



## Clinical trial results:

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

#### Summary

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

#### Results information

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

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | PVO-1A-301 |
|-----------------------|------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Clementia Pharmaceuticals Inc.  |
| Sponsor organisation address | 1000 De La Gauchetière West, Suite 1200 Montreal, Quebec, Canada, H3B 4W5 |
| Public contact               | Medical Director, Ipsen, clinical.trials@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                       | 07 September 2022 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 07 September 2022 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

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

To evaluate the safety of palovarotene in adult and pediatric participants with FOP.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

Notes:

**Subjects enrolled per age group**

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

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

|           |              |
|-----------|--------------|
| Arm title | Palovarotene |
|-----------|--------------|

Arm description:

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

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

Dosage and administration details:

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

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



## Baseline characteristics

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Overall |
|-----------------------|---------|

Reporting group description: -

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

## End points

### End points reporting groups

|  |                        |
|--|------------------------|
| Reporting group title  | Palovarotene           |
| Reporting group description:<br>Participants were administered 5 milligram (mg) palovarotene orally once daily up to 24 months. Participants with flare-up symptoms or traumatic events received palovarotene 20 mg once daily for 4 weeks after the flare-up confirmation by the Investigator. Followed by palovarotene 10 mg once daily for 8 weeks. |                        |
| Subject analysis set title   | Palovarotene           |
| Subject analysis set type  | Intention-to-treat     |
| Subject analysis set description:<br>Participants were administered 5 mg palovarotene orally once daily up to 24 months. Participants with flare-up symptoms or traumatic events received palovarotene 20 mg once daily for 4 weeks after the flare-up confirmation by the Investigator. Followed by palovarotene 10 mg once daily for 8 weeks.        |                        |
| Subject analysis set title   | Untreated (PVO-1A-001) |
| Subject analysis set type  | Full analysis          |
| Subject analysis set description:<br>Participants from study PVO-1A-001 (NCT02322255) were included with FOP caused by the R206H mutation and with baseline data. Participants were not administered palovarotene and compared as external control.  |                        |

### Primary: Annualized New Heterotopic Ossification (HO)

|  |   |
|--|---|
| End point title  | Annualized New Heterotopic Ossification (HO) <sup>[1]</sup> |
| End point description:<br>The annualized new HO was assessed by low-dose, whole body computed tomography (WBCT), excluding head. The weighted linear mixed effect method without square-root transformation and negatives included was used for annualized new HO analysis. The Principal Full Analysis Set (FAS) included all enrolled participants in the Principal EP who had a baseline HO volume measurement and at least 1 post-baseline HO volume measurement in PVO-1A-301. For study PVO-1A-001, the Principal FAS included participants enrolled with available baseline and at least 1 post-baseline HO volume measurement. Study PVO-1A-001 was used as an external control. Only data from the participants analyzed were reported. |   |
| End point type   | Primary   |
| End point timeframe:<br>Baseline (within one month of screening/Day 1) and up to 24 months   |   |
| Notes:<br>[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.<br>Justification: No additional statistical analysis was prespecified for this endpoint.   |   |

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

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Any New HO

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With Any New HO |
|-----------------|--|

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Body Regions With New HO

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12

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



## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Flare-Ups

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With Flare-Ups |
|-----------------|---|

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline (Day 1) up to Month 24

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

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Palovarotene |
|-----------------------|--------------|

Reporting group description:

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported