



Clinical trial results:

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of a RAR-Specific Agonist (Palovarotene) in the Treatment of Preosseous Flare-ups in Subjects with Fibrodysplasia Ossificans Progressiva (FOP).

Summary

EudraCT number	2014-001453-17
Trial protocol	GB
Global end of trial date	23 May 2016

Results information

Result version number	v1 (current)
This version publication date	01 June 2018
First version publication date	01 June 2018

Trial information

Trial identification

Sponsor protocol code	PVO-1A-201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02190747
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Clementia Pharmaceuticals Inc.
Sponsor organisation address	4150 Sainte-Catherine Street West, Suite 550, Montreal, Canada, H3Z 2Y5
Public contact	Clinical Trials Information, Clementia Pharmaceuticals Inc., clinicaltrials@clementiapharma.com
Scientific contact	Clinical Trials Information, Clementia Pharmaceuticals Inc., clinicaltrials@clementiapharma.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	14 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 May 2016
Global end of trial reached?	Yes
Global end of trial date	23 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective was to evaluate the ability of different doses of palovarotene to prevent heterotopic ossification (HO) at the flare-up site in subjects with FOP as assessed by plain radiographs.

Images were evaluated for HO and soft tissue edema by a central imaging laboratory using two independent treatment-blinded procedures: Primary Reads and Global Reads. For Primary Reads, two musculoskeletal radiologists independently evaluated the volume of HO and soft tissue edema from each relevant imaging modality with no comparisons across modalities. Global Reads were performed by one of these radiologists, an independent musculoskeletal consultant radiologist, an independent consultant ultrasound radiologist, and the Investigators. From Global Reads, HO was evaluated only after the review of all images across all modalities and time points.

Primary Reads were used to assess primary outcomes, per protocol. Global Reads were more holistic, and used to elucidate efficacy results.

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 ICH Good Clinical Practice (ICH GCP), EU Directive 2001/20/EC, US Food and Drug Administration (FDA) Code of Federal Regulations and other applicable local regulatory requirements, which ever afforded the greater subject protection. The study protocol and informed consent (ICF)/assent documents to be used in the clinical study were approved by an IRB/IEC prior to initiation of the study. The ICF was written in a language and in a form understandable to the subjects/parents.

Background therapy: -

Evidence for comparator:

Not Applicable

Actual start date of recruitment	14 July 2014
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	United States: 29
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 9
Worldwide total number of subjects	40
EEA total number of subjects	11

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	9
Adolescents (12-17 years)	9
Adults (18-64 years)	22
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eight subjects aged ≥ 15 years were randomized 3:1 to palovarotene:placebo in Cohort 1; 8 additional subjects were randomised 3:1 in an interim period between Cohorts 1 and 2 (included in the description of Cohort 1). In Cohort 2, additional FOP subjects aged ≥ 6 years were randomized 3:3:2 across two weight-based regimens of palovarotene or placebo.

Pre-assignment

Screening details:

The study included clinically diagnosed FOP subjects at least 6 years of age (Cohort 2) or 15 years of age and older (Cohort 1) with symptomatic onset of a flare-up within 7 days of treatment start and accessible for treatment and follow-up.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Palovarotene 10/5 mg

Arm description:

Subjects received palovarotene 10 mg for 14 days followed by 5 mg for 28 days during flare-ups (10/5-mg regimen). The subjects were followed for an additional 42 days without treatment. Subjects in Cohort 1 and Cohort 2 contributed to this arm.

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

Dosage and administration details:

Subjects received 10 mg once daily for 14 days followed by 5 mg once daily for 28 days (or weight-adjusted equivalent for skeletally immature subjects) during flare-ups, totaling 42 days of treatment. Palovarotene was to be taken orally with food at approximately the same time each day.

Arm title	Palovarotene 5/2.5 mg
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Arm description:

Subjects received palovarotene 5 mg for 14 days followed by 2.5 mg for 28 days during flare-ups (5/2.5-mg regimen). The subjects were followed for an additional 42 days without treatment. Only subjects in Cohort 2 contributed to this arm.

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

Dosage and administration details:

Subjects received a palovarotene 5 mg daily for 14 days followed by 2.5 mg daily for 28 days (or weight-adjusted equivalent for skeletally immature subjects) during flare-ups, totaling 42 days of treatment. Palovarotene was to be taken orally with food at approximately the same time each day.

Arm title	Placebo
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Arm description:

Subjects received placebo for 42 days during flare-ups. Subjects were followed for an additional 42 days without treatment. Subjects in Cohort 1 and Cohort 2 contributed to this arm.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo was taken orally with food at approximately the same time once daily for 42 days during flare-ups.

Number of subjects in period 1	Palovarotene 10/5 mg	Palovarotene 5/2.5 mg	Placebo
Started	21	9	10
Completed	21	9	10

Baseline characteristics

Reporting groups

Reporting group title	Palovarotene 10/5 mg
Reporting group description:	
Subjects received palovarotene 10 mg for 14 days followed by 5 mg for 28 days during flare-ups (10/5-mg regimen). The subjects were followed for an additional 42 days without treatment. Subjects in Cohort 1 and Cohort 2 contributed to this arm.	
Reporting group title	Palovarotene 5/2.5 mg
Reporting group description:	
Subjects received palovarotene 5 mg for 14 days followed by 2.5 mg for 28 days during flare-ups (5/2.5-mg regimen). The subjects were followed for an additional 42 days without treatment. Only subjects in Cohort 2 contributed to this arm.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo for 42 days during flare-ups. Subjects were followed for an additional 42 days without treatment. Subjects in Cohort 1 and Cohort 2 contributed to this arm.	

Reporting group values	Palovarotene 10/5 mg	Palovarotene 5/2.5 mg	Placebo
Number of subjects	21	9	10
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	3	4	2
Adolescents (12-17 years)	5	0	4
Adults (18-64 years)	13	5	4
From 65-84 years	0	0	0
Gender categorical Units: Subjects			
Female	9	6	7
Male	12	3	3

Reporting group values	Total		
Number of subjects	40		
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	9		
Adolescents (12-17 years)	9		
Adults (18-64 years)	22		
From 65-84 years	0		
Gender categorical Units: Subjects			
Female	22		
Male	18		

Subject analysis sets

Subject analysis set title	Full analysis
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) included all subjects who received at least one dose of study drug AND had at least one post-baseline radiograph sufficient for the determination of HO at the flare-up site.

Subject analysis set title	Per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) analysis set included all subjects who were eligible for the FAS, with no major protocol deviations, with at least 80% compliance with study medication, and had an evaluable radiograph or CT at Day 42 sufficient for the determination of HO at the flare-up site. Exclusions from the PP analysis set were identified prior to database lock, comprising one subject in the 10/5 mg palovarotene group who received less than 80% of the required dose.

Reporting group values	Full analysis	Per protocol	
Number of subjects	40	39	
Age categorical			
Units: Subjects			
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	9	9	
Adolescents (12-17 years)	9	8	
Adults (18-64 years)	22	22	
From 65-84 years	0	0	
Gender categorical			
Units: Subjects			
Female	22	22	
Male	18	17	

End points

End points reporting groups

Reporting group title	Palovarotene 10/5 mg
Reporting group description: Subjects received palovarotene 10 mg for 14 days followed by 5 mg for 28 days during flare-ups (10/5-mg regimen). The subjects were followed for an additional 42 days without treatment. Subjects in Cohort 1 and Cohort 2 contributed to this arm.	
Reporting group title	Palovarotene 5/2.5 mg
Reporting group description: Subjects received palovarotene 5 mg for 14 days followed by 2.5 mg for 28 days during flare-ups (5/2.5-mg regimen). The subjects were followed for an additional 42 days without treatment. Only subjects in Cohort 2 contributed to this arm.	
Reporting group title	Placebo
Reporting group description: Subjects received placebo for 42 days during flare-ups. Subjects were followed for an additional 42 days without treatment. Subjects in Cohort 1 and Cohort 2 contributed to this arm.	
Subject analysis set title	Full analysis
Subject analysis set type	Full analysis
Subject analysis set description: The Full Analysis Set (FAS) included all subjects who received at least one dose of study drug AND had at least one post-baseline radiograph sufficient for the determination of HO at the flare-up site.	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description: The Per Protocol (PP) analysis set included all subjects who were eligible for the FAS, with no major protocol deviations, with at least 80% compliance with study medication, and had an evaluable radiograph or CT at Day 42 sufficient for the determination of HO at the flare-up site. Exclusions from the PP analysis set were identified prior to database lock, comprising one subject in the 10/5 mg palovarotene group who received less than 80% of the required dose.	

Primary: Percentage of Responders (Subjects with No/Minimal New Flare-up Heterotopic Ossification Versus Baseline)

End point title	Percentage of Responders (Subjects with No/Minimal New Flare-up Heterotopic Ossification Versus Baseline)
End point description: Percentage of responders defined by no or minimal new heterotopic ossification at the flare-up site versus baseline as assessed by plain radiographs at Day 42. Analysis was performed on the FAS. Results from the Primary Read reviews are presented.	
End point type	Primary
End point timeframe: Day 42	

End point values	Palovarotene 10/5 mg	Palovarotene 5/2.5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	9	10	
Units: Percentage of subjects				
number (not applicable)	100	88.9	88.9	

Statistical analyses

Statistical analysis title	Overall trend test
Statistical analysis description: Cochran-Armitage test of trend (one-sided).	
Comparison groups	Palovarotene 10/5 mg v Palovarotene 5/2.5 mg v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.16
Method	Cochran-Armitage test of trend-one-sided

Secondary: Percentage of Subjects With New HO at Day 84

End point title	Percentage of Subjects With New HO at Day 84
End point description: Low dose CT scan was used as a secondary imaging assessment of heterotopic ossification and was performed at the same time points as plain radiographs. The percentage of subjects with new heterotopic ossification at the flare-up site as assessed by CT scan or plain radiographs at Day 84 was analysed. The analysis was performed on the per-protocol analysis set. The results are from Global Read reviews.	
End point type	Secondary
End point timeframe: Day 84	

End point values	Palovarotene 10/5 mg	Palovarotene 5/2.5 mg	Placebo	Per protocol
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	20	9	10	39
Units: Percentage of subjects				
number (not applicable)	15	44	40	39

Statistical analyses

Statistical analysis title	Overall trend test
Statistical analysis description: Cochran-Armitage test of trend (one-sided) using the per-protocol population.	
Comparison groups	Palovarotene 10/5 mg v Palovarotene 5/2.5 mg v Placebo

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.08
Method	Cochran-Armitage test of trend-one-sided

Secondary: Volume of New Heterotopic Ossification From CT Scan at Day 84

End point title	Volume of New Heterotopic Ossification From CT Scan at Day 84
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End point description:

Low dose CT scan was used as a secondary imaging assessment of heterotopic ossification (HO) and was performed at the same time points as plain radiographs. Interpretation of the CT scan documented the amount (volume) of HO at Screening/Baseline and the amount (volume) of new HO at Day 84. Analysis was performed on the PP analysis set. The results of new HO volume are from Primary Read reviews.

End point type	Secondary
End point timeframe:	
Day 84	

End point values	Palovarotene 10/5 mg	Palovarotene 5/2.5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	2	3	
Units: mm3				
number (not applicable)	16396	5332	53939	

Statistical analyses

Statistical analysis title	T test
Comparison groups	Palovarotene 10/5 mg v Placebo
Number of subjects included in analysis	7
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.17
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded from the time informed consent is signed through Study Day 84.

Adverse event reporting additional description:

Treatment-emergent AEs were those with a start date/time after the first dose of study medication. All AEs reported after the first dose and up to and including the Day 84 visit were considered treatment-emergent.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Palovarotene 10/5 mg
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Reporting group description:

Subjects received palovarotene 10 mg for 14 days followed by 5 mg for 28 days during flare-ups (or weight adjusted equivalent for skeletally immature subjects). The subjects were followed for an additional 42 days without treatment. Subjects in Cohort 1 and Cohort 2 contributed to this arm.

Reporting group title	Palovarotene 5/2.5 mg
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Reporting group description:

Subjects received palovarotene 5 mg for 14 days followed by 2.5 mg for 28 days (or weight adjusted equivalent for skeletally immature subjects) during flare-ups. The subjects were followed for an additional 42 days without treatment. Only subjects in Cohort 2 contributed to this arm.

Reporting group title	Placebo
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Reporting group description:

Subjects received placebo for 42 days during flare-ups. Subjects were followed for an additional 42 days without treatment. Subjects in Cohort 1 and Cohort 2 contributed to this arm.

Serious adverse events	Palovarotene 10/5 mg	Palovarotene 5/2.5 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 21 (9.52%)	1 / 9 (11.11%)	1 / 10 (10.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Myoclonus			
subjects affected / exposed	1 / 21 (4.76%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Condition aggravated			

subjects affected / exposed	2 / 21 (9.52%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Haemorrhagic ovarian cyst			
subjects affected / exposed	0 / 21 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthmatic crisis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Palovarotene 10/5 mg	Palovarotene 5/2.5 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 21 (100.00%)	9 / 9 (100.00%)	10 / 10 (100.00%)
Vascular disorders			
Pallor			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	11 / 21 (52.38%)	2 / 9 (22.22%)	3 / 10 (30.00%)
occurrences (all)	27	2	3
Pyrexia			
subjects affected / exposed	1 / 21 (4.76%)	3 / 9 (33.33%)	1 / 10 (10.00%)
occurrences (all)	2	4	1
Application site erythema			
subjects affected / exposed	0 / 21 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Fatigue			

subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Feeling cold subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Vessel puncture site bruise subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Chest pain subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 2
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Nasal congestion subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Irritability subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Investigations Haemoglobin decreased subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Lipase increased			

