

**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 | <ul style="list-style-type: none">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@ipson.com |
| Scientific contact | Medical Director, Ipsen, clinical.trials@ipson.com |

Notes:

Paediatric regulatory details

| | |
|----------------------------------------------------------------------|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-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 standard deviation | 21.0 ± 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). | |

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| 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

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|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| 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

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|-----------------|------------------------------------------------------------------|
| 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/Und ertreated 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/Und ertreated 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

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|-----------------|-----------------------------------------------------------------------------------------------------------------------|
| 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

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|-----------------|------------------------------------------------------------------|
| 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

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|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| 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 \pm 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 \pm 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 |
|-----------------|-------------------------------------------------------|

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) | 28386 (± 89918) | | | |
| Month 24 (n= 1) | 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 occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 20 (0.00%) 0 / 0 0 / 0 | 0 / 52 (0.00%) 0 / 0 0 / 0 | 6 / 46 (13.04%) 0 / 9 0 / 0 |
| Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 20 (0.00%) 0 / 0 0 / 0 | 0 / 52 (0.00%) 0 / 0 0 / 0 | 2 / 46 (4.35%) 2 / 2 0 / 0 |
| Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 20 (5.00%) 0 / 1 0 / 0 | 1 / 52 (1.92%) 0 / 1 0 / 0 | 4 / 46 (8.70%) 0 / 4 0 / 0 |
| Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 20 (0.00%) 0 / 0 0 / 0 | 1 / 52 (1.92%) 0 / 1 0 / 0 | 1 / 46 (2.17%) 0 / 1 0 / 0 |
| Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 20 (0.00%) 0 / 0 0 / 0 | 0 / 52 (0.00%) 0 / 0 0 / 0 | 1 / 46 (2.17%) 1 / 1 0 / 0 |
| Influenza subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 20 (0.00%) 0 / 0 0 / 0 | 1 / 52 (1.92%) 0 / 2 0 / 0 | 0 / 46 (0.00%) 0 / 0 0 / 0 |
| Parainfluenzae virus infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 20 (0.00%) 0 / 0 0 / 0 | 1 / 52 (1.92%) 0 / 1 0 / 0 | 0 / 46 (0.00%) 0 / 0 0 / 0 |
| Staphylococcal sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 20 (0.00%) 0 / 0 0 / 0 | 0 / 52 (0.00%) 0 / 0 0 / 0 | 2 / 46 (4.35%) 1 / 2 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 | | |
| Extraskkeletal 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 occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 52 (0.00%) 0 | 5 / 46 (10.87%) 5 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 14 / 52 (26.92%) 17 | 10 / 46 (21.74%) 11 |
| Dyspnoea subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 4 / 52 (7.69%) 5 | 4 / 46 (8.70%) 8 |
| Epistaxis subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 3 | 10 / 52 (19.23%) 16 | 5 / 46 (10.87%) 9 |
| Nasal congestion subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 7 / 52 (13.46%) 14 | 0 / 46 (0.00%) 0 |
| Nasal dryness subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 52 (0.00%) 0 | 3 / 46 (6.52%) 3 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 9 / 52 (17.31%) 15 | 5 / 46 (10.87%) 9 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 6 / 52 (11.54%) 7 | 3 / 46 (6.52%) 3 |
| Psychiatric disorders | | | |
| Anxiety subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 5 / 52 (9.62%) 8 | 5 / 46 (10.87%) 8 |
| Depressed mood subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 7 / 52 (13.46%) 9 | 4 / 46 (8.70%) 4 |
| Depression subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 52 (0.00%) 0 | 4 / 46 (8.70%) 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 occurrences (all) | 0 / 20 (0.00%) 0 | 6 / 52 (11.54%) 7 | 3 / 46 (6.52%) 3 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 7 / 52 (13.46%) 11 | 5 / 46 (10.87%) 10 |
| Headache subjects affected / exposed occurrences (all) | 5 / 20 (25.00%) 6 | 15 / 52 (28.85%) 28 | 13 / 46 (28.26%) 19 |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 3 / 20 (15.00%) 4 | 6 / 52 (11.54%) 7 | 5 / 46 (10.87%) 8 |
| Migraine subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 6 / 52 (11.54%) 6 | 7 / 46 (15.22%) 9 |
| Paraesthesia subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 3 | 3 / 52 (5.77%) 3 | 6 / 46 (13.04%) 7 |
| Presyncope subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 3 / 52 (5.77%) 3 | 0 / 46 (0.00%) 0 |
| Sciatica subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 52 (0.00%) 0 | 3 / 46 (6.52%) 3 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 0 / 52 (0.00%) 0 | 0 / 46 (0.00%) 0 |
| Ear and labyrinth disorders | | | |
| Ear congestion subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 3 / 52 (5.77%) 3 | 3 / 46 (6.52%) 3 |
| Ear pain subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 4 / 52 (7.69%) 5 | 3 / 46 (6.52%) 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 |

| | | | |
|-----------------------------|-----------------|------------------|------------------|
| Onychoclasia | | | |
| 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 occurrences (all) | 0 / 20 (0.00%) 0 | 5 / 52 (9.62%) 6 | 3 / 46 (6.52%) 6 |
| Skin lesion subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 3 / 52 (5.77%) 8 | 4 / 46 (8.70%) 7 |
| Swelling face subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 4 / 52 (7.69%) 4 | 0 / 46 (0.00%) 0 |
| Renal and urinary disorders | | | |
| Glycosuria subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 3 / 52 (5.77%) 3 | 0 / 46 (0.00%) 0 |
| Haematuria subjects affected / exposed occurrences (all) | 4 / 20 (20.00%) 6 | 6 / 52 (11.54%) 8 | 0 / 46 (0.00%) 0 |
| Nephrolithiasis subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 52 (0.00%) 0 | 4 / 46 (8.70%) 4 |
| Pollakiuria subjects affected / exposed occurrences (all) | 3 / 20 (15.00%) 4 | 0 / 52 (0.00%) 0 | 0 / 46 (0.00%) 0 |
| Proteinuria subjects affected / exposed occurrences (all) | 9 / 20 (45.00%) 12 | 6 / 52 (11.54%) 8 | 0 / 46 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 11 / 20 (55.00%) 23 | 25 / 52 (48.08%) 69 | 27 / 46 (58.70%) 66 |
| Back pain subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 3 | 17 / 52 (32.69%) 23 | 8 / 46 (17.39%) 12 |
| Extraskkeletal ossification subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 4 / 52 (7.69%) 4 | 6 / 46 (13.04%) 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 occurrences (all) | 7 / 20 (35.00%) 7 | 11 / 52 (21.15%) 21 | 11 / 46 (23.91%) 13 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 4 / 52 (7.69%) 5 | 5 / 46 (10.87%) 9 |
| Vulvovaginal mycotic infection subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 3 / 52 (5.77%) 5 | 0 / 46 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 5 / 52 (9.62%) 6 | 4 / 46 (8.70%) 4 |
| Hypercholesterolaemia subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 3 | 0 / 52 (0.00%) 0 | 0 / 46 (0.00%) 0 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 3 | 0 / 52 (0.00%) 0 | 0 / 46 (0.00%) 0 |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 5 | 3 / 52 (5.77%) 8 | 0 / 46 (0.00%) 0 |
| Vitamin D deficiency subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 0 / 52 (0.00%) 0 | 3 / 46 (6.52%) 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 occurrences (all) | 0 / 1 (0.00%) 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | | |

| | | | |
|-------------------------------------------------|---------------|--|--|
| Chills | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Condition aggravated | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Local swelling | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vessel puncture site bruise | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 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 occurrences (all) | 0 / 1 (0.00%) 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 | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Headache | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Migraine | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ear and labyrinth disorders | | | |
| Ear congestion | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| occurrences (all) | 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 | | |
| Onychoclasia | | | |
| 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 | | |
| Extraskkeletal 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 | <p>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.</p> |
| 01 September 2017 | <p>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.</p> |

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|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 06 June 2018 | <p>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.</p> |
| 08 March 2019 | <p>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 $>3 \times$ ULN if accompanied by any bilirubin increase of $>2 \times$ 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.</p> |
| 01 November 2019 | <p>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.</p> |

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| 30 November 2020 | <p>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.</p> |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 04 December 2019 | <p>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.</p> <p>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).</p> | 04 June 2020 |

Notes:

Limitations and caveats

None reported