



## Clinical trial results:

### A Phase 2, Open-Label, Efficacy and Safety Study of an RAR-Specific Agonist (Palovarotene) to Prevent Heterotopic Ossification in Subjects with Fibrodysplasia Ossificans Progressiva (FOP)

#### Summary

EudraCT number	2016-002526-36
Trial protocol	FR
Global end of trial date	28 June 2022

#### Results information

Result version number	v1 (current)
This version publication date	08 July 2023
First version publication date	08 July 2023
Summary attachment (see zip file)	Notice of Combined Results_2016-002526-36 (Notice of Combined Results_2016-002526-36_PVO-1A-204.doc)

#### Trial information

##### Trial identification

Sponsor protocol code	PVO-1A-204
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02979769
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Clementia Pharmaceuticals Inc.
Sponsor organisation address	1000 De La Gauchetière, Suite 1200, Montreal, Quebec, Canada, H3B 4W5
Public contact	Medical Director, Ipsen, clinical.trials@ipson.com
Scientific contact	Medical Director, Ipsen, clinical.trials@ipson.com

Notes:

##### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001662-PIP01-14
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 June 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 June 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of different palovarotene dosing regimens to prevent heterotopic ossification (HO) following a flare-up in participants with fibrodysplasia ossificans progressiva (FOP). Efficacy will be based on the ability of palovarotene to prevent HO as assessed by low-dose whole body computed tomography (WBCT) scan, excluding head.

99999 is "not applicable" value. As this study is a country-specific protocol (France) of PVO-1A-202 study, the safety and efficacy results were reported in PVO-1A-202 study (2014-002496-28).

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	28 November 2016
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	France: 99999
Worldwide total number of subjects	99999
EEA total number of subjects	99999

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)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	99999
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This Phase 2, open-label, France-specific study is equivalent to Parts B, C and D of PVO-1A-202 (2014-002496-28) study. A country-specific protocol was requested by French regulatory authorities.

### Pre-assignment

Screening details:

Participants who successfully completed Part A of PVO-1A-202 study were followed for up to 24 months. A total of 9 participants were enrolled in this France-specific study.

### 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
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Arm description:

All eligible participants from Part A of PVO-1A-202 study were enrolled in this study to receive palovarotene 5 milligram (mg) once daily for up to 24 months (weight-adjusted doses for skeletally immature participants). Participants with flare-ups received palovarotene 20 mg once daily for 4 weeks followed by 10 mg once daily for 8 weeks.

All weight-based dosing was ceased when participants were skeletally mature, but radiographic assessment of the growth plate continued until these participants achieved 100% skeletal maturity at both knee and hand/wrist locations.

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

Dosage and administration details:

Participants received palovarotene 20 mg daily for 4 weeks followed by 10 mg once daily for 8 weeks (or exposure-equivalent doses based on weight) during flare-ups, totaling 12 weeks of treatment. Palovarotene was to be taken orally with food at approximately the same time each day.

<b>Number of subjects in period 1</b>	Palovarotene
Started	99999
Completed	99999

## Baseline characteristics

### Reporting groups

Reporting group title	Palovarotene
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Reporting group description:

All eligible participants from Part A of PVO-1A-202 study were enrolled in this study to receive palovarotene 5 milligram (mg) once daily for up to 24 months (weight-adjusted doses for skeletally immature participants). Participants with flare-ups received palovarotene 20 mg once daily for 4 weeks followed by 10 mg once daily for 8 weeks.

All weight-based dosing was ceased when participants were skeletally mature, but radiographic assessment of the growth plate continued until these participants achieved 100% skeletal maturity at both knee and hand/wrist locations.

Reporting group values	Palovarotene	Total	
Number of subjects	99999	99999	
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)	0	0	
Adolescents (12-17 years)	99999	99999	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	99999	99999	
Male	0	0	

## End points

### End points reporting groups

Reporting group title	Palovarotene
Reporting group description: All eligible participants from Part A of PVO-1A-202 study were enrolled in this study to receive palovarotene 5 milligram (mg) once daily for up to 24 months (weight-adjusted doses for skeletally immature participants). Participants with flare-ups received palovarotene 20 mg once daily for 4 weeks followed by 10 mg once daily for 8 weeks. All weight-based dosing was ceased when participants were skeletally mature, but radiographic assessment of the growth plate continued until these participants achieved 100% skeletal maturity at both knee and hand/wrist locations.	

### Primary: Annualized Change in New HO Volume

End point title	Annualized Change in New HO Volume <sup>[1]</sup>
End point description: The annualized change in new HO volume was assessed by low-dose whole body computed tomography (WBCT) scan, excluding head.	
End point type	Primary
End point timeframe: Month 12	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Efficacy results were reported in PVO-1A-202 study (2014-002496-28).	

End point values	Palovarotene			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[2]</sup>			
Units: not applicable				
number (not applicable)				

Notes:  
[2] - Efficacy results were reported in PVO-1A-202 study (2014-002496-28).

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With New HO

End point title	Percentage of Participants With New HO
End point description: New HO was defined as total WBCT new HO volume >0.	
End point type	Secondary
End point timeframe: Months 12, 24, 36, 48, 60 and 72	

<b>End point values</b>	Palovarotene			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[3]</sup>			
Units: not applicable				
number (not applicable)				

Notes:

[3] - Efficacy results were reported in PVO-1A-202 study (2014-002496-28).

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Range of Motion (ROM) at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72

End point title	Change From Baseline in Range of Motion (ROM) at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72
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End point description:

The ROM was assessed by the Investigator using Cumulative Analogue Joint Involvement Scale. It includes 12 joints (shoulder, elbow, wrist, hip, knee, and ankle on both the right and left sides), and 3 body regions (jaw, cervical spine [neck], and thoracic/lumbar spine). Each joint/region was assessed as: 0=uninvolved; 1=partially involved; and 2=completely ankylosed. The total score range is 0 (no involvement) to 30 (maximally involved). Higher scores indicates worst outcome.

End point type	Secondary
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End point timeframe:

Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72

<b>End point values</b>	Palovarotene			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[4]</sup>			
Units: not applicable				
number (not applicable)				

Notes:

[4] - Efficacy results were reported in PVO-1A-202 study (2014-002496-28).

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Physical Function at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72

End point title	Change From Baseline in Physical Function at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72
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End point description:

The effect of palovarotene on physical function was determined using FOP-Physical Function Questionnaire. The questionnaire consisted of 28 items ranging from 1 (not able to do) to 5 (with no trouble; without help or assistive device). Lower scores denoted more difficulty, with items categorized into upper extremity and mobility sections.

End point type	Secondary
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End point timeframe:

Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72

<b>End point values</b>	Palovarotene			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[5]</sup>			
Units: not applicable				
number (not applicable)				

Notes:

[5] - Efficacy results were reported in PVO-1A-202 study (2014-002496-28).

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Physical and Mental Function for Participants $\geq 15$ Years Old and Mental Function for Participants $< 15$ Years Old at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72

End point title	Change From Baseline in Physical and Mental Function for Participants $\geq 15$ Years Old and Mental Function for Participants $< 15$ Years Old at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72
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End point description:

The patient reported outcomes measurement information system (PROMIS) global health scale was administered to evaluate the effect of palovarotene on physical and mental health in participants  $\geq 15$  years of age and mental health in participants  $< 15$  years of age, age-appropriate forms of the PROMIS global health scales were administered. A T-score of 50 is normal and increments of 10 are +/- standard deviation away from the norm. A T-score  $< 50$  indicates worse health, while a T-score  $> 50$  indicates better health. Higher values (positive changes) indicate better health.

End point type	Secondary
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End point timeframe:

Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72

<b>End point values</b>	Palovarotene			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[6]</sup>			
Units: not applicable				
number (not applicable)				

Notes:

[6] - Efficacy results were reported in PVO-1A-202 study (2014-002496-28).

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Information on adverse events were reported in PVO-1A-202 study (2014-002496-28).

Adverse event reporting additional description:

As this study is a country-specific protocol (France) of PVO-1A-202 study, the safety results will be reported in PVO-1A-202 study (2014-002496-28).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	999999
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### Reporting groups

Reporting group title	Palovarotene
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Reporting group description:

All eligible participants from Part A of PVO-1A-202 study were enrolled in this study to receive palovarotene 5 mg once daily for up to 24 months (weight-adjusted doses for skeletally immature participants). Participants with flare-ups received palovarotene 20 mg once daily for 4 weeks followed by 10 mg once daily for 8 weeks.

All weight-based dosing was ceased when participants were skeletally mature, but radiographic assessment of the growth plate continued until these participants achieved 100% skeletal maturity at both knee and hand/wrist locations.

Serious adverse events	Palovarotene		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 99999 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Palovarotene		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 99999 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: As this study is a country-specific protocol (France) of PVO-1A-202 study, the safety results will be reported in PVO-1A-202 study (2014-002496-28).

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 September 2016	Specified that Adult Cohort participants under the age of 18 years are to receive weight-adjusted doses of 20 mg palovarotene (for 28 days) and 10 mg palovarotene (for 56 days) during a flare-up. Added an electrocardiogram assessment on Flare-up Day 7 (Week 1).
22 March 2018	Blood sampling for pharmacokinetic analysis added during chronic dosing for all participants. Participants receiving weight-adjusted dosing for non-flare-up based treatment changed from "participants under the age of 18 years" to "skeletally immature participants." The Investigator will be notified about any protocol-specified safety laboratory test that could not be obtained despite at least two attempts. Included a reference to and description of the PVO-1A-301 Bone Safety Management Plan and additional safety assessments to be followed in this study. Added that if the study is closed due to safety concerns, then all participants exposed to the investigational drug will be followed for safety with the length of follow-up determined based on the safety risk.
08 March 2019	Changed the timing of clinical laboratory assessments during non-flare-up based treatment from every 3 months to every 6 months. Blood volumes were adjusted to reflect the change. Changed the timing of clinical laboratory assessments, Columbia-Suicide Severity Rating Scale, vital signs, and body weight determination during a Flare-Up Cycle. Noted that flare-up based dosing should be initiated if the Investigator confirms the presence of a substantial, high-risk traumatic event likely to lead to a flare-up.
31 October 2019	Added radiographic assessments of the knee and hand/wrist to be performed every 3 months in those participants who (1) received the flare-up dosing regimen in the period of time since their last radiographic assessment; and (2) had not achieved 100% skeletal maturity on their last radiographic assessment. Added 6-month radiographic assessments of the knee and hand/wrist in skeletally immature participants. During flare-up dosing, safety assessments will recur every 12 weeks (instead of every 8 weeks) after Flare-up Cycle Safety Day 1 until treatment of the last flare-up or traumatic event in the cycle is completed. The 4-week safety assessment will no longer be performed.
18 December 2020	References to Parts B/C/D are to PVO-1A-202 Parts B/C/D which corresponds to PVO-1A-204, ongoing in France. Part D was added for skeletally immature participants who stopped taking study medication for any reason before completion of Part A/B/C. In Part C, participants may continue on the study for up to an additional 12 months. Added assessments for spinal health carried out on low dose WBCT scans collected in the study.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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04 December 2019	<p>As of 04 December 2019, all participants &lt;14 years of age were required to interrupt study drug due to a partial clinical hold placed on the palovarotene clinical development program by the FDA.</p> <p>On 24-Jan-2020, treatment was temporarily halted in all participants over the age of 14 years in the palovarotene FOP trials including PVO-1A-202/204 when the futility boundary was crossed at an interim analysis in the Phase 3 PVO-1A-301 study. After post-hoc analyses showed that the pre-specified analyses may have skewed and negatively affected the results, dosing was re-initiated only in participants 14 years and above that were able and willing to re-start treatment (in the context of COVID-19 conditions, starting 04 June 2020).</p>	04 June 2020
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Notes:

## Limitations and caveats

None reported