



Clinical trial results:

Rollover Study; Multicentre, Phase III, Open-label Study to Further Evaluate the Safety and Efficacy of Palovarotene Capsules in Male and Female Participants Aged ≥ 14 Years with Fibrodysplasia Ossificans Progressiva (FOP) Who Have Completed Study PVO-1A-301 or PVO-1A-202/PVO-1A-204 and May Benefit from Palovarotene Therapy

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2021-002244-70 |
| Trial protocol | SE FR IT ES |
| Global end of trial date | 30 November 2024 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 14 June 2025 |
| First version publication date | 14 June 2025 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | CLIN-60120-452 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT05027802 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Ipsen Pharma SAS |
| Sponsor organisation address | 70 rue Balard, Paris, France, 75015 |
| Public contact | Medical Director, IPSEN Pharma SAS, clinical.trials@ipsen.com |
| Scientific contact | Medical Director, IPSEN Pharma SAS, clinical.trials@ipsen.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| 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 | 30 November 2024 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 November 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To further evaluate the safety and efficacy of palovarotene in adult and pediatric participants with Fibrodysplasia Ossificans Progressiva (FOP).

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 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 | 14 March 2022 |
| 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: 1 |
| Country: Number of subjects enrolled | Australia: 3 |
| Country: Number of subjects enrolled | Brazil: 5 |
| Country: Number of subjects enrolled | Canada: 2 |
| Country: Number of subjects enrolled | France: 15 |
| Country: Number of subjects enrolled | Italy: 2 |
| Country: Number of subjects enrolled | Sweden: 3 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | United States: 26 |
| Worldwide total number of subjects | 61 |
| EEA total number of subjects | 20 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 19 |
| Adults (18-64 years) | 41 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This single arm, rollover, multicenter, Phase III, open-label study was conducted in participants ≥ 14 years with FOP who had completed parent study PVO-1A-301 (NCT03312634) or PVO-1A-202 (NCT02279095)/PVO-1A-204 (NCT02979769) and continued to benefit from palovarotene therapy. 59 participants received treatment in this study.

Pre-assignment

Screening details:

This study consisted of an inclusion visit (Day 1), a continuous dosing treatment period (including a follow-up visit every 6 months), and an end of study [EOS]/early withdrawal [EW] visit. Participants were eligible whether they received chronic or flare-up treatment in the parent study at the time of transition.

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 | Palovarotene |
|-----------|--------------|

Arm description:

Participants continued to receive palovarotene 5 milligram (mg) orally once daily until it was reimbursed in the country where the study was being conducted or another access program became available or until the study end date, whichever occurred first, up to approximately 32 months.

In case of flare-up symptoms or substantial high risk traumatic events (likely to lead to a flare-up), participants received palovarotene 20 mg orally once daily for 4 weeks followed by 10 mg orally once daily for 8 weeks for a total of 12 weeks even if symptoms resolved earlier.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Palovarotene |
| Investigational medicinal product code | IPN60120 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Palovarotene 5 mg was administered orally once daily as specified in the protocol. In case of flare-ups, palovarotene 20 mg was administered orally once daily for 4 weeks followed by 10 mg orally once daily for 8 weeks for a total of 12 weeks even if symptoms resolved earlier. It was to be taken with food preferably at the same time each day.

| Number of subjects in period 1 ^[1] | Palovarotene |
|---|--------------|
| Started | 59 |
| Completed | 36 |
| Not completed | 23 |
| Adverse event, serious fatal | 2 |
| Consent withdrawn by subject | 18 |
| Adverse event, non-fatal | 2 |

| | |
|-------------|---|
| Unspecified | 1 |
|-------------|---|

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Results are presented by Full analysis set/Safety set.

Baseline characteristics

Reporting groups

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

Reporting group description:

Participants continued to receive palovarotene 5 milligram (mg) orally once daily until it was reimbursed in the country where the study was being conducted or another access program became available or until the study end date, whichever occurred first, up to approximately 32 months.

In case of flare-up symptoms or substantial high risk traumatic events (likely to lead to a flare-up), participants received palovarotene 20 mg orally once daily for 4 weeks followed by 10 mg orally once daily for 8 weeks for a total of 12 weeks even if symptoms resolved earlier.

| Reporting group values | Palovarotene | Total | |
|---------------------------|--------------|-------|--|
| Number of subjects | 59 | 59 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 22.4 | | |
| standard deviation | ± 8.9 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 28 | 28 | |
| Male | 31 | 31 | |
| Race | | | |
| Units: Subjects | | | |
| White | 38 | 38 | |
| Black or African American | 0 | 0 | |
| Asian | 3 | 3 | |
| Other | 1 | 1 | |
| Multiple | 2 | 2 | |
| Not Reported | 15 | 15 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 10 | 10 | |
| Not Hispanic or Latino | 33 | 33 | |
| Unknown or Not Reported | 16 | 16 | |

End points

End points reporting groups

| | |
|---|--------------|
| Reporting group title | Palovarotene |
| Reporting group description: | |
| Participants continued to receive palovarotene 5 milligram (mg) orally once daily until it was reimbursed in the country where the study was being conducted or another access program became available or until the study end date, whichever occurred first, up to approximately 32 months. In case of flare-up symptoms or substantial high risk traumatic events (likely to lead to a flare-up), participants received palovarotene 20 mg orally once daily for 4 weeks followed by 10 mg orally once daily for 8 weeks for a total of 12 weeks even if symptoms resolved earlier. | |

Primary: Number of Participants With All Treatment-emergent Adverse Events (TEAEs), Serious and Non-serious Treatment-emergent Adverse Events and Serious and Non-serious Treatment-related Treatment-emergent Adverse Events

| | |
|-----------------|---|
| End point title | Number of Participants With All Treatment-emergent Adverse Events (TEAEs), Serious and Non-serious Treatment-emergent Adverse Events and Serious and Non-serious Treatment-related Treatment-emergent Adverse Events ^[1] |
|-----------------|---|

End point description:

An adverse event (AE) was any untoward medical occurrence in a clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. An SAE was defined as any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect or significant medical event. A TEAE was defined as any AE that occurred after signing the informed consent form of this study or an ongoing AE from the parent study with a worsening in severity or relationship to the study treatment following transition to this study. The full analysis set (FAS)/safety set included all participants who received at least 1 dose of palovarotene in this study.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From signing the informed consent form (Day 1) up to 30 days post last dose, approximately 32 months

Notes:

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

Justification: As the endpoint was descriptive in nature, statistical analysis is not presented.

| End point values | Palovarotene | | | |
|-------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 59 | | | |
| Units: participants | | | | |
| All TEAEs | 54 | | | |
| Serious TEAEs | 9 | | | |
| Non-serious TEAEs | 53 | | | |
| Serious treatment-related TEAEs | 1 | | | |
| Non-serious treatment-related TEAEs | 38 | | | |

Statistical analyses

Secondary: Change From the Inclusion Visit in Cumulative Analogue Joint Involvement Scale (CAJIS) Total Score at Months 6, 12, 18, 24 and 30

| | |
|-----------------|---|
| End point title | Change From the Inclusion Visit in Cumulative Analogue Joint Involvement Scale (CAJIS) Total Score at Months 6, 12, 18, 24 and 30 |
|-----------------|---|

End point description:

The CAJIS is an objective measure of joint movement completed by the investigator to document total joint involvement. This scale assesses functional disability by categorizing range of motion across 12 joints (both right and left shoulder, elbow, wrist, hip, knee and ankle joints) and 3 body regions (cervical spine, thoracic/lumbar spine and jaw), with each joint/region assessed as: 0=normal (<10% deficit); 1=partially impaired (10% to 90% deficit) and 2=functionally ankylosed (>90% deficit). The CAJIS total score is calculated as the sum of the scores of all joints/regions and ranges from 0 (no involvement) to 30 (maximally involved). Higher score indicated worse outcome. The Inclusion Visit was the first study visit (Day 1) and first administration of palovarotene in this study. The FAS/safety set included all participants who received at least 1 dose of palovarotene in this study. Here, n=Only those participants with data collected at specified timepoints.

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

End point timeframe:

Inclusion Visit (Day 1) and Months 6, 12, 18, 24, 30

| End point values | Palovarotene | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 53 | | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 6 (n=52) | 0.6 (± 1.3) | | | |
| Month 12 (n=53) | 1.1 (± 2.0) | | | |
| Month 18 (n=45) | 1.5 (± 2.3) | | | |
| Month 24 (n=25) | 1.5 (± 2.6) | | | |
| Month 30 (n=8) | 2.0 (± 4.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From the Inclusion Visit in the use of Assistive Devices and Adaptations (Aids) for Daily Living at Months 6, 12, 18, 24 and 30

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|-----------------|--|
| End point title | Change From the Inclusion Visit in the use of Assistive Devices and Adaptations (Aids) for Daily Living at Months 6, 12, 18, 24 and 30 |
|-----------------|--|

End point description:

The use of assistive devices and adaptations (aids) for daily living was collected using the FOP assistive devices assessment at each visit. Assistive devices and adaptations include mobility aids, eating tools, personal care tools, bathroom aids and devices, bedroom aids and devices, home adaptations, work environment adaptations, technology adaptations, sports and recreation adaptations, school adaptations and medical therapies for daily living. The mean of total number of assistive devices and adaptations for daily living being used is presented. The Inclusion Visit was the first study visit (Day 1) and first administration of palovarotene in this study. The FAS/safety set included all participants who received at least 1 dose of palovarotene in this study. Here, n=Only those participants with data collected for specified categories at specified timepoints.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Inclusion Visit (Day 1) and Months 6, 12, 18, 24 and 30 | |

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | Palovarotene | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 53 | | | |
| Units: number of aids | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 6 (n=53) | -0.7 (± 3.4) | | | |
| Month 12 (n=51) | 1.1 (± 4.7) | | | |
| Month 18 (n=46) | 1.4 (± 5.7) | | | |
| Month 24 (n=23) | 1.2 (± 5.1) | | | |
| Month 30 (n=6) | 2.8 (± 7.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From the Inclusion Visit in Percentage of Worst Score Using the Adult Form of the Fibrodysplasia Ossificans Progressiva Physical Function Questionnaire (FOP-PFQ) at Months 6, 12, 18, 24 and 30

| | |
|-----------------|---|
| End point title | Change From the Inclusion Visit in Percentage of Worst Score Using the Adult Form of the Fibrodysplasia Ossificans Progressiva Physical Function Questionnaire (FOP-PFQ) at Months 6, 12, 18, 24 and 30 |
|-----------------|---|

End point description:

FOP-PFQ is disease-specific patient-reported outcome measure of physical impairment, includes 28 questions related to activities of daily living and physical performance scored on scale of 1 to 5 with lower scores indicating that participant has more difficulty completing those tasks. Total score, upper extremities subscore and mobility subscore is calculated as: total score: sum of scores from each question (range 28 to 140); upper extremities subscore: sum of scores from 15 questions (questions 1-12, 14, 25 and 26; range 15 to 75); mobility subscore: sum of scores from 13 questions (questions 13, 15-24, 27 and 28; range 13 to 65). Scores were transformed to reflect a percentage of worst score which ranged from 0-100% with 0% indicating best possible function and 100% (higher score) indicating worst possible function. Inclusion Visit was first study visit (Day 1) & first administration of palovarotene in this study. FAS/safety set. n=Participants with data collected for specified categories.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Inclusion Visit (Day 1) and Months 6, 12, 18, 24 and 30 | |

| End point values | Palovarotene | | | |
|---|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 | | | |
| Units: percentage of score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 6: total score (n=54) | 0.74 (± 6.37) | | | |
| Month 12: total score (n=52) | 2.39 (± 10.21) | | | |
| Month 18: total score (n=47) | 4.77 (± 12.39) | | | |
| Month 24: total score (n=25) | 7.80 (± 15.15) | | | |
| Month 30: total score (n=9) | 13.79 (± 21.98) | | | |
| Month 6: upper extremity subscore (n=54) | 0.70 (± 6.87) | | | |
| Month 12: upper extremity subscore (n=52) | 1.12 (± 8.52) | | | |
| Month 18: upper extremity subscore (n=47) | 3.24 (± 11.28) | | | |
| Month 24: upper extremity subscore (n=25) | 5.54 (± 12.42) | | | |
| Month 30: upper extremity subscore (n=9) | 8.15 (± 11.50) | | | |
| Month 6: mobility subscore (n=54) | 0.74 (± 9.15) | | | |
| Month 12: mobility subscore (n=52) | 3.90 (± 14.98) | | | |
| Month 18: mobility subscore (n=47) | 6.53 (± 17.45) | | | |
| Month 24: mobility subscore (n=25) | 10.38 (± 23.08) | | | |
| Month 30: mobility subscore (n=9) | 20.30 (± 36.44) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Healthcare Utilization (HU) in Participants With Fibrodysplasia Ossificans Progressiva

| | |
|-----------------|---|
| End point title | Annualized Rate of Healthcare Utilization (HU) in Participants With Fibrodysplasia Ossificans Progressiva |
|-----------------|---|

End point description:

Annualized HU rate was defined as the (number of HU during the study/duration of participant participation in the study in days) * 365.25. Annualized rate for total health care services utilized is presented. The FAS/safety set included all participants who received at least 1 dose of palovarotene in this study. Only those participants with data collected at specified timepoints are reported.

| | |
|-------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 32 months | |

| | | | | |
|--------------------------------------|--------------------|--|--|--|
| End point values | Palovarotene | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 55 | | | |
| Units: HU per participant year | | | | |
| arithmetic mean (standard deviation) | 21.7 (\pm 31.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From the Inclusion Visit in Percent Predicted Forced Vital Capacity (FVC) at Months 6, 12, 18, 24 and 30

| | |
|-----------------|---|
| End point title | Change From the Inclusion Visit in Percent Predicted Forced Vital Capacity (FVC) at Months 6, 12, 18, 24 and 30 |
|-----------------|---|

End point description:

Lung function parameters including FVC were obtained by spirometry. The Inclusion Visit was the first study visit (Day 1) and first administration of palovarotene in this study. The FAS/safety set included all participants who received at least 1 dose of palovarotene in this study. Here, n=Only those participants with data collected at specified categories at specified timepoints.

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

End point timeframe:

Inclusion Visit (Day 1) and Months 6, 12, 18, 24 and 30

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | Palovarotene | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 38 | | | |
| Units: percent predicted FVC | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 6 (n=17) | 1.2 (\pm 5.5) | | | |
| Month 12 (n=38) | -0.7 (\pm 6.8) | | | |
| Month 18 (n=16) | -3.9 (\pm 9.8) | | | |
| Month 24 (n=15) | -1.6 (\pm 5.8) | | | |
| Month 30 (n=4) | -2.8 (\pm 3.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From the Inclusion Visit in Percent Predicted Forced Expiratory Volume in One Second (FEV1) at Months 6, 12, 18, 24 and 30

| | |
|-----------------|---|
| End point title | Change From the Inclusion Visit in Percent Predicted Forced Expiratory Volume in One Second (FEV1) at Months 6, 12, 18, 24 and 30 |
|-----------------|---|

End point description:

Lung function parameters including FEV1 were obtained by spirometry. The Inclusion Visit was the first study visit (Day 1) and first administration of palovarotene in this study. The FAS/safety set included all

participants who received at least 1 dose of palovarotene in this study. Here, n=Only those participants with data collected at specified categories at specified timepoints.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Inclusion Visit (Day 1) and Months 6, 12, 18, 24 and 30 | |

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | Palovarotene | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 38 | | | |
| Units: percent predicted FEV1 | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 6 (n=17) | 1.8 (± 5.9) | | | |
| Month 12 (n=38) | -3.1 (± 9.6) | | | |
| Month 18 (n=16) | -5.3 (± 11.8) | | | |
| Month 24 (n=15) | -3.8 (± 6.6) | | | |
| Month 30 (n=4) | -10.0 (± 11.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From the Inclusion Visit in Predicted FEV1/FVC Ratio at Months 6, 12, 18, 24 and 30

| | |
|-----------------|--|
| End point title | Change From the Inclusion Visit in Predicted FEV1/FVC Ratio at Months 6, 12, 18, 24 and 30 |
|-----------------|--|

End point description:

The ratio of FEV1 to FVC was calculated. Lung function parameters were obtained by spirometry. The Inclusion Visit was the first study visit (Day 1) and first administration of palovarotene in this study. The FAS/safety set included all participants who received at least 1 dose of palovarotene in this study. Here, n=Only those participants with data collected at specified categories at specified timepoints.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Inclusion Visit (Day 1) and Months 6, 12, 18, 24 and 30 | |

| | | | | |
|--------------------------------------|--------------------|--|--|--|
| End point values | Palovarotene | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 38 | | | |
| Units: ratio | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 6 (n=17) | 0.0163 (± 0.0574) | | | |
| Month 12 (n=38) | -0.0323 (± 0.1358) | | | |

| | | | | |
|-----------------|-------------------------|--|--|--|
| Month 18 (n=16) | -0.0137 (\pm 0.0888) | | | |
| Month 24 (n=15) | -0.0365 (\pm 0.0994) | | | |
| Month 30 (n=4) | -0.1268 (\pm 0.1564) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From the Inclusion Visit in Percent Predicted Diffusion Capacity of the Lung for Carbon Monoxide (DLCO) at Months 6, 12, 18, 24 and 30

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|-----------------|---|
| End point title | Change From the Inclusion Visit in Percent Predicted Diffusion Capacity of the Lung for Carbon Monoxide (DLCO) at Months 6, 12, 18, 24 and 30 |
|-----------------|---|

End point description:

The DLCO test provides information on the efficiency of gas transfer from alveolar air into the bloodstream. The Inclusion Visit was the first study visit (Day 1) and first administration of palovarotene in this study. The FAS/safety set included all participants who received at least 1 dose of palovarotene in this study. Here, n=Only those participants with data collected at specified categories at specified timepoints.

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

End point timeframe:

Inclusion Visit (Day 1) and Months 6, 12, 18, 24 and 30

| End point values | Palovarotene | | | |
|--------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 36 | | | |
| Units: percent predicted DLCO | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 6 (n=14) | -1.5 (\pm 7.9) | | | |
| Month 12 (n=36) | -5.3 (\pm 12.6) | | | |
| Month 18 (n=14) | -4.4 (\pm 16.5) | | | |
| Month 24 (n=14) | -4.8 (\pm 11.4) | | | |
| Month 30 (n=3) | -20.0 (\pm 20.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From the Inclusion Visit in Physical and Mental Function Using Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale at Months 6, 12, 18, 24 and 30

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|-----------------|--|
| End point title | Change From the Inclusion Visit in Physical and Mental Function Using Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale at Months 6, 12, 18, 24 and 30 |
|-----------------|--|

End point description:

The PROMIS Global Health Scale is a patient-reported outcome measure of physical and mental function. The adult form (developed for participants ≥ 15 years old) was used for all participants, consists of 10 questions from which 2 scores are calculated: global physical health score (GPH) and global mental health (GMH) score, each ranging from 4 (worse health) to 20 (better health). GPH score: sum of scores from Questions 3, 6, 7 and 8 and GMH score: sum of scores from Questions 2, 4, 5 and 10. These scores were converted to a T-score whose distributions were standardized such that value of 50 represented average (mean) for the general population and increments of ± 10 points represented ± 1 standard deviation away from the norm. Higher T-scores indicated better physical/mental health. T-score < 50 indicated worse health than general population, while a T-score > 50 indicated better health. The FAS/safety set. n=Only those participants with data collected are reported.

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

End point timeframe:

Inclusion Visit (Day 1) and Months 6, 12, 18, 24 and 30

| End point values | Palovarotene | | | |
|--------------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 | | | |
| Units: T-score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 6: GPH (n=54) | -0.6 (± 4.4) | | | |
| Month 12: GPH (n=53) | -1.7 (± 5.0) | | | |
| Month 18: GPH (n=48) | -2.9 (± 5.0) | | | |
| Month 24: GPH (n=24) | -1.9 (± 5.8) | | | |
| Month 30: GPH (n=8) | -3.9 (± 7.0) | | | |
| Month 6: GMH (n=54) | -1.0 (± 4.8) | | | |
| Month 12: GMH (n=53) | -1.5 (± 6.3) | | | |
| Month 18: GMH (n=48) | -2.3 (± 6.9) | | | |
| Month 24: GMH (n=24) | -2.2 (± 6.0) | | | |
| Month 30: GMH (n=8) | -5.7 (± 5.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Flare-ups and Flare-up Outcomes

| | |
|-----------------|---|
| End point title | Number of Participants With Flare-ups and Flare-up Outcomes |
|-----------------|---|

End point description:

Number of participants with at least 1 flare-up and intercurrent flare-ups since last visit is presented. Intercurrent flare-ups were defined as a new flare-up or marked worsening of the original flare up at any time during a flare-up-based treatment cycle. Outcome of flare-ups resulting in movement restriction and bone formations in participants is presented. Movement restriction includes categories like better, same, slightly worse, moderately worse and severely worse movement than before. The FAS/safety set included all participants who received at least 1 dose of palovarotene in this study.

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

End point timeframe:

Months 6, 12, 18 and 24

| End point values | Palovarotene | | | |
|---|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 59 | | | |
| Units: participants | | | | |
| Month 6: at least 1 flare up since last visit | 27 | | | |
| Month 12: at least 1 flare up since last visit | 26 | | | |
| Month 18: at least 1 flare up since last visit | 15 | | | |
| Month 24: at least 1 flare up since last visit | 4 | | | |
| Month 6: intercurrent flare-ups since last visit | 7 | | | |
| Month 12: intercurrent flare-ups since last visit | 4 | | | |
| Month 18: intercurrent flare-ups since last visit | 4 | | | |
| Month 24: intercurrent flare-ups since last visit | 0 | | | |
| Month 6: better movement | 0 | | | |
| Month 6: same movement | 22 | | | |
| Month 6: slightly worse movement | 7 | | | |
| Month 6: moderately worse movement | 5 | | | |
| Month 6: severely worse movement | 1 | | | |
| Month 12: better movement | 1 | | | |
| Month 12: same movement | 17 | | | |
| Month 12: slightly worse movement | 10 | | | |
| Month 12: moderately worse movement | 5 | | | |
| Month 12: severely worse movement | 0 | | | |
| Month 18: better movement | 0 | | | |
| Month 18: same movement | 7 | | | |
| Month 18: slightly worse movement | 7 | | | |
| Month 18: moderately worse movement | 1 | | | |
| Month 18: severely worse movement | 1 | | | |
| Month 24: better movement | 0 | | | |
| Month 24: same movement | 1 | | | |
| Month 24: slightly worse movement | 3 | | | |
| Month 24: moderately worse movement | 0 | | | |
| Month 24: severely worse movement | 1 | | | |
| Month 6: bone formation | 5 | | | |
| Month 12: bone formation | 5 | | | |
| Month 18: bone formation | 1 | | | |
| Month 24: bone formation | 0 | | | |

Statistical analyses

Secondary: Number of Participants With Flare-ups by Body Location

| | |
|--|--|
| End point title | Number of Participants With Flare-ups by Body Location |
| End point description: | |
| Number of participants with flare-ups by body locations including shoulder, elbow, hip, knee, ankle or foot, back, jaw and submandibular area and other (includes all other locations than mentioned) is presented. The FAS/safety set included all participants who received at least 1 dose of palovarotene in this study. | |
| End point type | Secondary |
| End point timeframe: | |
| Months 6, 12, 18 and 24 | |

| End point values | Palovarotene | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 59 | | | |
| Units: participants | | | | |
| Month 6: shoulder | 8 | | | |
| Month 6: elbow | 3 | | | |
| Month 6: hip | 5 | | | |
| Month 6: knee | 5 | | | |
| Month 6: ankle or foot | 3 | | | |
| Month 6: back | 4 | | | |
| Month 6: jaw and submandibular area | 4 | | | |
| Month 6: other | 14 | | | |
| Month 12: shoulder | 4 | | | |
| Month 12: elbow | 2 | | | |
| Month 12: hip | 5 | | | |
| Month 12: knee | 3 | | | |
| Month 12: ankle or foot | 5 | | | |
| Month 12: back | 2 | | | |
| Month 12: jaw and submandibular area | 3 | | | |
| Month 12: other | 12 | | | |
| Month 18: shoulder | 4 | | | |
| Month 18: elbow | 1 | | | |
| Month 18: hip | 3 | | | |
| Month 18: knee | 2 | | | |
| Month 18: ankle or foot | 2 | | | |
| Month 18: back | 1 | | | |
| Month 18: jaw and submandibular area | 0 | | | |
| Month 18: other | 8 | | | |
| Month 24: shoulder | 1 | | | |
| Month 24: elbow | 0 | | | |
| Month 24: hip | 0 | | | |
| Month 24: knee | 1 | | | |
| Month 24: ankle or foot | 1 | | | |
| Month 24: back | 0 | | | |
| Month 24: jaw and submandibular area | 0 | | | |

| | | | | |
|-----------------|---|--|--|--|
| Month 24: other | 2 | | | |
|-----------------|---|--|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Flare-up at Months 6, 12, 18 and 24

| | |
|---|---|
| End point title | Duration of Flare-up at Months 6, 12, 18 and 24 |
| End point description: Duration of flare-up was defined as (date of end of flare-up – date of start of flare-up + 1). The FAS/safety set included all participants who received at least 1 dose of palovarotene in this study. Here, n=Only those participants with data collected at specified categories at specified timepoints are reported. | |
| End point type | Secondary |
| End point timeframe: Months 6, 12, 18 and 24 | |

| End point values | Palovarotene | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 | | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 6 (n=27) | 130.7 (± 153.3) | | | |
| Month 12 (n=26) | 121.7 (± 102.7) | | | |
| Month 18 (n=15) | 72.4 (± 42.6) | | | |
| Month 24 (n=4) | 72.3 (± 53.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Extra Bone Growth at Months 6, 12, 18 and 24

| | |
|--|--|
| End point title | Percentage of Participants With Extra Bone Growth at Months 6, 12, 18 and 24 |
| End point description: Percentage of participants with at least 1 extra bone growth associated or not with a flare-up since last visit is presented. The FAS/safety set included all participants who received at least 1 dose of palovarotene in this study. | |
| End point type | Secondary |
| End point timeframe: Months 6, 12, 18 and 24 | |

| | | | | |
|-----------------------------------|-----------------|--|--|--|
| End point values | Palovarotene | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 59 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Month 6: associated | 8.5 | | | |
| Month 6: not associated | 3.4 | | | |
| Month 12: associated | 8.5 | | | |
| Month 12: not associated | 8.5 | | | |
| Month 18: associated | 1.7 | | | |
| Month 18: not associated | 3.4 | | | |
| Month 24: associated | 0 | | | |
| Month 24: not associated | 3.4 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and deaths were collected from signing the informed consent form (Day 1) up to 30 days post last dose, approximately 32 months

Adverse event reporting additional description:

The FAS/safety set included all participants who received at least 1 dose of palovarotene in this study.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 27.1 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Participants continued to receive palovarotene 5 mg orally once daily until it was reimbursed in the country where the study was being conducted or another access program became available or until the study end date, whichever occurred first, up to approximately 32 months.

In case of flare-up symptoms or substantial high risk traumatic events (likely to lead to a flare-up), participants received palovarotene 20 mg orally once daily for 4 weeks followed by 10 mg orally once daily for 8 weeks for a total of 12 weeks even if symptoms resolved earlier.

| Serious adverse events | Palovarotene | | |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 59 (15.25%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | 2 | | |
| Investigations | | | |
| SARS-CoV-2 test positive | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Fibula fracture | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------|--|--|
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| 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 | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Callus formation delayed | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |

| | | | |
|---|----------------|--|--|
| COVID-19 | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| 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 | 45 / 59 (76.27%) | | |
| Injury, poisoning and procedural complications | | | |
| Extraskkeletal ossification | | | |
| subjects affected / exposed | 4 / 59 (6.78%) | | |
| occurrences (all) | 6 | | |
| Fall | | | |
| subjects affected / exposed | 10 / 59 (16.95%) | | |
| occurrences (all) | 12 | | |
| Skin abrasion | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 7 / 59 (11.86%) 8 | | |
| Vascular disorders Lymphoedema subjects affected / exposed occurrences (all) | 5 / 59 (8.47%) 5 | | |
| General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all) | 4 / 59 (6.78%) 6 | | |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 5 / 59 (8.47%) 5 | | |
| Gastrointestinal disorders Lip dry subjects affected / exposed occurrences (all) | 4 / 59 (6.78%) 4 | | |
| Respiratory, thoracic and mediastinal disorders Lung diffusion disorder subjects affected / exposed occurrences (all) | 3 / 59 (5.08%) 4 | | |
| Skin and subcutaneous tissue disorders Decubitus ulcer subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Pruritus | 3 / 59 (5.08%) 5 14 / 59 (23.73%) 16 4 / 59 (6.78%) 5 4 / 59 (6.78%) 4 | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 5 / 59 (8.47%) | | |
| occurrences (all) | 6 | | |
| Rash | | | |
| subjects affected / exposed | 4 / 59 (6.78%) | | |
| occurrences (all) | 6 | | |
| Skin disorder | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | | |
| occurrences (all) | 3 | | |
| Skin exfoliation | | | |
| subjects affected / exposed | 4 / 59 (6.78%) | | |
| occurrences (all) | 4 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 6 / 59 (10.17%) | | |
| occurrences (all) | 8 | | |
| Back pain | | | |
| subjects affected / exposed | 7 / 59 (11.86%) | | |
| occurrences (all) | 9 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 5 / 59 (8.47%) | | |
| occurrences (all) | 7 | | |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 11 / 59 (18.64%) | | |
| occurrences (all) | 11 | | |
| Localised infection | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | | |
| occurrences (all) | 3 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | | |
| occurrences (all) | 4 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 5 / 59 (8.47%) | | |
| occurrences (all) | 5 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|---------------------|--|--|
| Vitamin D deficiency subjects affected / exposed occurrences (all) | 3 / 59 (5.08%) 3 | | |
|--|---------------------|--|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 01 October 2021 | Clarified that some assessments performed at the parent EOS visit were also considered as the Inclusion Visit assessments for this study. Updated the maximum number of participants of parent studies who were eligible for this study. Introduced section 10.2.3 collection of pregnancy information. Added the correctly named Independent Data Monitoring Committee (IDMC) in place of the Data Safety Monitoring Board. Made minor corrections. |
| 28 April 2022 | Updated the exclusion criterion to reflect the new risk of 'radiological vertebral fracture'. Added the spinal health assessment to the schedule of activities and a new section in the safety assessments section and added a preventive medication section to reflect the radiological vertebral fracture' risk. Removed all references of the caregiver interview; interviews were only conducted for study participants. Clarified that the Inclusion and EOS/EW Visit could be performed remotely. Stated that the participant interviews were conducted within 1 year of the Inclusion Visit. Clarified that the interviews were conducted by the Principal investigator or qualified site staff and that participants continued to be treated with palovarotene in this trial until palovarotene was reimbursed, or another access program became available, or until the study end date of November 2024 was reached, whichever occurred first. Clarified that monthly pregnancy tests might be performed at home with the assistance of a study nurse or self-administered. Clarified the collection of FOP-PFQ and PROMIS questionnaire date for participants <15 years. Updated the number of IDMC meetings (from 2 to 3). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported