	3	0	0
Bone density decreased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	11 / 46 (23.91%)
occurrences (all)	0	0	15
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	5	0
Lipase increased			
subjects affected / exposed	4 / 20 (20.00%)	5 / 52 (9.62%)	0 / 46 (0.00%)
occurrences (all)	5	7	0
Urine analysis abnormal			
subjects affected / exposed	0 / 20 (0.00%)	6 / 52 (11.54%)	0 / 46 (0.00%)
occurrences (all)	0	22	0
Urobilinogen urine increased			

subjects affected / exposed	2 / 20 (10.00%)	0 / 52 (0.00%)	0 / 46 (0.00%)
occurrences (all)	2	0	0
Weight decreased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	4 / 46 (8.70%)
occurrences (all)	0	0	4
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	5	0
Contusion			
subjects affected / exposed	0 / 20 (0.00%)	7 / 52 (13.46%)	7 / 46 (15.22%)
occurrences (all)	0	15	8
Excoriation			
subjects affected / exposed	2 / 20 (10.00%)	17 / 52 (32.69%)	9 / 46 (19.57%)
occurrences (all)	3	41	14
Fall			
subjects affected / exposed	4 / 20 (20.00%)	6 / 52 (11.54%)	13 / 46 (28.26%)
occurrences (all)	7	10	23
Head injury			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Joint injury			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	3 / 46 (6.52%)
occurrences (all)	0	3	3
Laceration			
subjects affected / exposed	0 / 20 (0.00%)	8 / 52 (15.38%)	5 / 46 (10.87%)
occurrences (all)	0	9	7
Post-traumatic pain			
subjects affected / exposed	2 / 20 (10.00%)	12 / 52 (23.08%)	5 / 46 (10.87%)
occurrences (all)	6	15	9
Sunburn			
subjects affected / exposed	0 / 20 (0.00%)	5 / 52 (9.62%)	4 / 46 (8.70%)
occurrences (all)	0	8	4
Cardiac disorders			

Tachycardia			
subjects affected / exposed	0 / 20 (0.00%)	6 / 52 (11.54%)	3 / 46 (6.52%)
occurrences (all)	0	7	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	7 / 52 (13.46%)	5 / 46 (10.87%)
occurrences (all)	0	11	10
Headache			
subjects affected / exposed	5 / 20 (25.00%)	15 / 52 (28.85%)	13 / 46 (28.26%)
occurrences (all)	6	28	19
Hypoaesthesia			
subjects affected / exposed	3 / 20 (15.00%)	6 / 52 (11.54%)	5 / 46 (10.87%)
occurrences (all)	4	7	8
Migraine			
subjects affected / exposed	0 / 20 (0.00%)	6 / 52 (11.54%)	7 / 46 (15.22%)
occurrences (all)	0	6	9
Paraesthesia			
subjects affected / exposed	2 / 20 (10.00%)	3 / 52 (5.77%)	6 / 46 (13.04%)
occurrences (all)	3	3	7
Presyncope			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Sciatica			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 52 (0.00%)	0 / 46 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	3 / 46 (6.52%)
occurrences (all)	0	3	3
Ear pain			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	3 / 46 (6.52%)
occurrences (all)	0	5	3
Eye disorders			

Dry eye			
subjects affected / exposed	4 / 20 (20.00%)	12 / 52 (23.08%)	12 / 46 (26.09%)
occurrences (all)	5	15	13
Eye irritation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Eyelid skin dryness			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	0 / 46 (0.00%)
occurrences (all)	0	4	0
Ocular hyperaemia			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	3 / 46 (6.52%)
occurrences (all)	0	4	3
Vision blurred			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	4 / 46 (8.70%)
occurrences (all)	0	0	4
Abdominal distension			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	7 / 46 (15.22%)
occurrences (all)	0	0	7
Abdominal pain			
subjects affected / exposed	4 / 20 (20.00%)	4 / 52 (7.69%)	12 / 46 (26.09%)
occurrences (all)	5	9	12
Abdominal pain upper			
subjects affected / exposed	0 / 20 (0.00%)	5 / 52 (9.62%)	5 / 46 (10.87%)
occurrences (all)	0	11	6
Chapped lips			
subjects affected / exposed	2 / 20 (10.00%)	7 / 52 (13.46%)	4 / 46 (8.70%)
occurrences (all)	3	14	6
Cheilitis			
subjects affected / exposed	0 / 20 (0.00%)	6 / 52 (11.54%)	3 / 46 (6.52%)
occurrences (all)	0	6	3
Constipation			

subjects affected / exposed	2 / 20 (10.00%)	4 / 52 (7.69%)	8 / 46 (17.39%)
occurrences (all)	2	4	9
Dental caries			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	3 / 46 (6.52%)
occurrences (all)	0	3	4
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	14 / 52 (26.92%)	8 / 46 (17.39%)
occurrences (all)	0	19	11
Dry mouth			
subjects affected / exposed	0 / 20 (0.00%)	6 / 52 (11.54%)	8 / 46 (17.39%)
occurrences (all)	0	7	9
Dyspepsia			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	3 / 46 (6.52%)
occurrences (all)	0	4	3
Dysphagia			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	0 / 46 (0.00%)
occurrences (all)	0	9	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	9 / 46 (19.57%)
occurrences (all)	0	0	9
Haematochezia			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	0 / 46 (0.00%)
occurrences (all)	0	6	0
Lip dry			
subjects affected / exposed	13 / 20 (65.00%)	32 / 52 (61.54%)	26 / 46 (56.52%)
occurrences (all)	17	43	31
Nausea			
subjects affected / exposed	2 / 20 (10.00%)	15 / 52 (28.85%)	10 / 46 (21.74%)
occurrences (all)	2	24	17
Toothache			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	7 / 46 (15.22%)
occurrences (all)	0	4	9
Vomiting			
subjects affected / exposed	3 / 20 (15.00%)	18 / 52 (34.62%)	14 / 46 (30.43%)
occurrences (all)	3	40	19
Skin and subcutaneous tissue disorders			

Acne			
subjects affected / exposed	2 / 20 (10.00%)	5 / 52 (9.62%)	7 / 46 (15.22%)
occurrences (all)	3	5	8
Alopecia			
subjects affected / exposed	0 / 20 (0.00%)	26 / 52 (50.00%)	20 / 46 (43.48%)
occurrences (all)	0	30	25
Blister			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	6 / 46 (13.04%)
occurrences (all)	0	8	7
Cold sweat			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	4 / 46 (8.70%)
occurrences (all)	0	6	5
Decubitus ulcer			
subjects affected / exposed	0 / 20 (0.00%)	5 / 52 (9.62%)	3 / 46 (6.52%)
occurrences (all)	0	7	8
Drug eruption			
subjects affected / exposed	0 / 20 (0.00%)	6 / 52 (11.54%)	12 / 46 (26.09%)
occurrences (all)	0	8	21
Dry skin			
subjects affected / exposed	15 / 20 (75.00%)	44 / 52 (84.62%)	38 / 46 (82.61%)
occurrences (all)	51	130	86
Eczema			
subjects affected / exposed	5 / 20 (25.00%)	11 / 52 (21.15%)	6 / 46 (13.04%)
occurrences (all)	11	36	11
Erythema			
subjects affected / exposed	5 / 20 (25.00%)	23 / 52 (44.23%)	16 / 46 (34.78%)
occurrences (all)	7	49	29
Hyperhidrosis			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Ingrowing nail			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	4 / 46 (8.70%)
occurrences (all)	0	5	6
Madarosis			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	3 / 46 (6.52%)
occurrences (all)	0	3	5

Onychoclasis			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	5 / 46 (10.87%)
occurrences (all)	0	3	7
Pain of skin			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	4	0
Pruritus			
subjects affected / exposed	7 / 20 (35.00%)	28 / 52 (53.85%)	18 / 46 (39.13%)
occurrences (all)	15	60	29
Pruritus generalised			
subjects affected / exposed	4 / 20 (20.00%)	21 / 52 (40.38%)	9 / 46 (19.57%)
occurrences (all)	5	30	12
Rash			
subjects affected / exposed	3 / 20 (15.00%)	24 / 52 (46.15%)	16 / 46 (34.78%)
occurrences (all)	3	47	32
Rash erythematous			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	4	0
Seborrhoea			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	0 / 46 (0.00%)
occurrences (all)	0	6	0
Skin burning sensation			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	5	0
Skin discolouration			
subjects affected / exposed	0 / 20 (0.00%)	7 / 52 (13.46%)	5 / 46 (10.87%)
occurrences (all)	0	8	5
Skin disorder			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Skin exfoliation			
subjects affected / exposed	0 / 20 (0.00%)	22 / 52 (42.31%)	19 / 46 (41.30%)
occurrences (all)	0	61	37
Skin fissures			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	6 / 46 (13.04%)
occurrences (all)	0	4	8

Skin irritation			
subjects affected / exposed	0 / 20 (0.00%)	5 / 52 (9.62%)	3 / 46 (6.52%)
occurrences (all)	0	6	6
Skin lesion			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	4 / 46 (8.70%)
occurrences (all)	0	8	7
Swelling face			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	0 / 46 (0.00%)
occurrences (all)	0	4	0
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Haematuria			
subjects affected / exposed	4 / 20 (20.00%)	6 / 52 (11.54%)	0 / 46 (0.00%)
occurrences (all)	6	8	0
Nephrolithiasis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	4 / 46 (8.70%)
occurrences (all)	0	0	4
Pollakiuria			
subjects affected / exposed	3 / 20 (15.00%)	0 / 52 (0.00%)	0 / 46 (0.00%)
occurrences (all)	4	0	0
Proteinuria			
subjects affected / exposed	9 / 20 (45.00%)	6 / 52 (11.54%)	0 / 46 (0.00%)
occurrences (all)	12	8	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 20 (55.00%)	25 / 52 (48.08%)	27 / 46 (58.70%)
occurrences (all)	23	69	66
Back pain			
subjects affected / exposed	2 / 20 (10.00%)	17 / 52 (32.69%)	8 / 46 (17.39%)
occurrences (all)	3	23	12
Extraskeletal ossification			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	6 / 46 (13.04%)
occurrences (all)	0	4	6
Groin pain			

subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	5 / 46 (10.87%)
occurrences (all)	0	7	5
Joint range of motion decreased			
subjects affected / exposed	2 / 20 (10.00%)	10 / 52 (19.23%)	4 / 46 (8.70%)
occurrences (all)	2	13	6
Joint stiffness			
subjects affected / exposed	2 / 20 (10.00%)	5 / 52 (9.62%)	0 / 46 (0.00%)
occurrences (all)	3	7	0
Joint swelling			
subjects affected / exposed	3 / 20 (15.00%)	15 / 52 (28.85%)	13 / 46 (28.26%)
occurrences (all)	3	20	21
Muscle fatigue			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Muscle spasms			
subjects affected / exposed	0 / 20 (0.00%)	5 / 52 (9.62%)	3 / 46 (6.52%)
occurrences (all)	0	8	3
Muscular weakness			
subjects affected / exposed	2 / 20 (10.00%)	0 / 52 (0.00%)	0 / 46 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal chest pain			
subjects affected / exposed	2 / 20 (10.00%)	5 / 52 (9.62%)	6 / 46 (13.04%)
occurrences (all)	3	10	6
Musculoskeletal discomfort			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	6 / 46 (13.04%)
occurrences (all)	0	5	6
Musculoskeletal pain			
subjects affected / exposed	4 / 20 (20.00%)	11 / 52 (21.15%)	10 / 46 (21.74%)
occurrences (all)	4	15	10
Musculoskeletal stiffness			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	0 / 46 (0.00%)
occurrences (all)	0	4	0
Myalgia			
subjects affected / exposed	2 / 20 (10.00%)	5 / 52 (9.62%)	8 / 46 (17.39%)
occurrences (all)	3	6	8
Neck pain			

subjects affected / exposed	2 / 20 (10.00%)	8 / 52 (15.38%)	5 / 46 (10.87%)
occurrences (all)	2	36	9
Osteoporosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	9 / 46 (19.57%)
occurrences (all)	0	0	10
Pain in extremity			
subjects affected / exposed	10 / 20 (50.00%)	26 / 52 (50.00%)	23 / 46 (50.00%)
occurrences (all)	17	52	46
Pain in jaw			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Tendonitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	5	0
Conjunctivitis			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Ear infection			
subjects affected / exposed	0 / 20 (0.00%)	6 / 52 (11.54%)	7 / 46 (15.22%)
occurrences (all)	0	9	11
Folliculitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Fungal skin infection			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Gastroenteritis			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	4 / 46 (8.70%)
occurrences (all)	0	3	6
Hordeolum			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	6

Impetigo			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	7	0
Influenza			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Lower respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Nasopharyngitis			
subjects affected / exposed	0 / 20 (0.00%)	14 / 52 (26.92%)	14 / 46 (30.43%)
occurrences (all)	0	24	19
Onychomycosis			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	6 / 46 (13.04%)
occurrences (all)	0	5	6
Oral herpes			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Paronychia			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	5 / 46 (10.87%)
occurrences (all)	0	5	10
Pharyngitis			
subjects affected / exposed	5 / 20 (25.00%)	0 / 52 (0.00%)	0 / 46 (0.00%)
occurrences (all)	5	0	0
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	4 / 46 (8.70%)
occurrences (all)	0	5	5
Sinusitis			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Skin infection			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	3 / 46 (6.52%)
occurrences (all)	0	4	5
Subcutaneous abscess			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	6	0

Upper respiratory tract infection			
subjects affected / exposed	7 / 20 (35.00%)	11 / 52 (21.15%)	11 / 46 (23.91%)
occurrences (all)	7	21	13
Urinary tract infection			
subjects affected / exposed	0 / 20 (0.00%)	4 / 52 (7.69%)	5 / 46 (10.87%)
occurrences (all)	0	5	9
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	0	5	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 20 (10.00%)	5 / 52 (9.62%)	4 / 46 (8.70%)
occurrences (all)	2	6	4
Hypercholesterolaemia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 52 (0.00%)	0 / 46 (0.00%)
occurrences (all)	3	0	0
Hyperglycaemia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 52 (0.00%)	0 / 46 (0.00%)
occurrences (all)	3	0	0
Hypertriglyceridaemia			
subjects affected / exposed	2 / 20 (10.00%)	3 / 52 (5.77%)	0 / 46 (0.00%)
occurrences (all)	5	8	0
Vitamin D deficiency			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	4

Non-serious adverse events	Part D		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

Chills subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Condition aggravated subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Fatigue subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Feeling cold subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Gait disturbance subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Influenza like illness subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Local swelling subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Pyrexia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Vessel puncture site bruise subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Reproductive system and breast disorders			
Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nasal dryness			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Depressed mood			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Irritability			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Investigations			
Amylase increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Bone density decreased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Lipase increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Urine analysis abnormal			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Urobilinogen urine increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Weight decreased			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Excoriation			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Head injury			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Joint injury			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Laceration			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Post-traumatic pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Sunburn			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Migraine subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Paraesthesia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Presyncope subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Sciatica subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Ear and labyrinth disorders Ear congestion subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Ear pain subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Eye disorders Dry eye subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 1		
Eye irritation			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Eyelid skin dryness			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Ocular hyperaemia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Abdominal distension			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Chapped lips			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cheilitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Dental caries			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

Diarrhoea			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Dysphagia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Haematochezia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Lip dry			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Alopecia			

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Blister				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Cold sweat				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Decubitus ulcer				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Drug eruption				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Dry skin				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Eczema				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Erythema				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Hyperhidrosis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Ingrowing nail				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Madarosis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Onychoclasis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain of skin				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pruritus				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pruritus generalised				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Rash				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Rash erythematous				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Seborrhoea				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin burning sensation				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin discolouration				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin disorder				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin exfoliation				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin fissures				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin irritation				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin lesion				

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Swelling face			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Haematuria			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nephrolithiasis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Pollakiuria			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Proteinuria			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Extraskeletal ossification			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Groin pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Joint range of motion decreased			

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Joint stiffness				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Joint swelling				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Muscle fatigue				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Muscle spasms				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Muscular weakness				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Musculoskeletal chest pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Musculoskeletal discomfort				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Musculoskeletal pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Musculoskeletal stiffness				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Myalgia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Neck pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Osteoporosis				

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Pain in jaw			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Tendonitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Ear infection			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Folliculitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Fungal skin infection			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Hordeolum			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Impetigo			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

Influenza				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Onychomycosis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Oral herpes				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Paronychia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pharyngitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pneumonia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Subcutaneous abscess				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			

Urinary tract infection subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2014	Added that any participant unable to attend the site visits at study Months 6 and/or 12 would undergo all assessments that could be performed either by telephone or remotely in order to continue to monitor participants who were unable to attend site visits during the follow-up component. Specified that any participant with a flare-up who did not meet the inclusion/exclusion criteria for the flare-up component would not receive palovarotene, but that these participants would undergo all assessments that could be performed either by telephone or remotely in order to continue to monitor the flare-ups of these participants.
22 June 2015	Noted that in the follow-up component, the original flare-up from study PVO-1A-201 would be assessed at only 1 additional time point at study Month 12 and assessments for this visit could be performed in conjunction with any of the visits for the flare-up component that occurred no more than 7 months before the study Month 12 visit. Added that the FPS-R would be used to assess flare-up pain in participants under 8 years of age. In addition, swelling would be assessed by parents using the NRS. Noted that the C-SSRS was to be administered to participants 8 years of age and older. Added that the FOP assistive devices and adaptations questionnaire could be completed by the participant or parent. Added participant (or parent of participant under 8 years of age) and Investigator global assessment of movement to include an overall assessment of flare-up joint movement as evaluated by participants and Investigators. Added the CAJIS to obtain an additional assessment of range of motion. Added the use of US to evaluate soft tissue swelling at the time of a new, distinct flare-up to allow for the evaluation of soft tissue swelling in participants unable to undergo MRI. Clarified that for participants experiencing a new, distinct flare-up, HO would be assessed by low-dose CT scan or plain radiographs for participants that were unable to undergo CT scan. Added that if a participant required dose de-escalation due to an intolerable side effect in study PVO-1A-201, then the dose the participant would receive for a subsequent flare-up would be determined by the Investigator and the Medical Monitor. Added that if a participant required dose de-escalation, and the participant was already receiving the lowest possible dose, then study drug was discontinued to ensure the safety of participants. Added abdomen and chest to flare-up site to include additional flare-up sites with a high likelihood of forming HO.

10 March 2016	Noted that the study would be conducted in 2 parts to allow for the analysis of data obtained with dosing regimens specific to the protocol amendments. Part A included all data obtained prior to amendment 3. Part B included all data obtained under amendment 3. Specified that the primary objective would evaluate the safety and efficacy of different palovarotene dosing regimens in preventing HO following a flare-up in order to expand the dose range being evaluated in the palovarotene Phase 2 development program. Revised the total study population to include 40 participants who successfully completed study PVO-1A-201 and up to 20 new adult cohort participants who had a confirmed R206H mutation, at least 2 acute symptomatic flare-ups in the past 2 years but no flare-up symptoms in the past 4 weeks, a CAJIS score of 6 to 16, inclusive, and must have been able to receive chronic dosing. Added chronic treatment of 5 mg palovarotene once daily to participants in the adult cohort. Noted that dosing could be extended beyond Week 12 (84 days; in 4-week intervals) if the flare-up was ongoing and continue until the flare-up resolved, with remote visits performed every 2 weeks while on treatment. Added neck and lower back to eligible flare-up locations to allow for the evaluation of HO formation across the majority of body regions affected by FOP. Added that skin protectants may have been used prophylactically to minimize any potential tolerability issues related to study drug. Added that palovarotene was to be supplied as 10.0, 6.0 (2x3 mg), 5.0, 4.0, 3.0, and 2.5 mg to update the palovarotene dosage strengths that were provided to participants. Added remote visits every 3 months for participants in the adult cohort receiving chronic treatment to assess for any safety concerns associated with chronic treatment. Updated total blood volume drawn for the participants in the adult and pediatric cohorts to ensure that the total blood volume drawn was within established limits.
01 September 2017	Specified that data from Part C would be obtained under Amendment 4 to allow for the analysis of the data obtained with the dosing regimens utilized under Amendment 4. Noted that in Part C, participants who participated in Part B would be followed for up to an additional 36 months to allow for provision of study medication until commercial availability. Revised the assessment of efficacy to be assessed by low-dose WBCT scan, excluding head, to reduce participant burden and better assess development of new HO by omitting low-dose, flare-up site-specific CT scan, MRI, ultrasound, and/or plain radiographs, and utilizing only annual low-dose WBCT scan to assess new HO. Included information for end of treatment and end of study assessments in the protocol to provide direction for study sites when participants completed treatment or finished the study. Added chronic treatment with 5 mg palovarotene once daily (weight-adjusted doses) for skeletally immature participants. Added FOP-PFQ and PROMIS Global Health Scale to chronic treatment secondary endpoints to continue to monitor patient-reported assessment of physical function (FOP-PFQ), and physical and mental health (PROMIS Global Health Scale). Added FOP-PFQ, PROMIS Global Health Scale, and CAJIS to the remote assessments performed every 6 months to continue to monitor FOP-PFQ, PROMIS Global Health Scale, and CAJIS throughout the study. Removed assessment of assistive devices and adaptations, and removed coagulation and biomarkers from clinical laboratory tests for chronic treatment to reduce participant burden. Added a study diary for chronic treatment to document dose of study drug taken each day. Removed the specification that treatment would only occur for up to 3 flare-ups during the entire study to provide continued treatment for participants who experienced greater than 3 flare-ups over the course of the study.

06 June 2018	Specified that data from Part C would be obtained under Amendment 4 and subsequent amendments to allow for the analysis of the data obtained with the dosing regimens utilized under Amendment 4 and any subsequent amendments. Added blood sampling for PK analysis during chronic dosing for all participants to evaluate palovarotene PK during chronic dosing. Added that herbal preparations containing vitamin A or beta carotene were not permitted from the day before the start of treatment until the last day of treatment to clarify the content of herbal preparations that are excluded. Included a reference to and description of the PVO-1A-301 BSMP and additional safety assessments to be followed in this study to enhance participant safety monitoring. Added that participants were to be reassessed for child bearing status (females only) and pregnancy prevention measures (females and males) every 3 month to provide continued safety monitoring. Changed visit windows from ±3 days to ±5 days for flare-up based treatment to allow for flexibility for assessments to be performed. Added that the Investigator would be notified about any protocol-specified safety laboratory test that could not be obtained or was not usable. Added that if the study was closed due to safety concerns, then all participants exposed to the investigational drug would be followed for safety with the length of follow-up determined based on the safety risk. This change was to clarify procedures of safety monitoring in the event of safety-based study termination.
08 March 2019	Changed the timing of clinical laboratory assessments during chronic treatment from every 3 months to every 6 months. Blood volumes were adjusted to reflect the change. Changed the timing of clinical laboratory assessments, C-SSRS, vital signs, and body weight determination during a flare-up cycle. Noted that flare-up based dosing was to be initiated if the Investigator confirmed the presence of a substantial, high-risk traumatic event likely to lead to a flare-up. Increased the window from ±2 to ±4 weeks for when a flare-up safety visit was required after the final flare-up safety visit in a previous cycle to ensure that all assessments were performed within a workable timeframe. Changed the criteria to discontinue palovarotene in the event that ALT was >3× ULN if accompanied by any bilirubin increase of >2× ULN. Specified the conditions in which participants were to receive the flare-up based treatment regimen. Added dose-adjusted equivalents for 2.5 mg to tables in the protocol synopsis. Also, deleted inaccurate text indicating that dose de-escalation were associated with only flare-up based dosing. Added text and literature references describing the influence of trauma on flare-up and HO formation.
01 November 2019	Added radiographic assessments of the knee and hand/wrist to be performed every 3 months in those participants who (1) received the flare-up dosing regimen in the period of time since their last radiographic assessment; and (2) had not achieved 100% skeletal maturity on their last radiographic assessment. Added 6-month radiographic assessments of the knee and hand/wrist in skeletally immature participants to enhance participant safety and align with the more rigorous safety procedures in the Phase 3 study. During flare-up dosing, timing of safety assessments were changed to recur every 12 weeks (instead of every 8 weeks) after flare-up cycle safety Day 1 until treatment of the last flare-up or traumatic event in the cycle was completed. The 4-week safety assessment would no longer be performed. Updated palovarotene, PK, efficacy, and safety findings from the FOP interventional trials to make the most relevant clinical information available to the study sites. Revised the vendor contact information to ensure that contact information was up-to-date. Added the process for selecting the Coordinating Investigator to comply with EMA regulations.

30 November 2020	Added Part D for skeletally immature participants who stopped taking study drug for any reason before completion of Part C. Part D includes yearly visits for up to a 2-year follow-up period following the last dose. No dosing occurs during Part D. The up to 2-year period begins the last day the participant stops receiving study drug in Part C. The total duration of participation in Part C and Part D is a maximum of 4 years. Secondary objective added for Part D to monitor off treatment longer-term safety in skeletally immature participants off treatment. Safety was also summarized for Part D. In Part C, participants could continue on the study for up to an additional 12 months to allow for the provision of study medication until commercial availability. Added assessments for spinal health carried out on low-dose WBCT scans collected in the study. Emerging data from the PVO-2A-201 trial in the multiple osteochondroma indication has suggested a potential effect of PVO on bone mineral accrual. Integrated protocol amendment 7 addendum previously created to describe temporary measures applied during the corona virus disease 2019 (COVID-19) pandemic. Additional update to these temporary measures was included to clarify that radiographic assessments are required for participants ≥14 years (who were skeletally immature at their last assessment) as part of the minimal safety procedures prior to re-initiation of palovarotene. This was added to assess skeletal maturity in participants ≥14 years re-initiating treatment to ensure appropriate safety follow up as well as determine if weight-based dosing is required.

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 14 years and older in the palovarotene FOP trials including PVO-1A-202/204 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 who were able and willing to re-start treatment (in the context of COVID-19 conditions, starting 04 June 2020).	04 June 2020

Notes:

Limitations and caveats

None reported