subjects affected / exposed	2 / 21 (9.52%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	5	0	5
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Blood bilirubin increased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	2
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Amylase increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	3
Blood potassium increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Thyroxine free increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Thyroxine increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 21 (4.76%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Excoriation			
subjects affected / exposed	2 / 21 (9.52%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Post-traumatic pain			

subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 4	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	8 / 21 (38.10%) 9	1 / 9 (11.11%) 1	3 / 10 (30.00%) 5
Dizziness subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 2	1 / 9 (11.11%) 2	0 / 10 (0.00%) 0
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	2 / 9 (22.22%) 3	2 / 10 (20.00%) 5
Migraine subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Blood and lymphatic system disorders			
Leukocytosis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 9 (11.11%) 1	1 / 10 (10.00%) 1
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Eye disorders			
Dry eye subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	2 / 9 (22.22%) 2	0 / 10 (0.00%) 0
Eye pruritus subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Vision blurred			

subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Gastrointestinal disorders			
Lip dry			
subjects affected / exposed	7 / 21 (33.33%)	5 / 9 (55.56%)	1 / 10 (10.00%)
occurrences (all)	8	5	1
Nausea			
subjects affected / exposed	6 / 21 (28.57%)	1 / 9 (11.11%)	2 / 10 (20.00%)
occurrences (all)	7	1	2
Chapped lips			
subjects affected / exposed	5 / 21 (23.81%)	0 / 9 (0.00%)	2 / 10 (20.00%)
occurrences (all)	6	0	2
Diarrhoea			
subjects affected / exposed	4 / 21 (19.05%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	4	0	1
Dry mouth			
subjects affected / exposed	3 / 21 (14.29%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	3	1	0
Abdominal pain			
subjects affected / exposed	1 / 21 (4.76%)	1 / 9 (11.11%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Vomiting			
subjects affected / exposed	1 / 21 (4.76%)	1 / 9 (11.11%)	2 / 10 (20.00%)
occurrences (all)	1	1	2
Constipation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 21 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Frequent bowel movements			
subjects affected / exposed	0 / 21 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	17 / 21 (80.95%)	5 / 9 (55.56%)	3 / 10 (30.00%)
occurrences (all)	38	5	3
Erythema			
subjects affected / exposed	3 / 21 (14.29%)	2 / 9 (22.22%)	0 / 10 (0.00%)
occurrences (all)	6	2	0
Pruritus generalised			
subjects affected / exposed	4 / 21 (19.05%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	5	1	0
Dermatitis acneiform			
subjects affected / exposed	4 / 21 (19.05%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	5	0	0
Pruritus			
subjects affected / exposed	4 / 21 (19.05%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	5	0	0
Eczema			
subjects affected / exposed	2 / 21 (9.52%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	3	2	0
Rash maculo-papular			
subjects affected / exposed	2 / 21 (9.52%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Skin exfoliation			
subjects affected / exposed	2 / 21 (9.52%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Dandruff			
subjects affected / exposed	0 / 21 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
subjects affected / exposed	0 / 21 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Ecchymosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Rash			

subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 9 (11.11%) 2	0 / 10 (0.00%) 0
Macule subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Pain of skin subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Skin hypopigmentation subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Renal and urinary disorders			
Pollakiuria subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 3	2 / 9 (22.22%) 2	0 / 10 (0.00%) 0
Haematuria subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Polyuria subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Glycosuria subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	10 / 21 (47.62%) 13	1 / 9 (11.11%) 4	6 / 10 (60.00%) 14
Pain in extremity subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2	3 / 9 (33.33%) 4	2 / 10 (20.00%) 3
Joint swelling subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2	1 / 9 (11.11%) 2	0 / 10 (0.00%) 0
Joint stiffness			

subjects affected / exposed	2 / 21 (9.52%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal stiffness			
subjects affected / exposed	2 / 21 (9.52%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Neck pain			
subjects affected / exposed	1 / 21 (4.76%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Back pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 9 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	2
Groin pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Bone pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	1 / 21 (4.76%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 21 (4.76%)	2 / 9 (22.22%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Influenza			
subjects affected / exposed	2 / 21 (9.52%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Pharyngitis			
subjects affected / exposed	1 / 21 (4.76%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0

Oral candidiasis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Metabolism and nutrition disorders			
Hypercholesterolaemia subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Increased appetite subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 February 2015	Changes in the conduct of the study.
29 May 2015	Changes in the conduct of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Radiography was less sensitive than CT for detecting new HO. Also, some subjects had new HO only at Week 12. Thus, Global Read data are presented where available using more sensitive CT scans at Week 12 in the PP population.

Notes: