Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Palovarotene in Subjects with Multiple Osteochondromas

Summary

EudraCT number	2017-002751-28
Trial protocol	ES GB PT FR IT NL BE Outside EU/EEA
Global end of trial date	30 October 2020

Results information

Result version number	v2 (current)
This version publication date	23 July 2022
First version publication date	29 August 2021
Version creation reason	• New data added to full data set Additional analyses provided

Trial information

Trial identification

Sponsor protocol code	PVO-2A-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03442985
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001662-PIP03-17
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 October 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 October 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the efficacy of 2 dosage regimens of palovarotene with placebo in preventing the formation of new osteochondromas (OCs) in participants with multiple osteochondromas (MO) due to exostosin 1 (EXT1) or exostosin 2 (EXT2) mutations.

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 Harmonization Good Clinical Practice (E6), European Union (EU) Directive 2001/20/EC, United States Food and Drug Administration Code of Federal Regulations, and other applicable local regulatory requirements, whichever affords the greater participant protection.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 March 2018
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	Australia: 2
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Japan: 7
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	United States: 122
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 16
Worldwide total number of subjects	193
EEA total number of subjects	24

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)	174
Adolescents (12-17 years)	19
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase 2 placebo-controlled study was conducted in pediatric participants with MO at 29 study sites in 11 countries. For sites in the EU, participants from 7 to <15 years of age were enrolled first and participants from 2 to <7 years of age were enrolled after the 6-month bone safety data from at least 20 skeletally immature participants.

Pre-assignment

Screening details:

Study consisted of a screening period (up to 35 days), followed by a double-blind treatment period (24 months) and follow-up period (6 months). Participants were randomized in a 1:1:1 ratio to palovarotene 2.5 milligram (mg) or 5.0 mg or placebo. A total of 193 participants received at least 1 dose of study drug and were included in study analysis.

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	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants were to receive placebo matching with palovarotene capsules orally once daily, for up to 24 months.

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

Dosage and administration details:

Placebo (matching with palovarotene) capsules were to administer at approximately the same time each day, preferably immediately after the first meal of the day up to 24 months. Participants who had difficulty swallowing intact capsules were permitted to sprinkle the contents of the capsule onto a spoonful of specific foods and eaten.

Arm title	Palovarotene 2.5 mg

Arm description:

Participants were to receive weight-adjusted dose equivalent of palovarotene 2.5 mg capsules orally once daily, for up to 24 months.

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

Dosage and administration details:

Palovarotene 2.5 mg capsules were to administer at approximately the same time each day, preferably immediately after the first meal of the day up to 24 months. Participants who had difficulty swallowing intact capsules were permitted to sprinkle the contents of the capsule onto a spoonful of specific foods and eaten.

Arm title	Palovarotene 5.0 mg

Arm description:

Participants were to receive weight-adjusted dose equivalent of palovarotene 5.0 mg capsules orally once daily, for up to 24 months.

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

Dosage and administration details:

Palovarotene 5.0 mg capsules were to administer at approximately the same time each day, preferably immediately after the first meal of the day up to 24 months. Participants who had difficulty swallowing intact capsules were permitted to sprinkle the contents of the capsule onto a spoonful of specific foods and eaten.

Number of subjects in period 1	Placebo	Palovarotene 2.5 mg	Palovarotene 5.0 mg
Started	62	66	65
Completed	0	0	0
Not completed	62	66	65
Consent withdrawn by subject	2	3	4
Adverse event, non-fatal	-	1	-
Lost to follow-up	5	2	7
Sponsor Request	55	60	54

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants were to receive placebo matching with palovarotene capsules orally once daily, for up to 24 months.	
Reporting group title	Palovarotene 2.5 mg
Reporting group description:	
Participants were to receive weight-adjusted dose equivalent of palovarotene 2.5 mg capsules orally once daily, for up to 24 months.	
Reporting group title	Palovarotene 5.0 mg
Reporting group description:	
Participants were to receive weight-adjusted dose equivalent of palovarotene 5.0 mg capsules orally once daily, for up to 24 months.	

Reporting group values	Placebo	Palovarotene 2.5 mg	Palovarotene 5.0 mg
Number of subjects	62	66	65
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	56	58	60
Adolescents (12-17 years)	6	8	5
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	7.9	7.8	7.4
standard deviation	± 2.5	± 3.1	± 3.1
Gender categorical Units: Subjects			
Female	23	26	27
Male	39	40	38
Race Units: Subjects			
White	48	50	52
Black Or African American	0	2	2
Asian	5	3	3
American Indian Or Alaska Native	0	1	0
Multiple	6	7	5
Other	0	0	1
Missing	3	3	2
Ethnicity Units: Subjects			

Hispanic or Latino	6	7	7
Not Hispanic or Latino	56	58	57
Missing	0	1	1

Reporting group values	Total		
Number of subjects	193		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	174		
Adolescents (12-17 years)	19		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	76		
Male	117		
Race Units: Subjects			
White	150		
Black Or African American	4		
Asian	11		
American Indian Or Alaska Native	1		
Multiple	18		
Other	1		
Missing	8		
Ethnicity Units: Subjects			
Hispanic or Latino	20		
Not Hispanic or Latino	171		
Missing	2		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants were to receive placebo matching with palovarotene capsules orally once daily, for up to 24 months.	
Reporting group title	Palovarotene 2.5 mg
Reporting group description:	
Participants were to receive weight-adjusted dose equivalent of palovarotene 2.5 mg capsules orally once daily, for up to 24 months.	
Reporting group title	Palovarotene 5.0 mg
Reporting group description:	
Participants were to receive weight-adjusted dose equivalent of palovarotene 5.0 mg capsules orally once daily, for up to 24 months.	

Primary: Annualized Rate of New OCs

End point title	Annualized Rate of New OCs
End point description:	
The annualized rate of new OCs was assessed by whole-body magnetic resonance imaging (MRI) (that is, the total number of new OCs divided by the time in years between the baseline and latest post-baseline MRI). The Full Analysis Set (FAS) included randomized participants who received at least 1 dose of study drug. Only data from the 56 participants for whom Month 12 efficacy imaging data were available were included in the analysis.	
End point type	Primary
End point timeframe:	
Month 12	

End point values	Placebo	Palovarotene 2.5 mg	Palovarotene 5.0 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	17	23	
Units: number of new OCs per year				
least squares mean (confidence interval 95%)	0.119 (0.031 to 0.461)	0.363 (0.148 to 0.888)	0.172 (0.073 to 0.404)	

Statistical analyses

Statistical analysis title	Risk ratio for annualized rate of new OCs 1
Statistical analysis description:	
The annualized rate for number of new OCs was estimated using an unadjusted negative binomial regression model, offsetted by log-transformed follow-up time (years) to obtain annualized rate.	
Comparison groups	Palovarotene 2.5 mg v Palovarotene 5.0 mg

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2556 [1]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	2.109
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.583
upper limit	7.638

Notes:

[1] - The p-values were not adjusted for multiple testing due to small sample size.

Statistical analysis title	Risk ratio for annualized rate of new OCs 2

Statistical analysis description:

The annualized rate for number of new OCs was estimated using an unadjusted negative binomial regression model, offsetted by log-transformed follow-up time (years) to obtain annualized rate.

Comparison groups	Palovarotene 2.5 mg v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1788 [2]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	3.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.601
upper limit	15.373

Notes:

[2] - The p-values were not adjusted for multiple testing due to small sample size.

Statistical analysis title	Risk ratio for annualized rate of new OCs 3

Statistical analysis description:

The annualized rate for number of new OCs was estimated using an unadjusted negative binomial regression model, offsetted by log-transformed follow-up time (years) to obtain annualized rate.

Comparison groups	Palovarotene 5.0 mg v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.657 [3]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	1.441

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.287
upper limit	7.234

Notes:

[3] - The p-values were not adjusted for multiple testing due to small sample size.

Secondary: Mean Change From Baseline in the Total Volume of New OCs at Month 12

End point title	Mean Change From Baseline in the Total Volume of New OCs at Month 12

End point description:

The change from baseline in the total volume of OCs was assessed by whole-body MRI. Baseline was defined as the last available value prior to first administration of study drug. The FAS included randomized participants who received at least 1 dose of study drug. Only data from the 56 participants for whom Month 12 efficacy imaging data were available were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Month 12

End point values	Placebo	Palovarotene 2.5 mg	Palovarotene 5.0 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	17	23	
Units: cubic millimeter				
arithmetic mean (standard deviation)	10476.7 (± 23294.9)	5250.5 (± 11754.7)	10911.0 (± 35869.6)	

Statistical analyses

Statistical analysis title	Risk ratio for total volume of new OCs 1

Statistical analysis description:

The mean difference in the change from baseline for total OC volume was estimated using an unadjusted estimation equation model with independent working covariance matrix to address potential correlation within the same family members.

Comparison groups	Palovarotene 2.5 mg v Palovarotene 5.0 mg
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4252 [4]
Method	Unadjusted estimation equation model
Parameter estimate	Risk ratio (RR)
Point estimate	-4412.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15257.3
upper limit	6432.1

Notes:

[4] - The p-values were not adjusted for multiple testing due to small sample size.

Statistical analysis title	Risk ratio for total volume of new OCs 2

Statistical analysis description:

The mean difference in the change from baseline for total OC volume was estimated using an unadjusted estimation equation model with independent working covariance matrix to address potential correlation within the same family members.

Comparison groups	Palovarotene 2.5 mg v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4053 [5]
Method	Unadjusted estimation equation model
Parameter estimate	Risk ratio (RR)
Point estimate	-4640.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15570.8
upper limit	6289

Notes:

[5] - The p-values were not adjusted for multiple testing due to small sample size.

Statistical analysis title	Risk ratio for total volume of new OCs 3

Statistical analysis description:

The mean difference in the change from baseline for total OC volume was estimated using an unadjusted estimation equation model with independent working covariance matrix to address potential correlation within the same family members.

Comparison groups	Palovarotene 5.0 mg v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9677 [6]
Method	Unadjusted estimation equation model
Parameter estimate	Risk ratio (RR)
Point estimate	-228.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11265
upper limit	10808.4

Notes:

[6] - The p-values were not adjusted for multiple testings due to small sample size.

Secondary: Percentage of Participants With No New OCs

End point title	Percentage of Participants With No New OCs

End point description:

The percentage of participants with no new OCs as assessed by whole-body MRI. Participants with new OCs not identified by MRI due to surgical resection during the treatment period were categorized as having new OCs for this analysis. The FAS included randomized participants who received at least 1 dose of study drug. Only data from the 56 participants for whom Month 12 efficacy imaging data were

available were included in the analysis.

End point type	Secondary

End point timeframe:

Month 12

End point values	Placebo	Palovarotene 2.5 mg	Palovarotene 5.0 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	17	23	
Units: percentage of participants				
number (not applicable)	62.5	47.1	56.5	

Statistical analyses

Statistical analysis title	Odds ratio for participants with no new OCs 1
Comparison groups	Palovarotene 2.5 mg v Palovarotene 5.0 mg
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5025 [7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.643
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.177
upper limit	2.335

Notes:

[7] - Logistic regression was adjusted for the following covariates: baseline age, sex, and Ext1/2 mutation status.

Statistical analysis title	Odds ratio for participants with no new OCs 2
Comparison groups	Palovarotene 2.5 mg v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3763 [8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.528
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.128
upper limit	2.175

Notes:

[8] - Logistic regression was adjusted for the following covariates: baseline age, sex, and Ext1/2 mutation status.

Statistical analysis title	Odds ratio for participants with no new OCs 3
Comparison groups	Palovarotene 5.0 mg v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7714 [9]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.215
upper limit	3.123

Notes:

[9] - Logistic regression was adjusted for the following covariates: baseline age, sex, and Ext1/2 mutation status.

Secondary: Annualized Rate of New or Worsening Deformities

End point title	Annualized Rate of New or Worsening Deformities

End point description:

The annualized rate of new or worsening deformities as assessed by radiographic imaging of both upper and lower limbs. The FAS included randomized participants who received at least 1 dose of study drug. Only data from the 56 participants for whom Month 12 efficacy imaging data were available were included in the analysis.

End point type	Secondary

End point timeframe:

Month 12

End point values	Placebo	Palovarotene 2.5 mg	Palovarotene 5.0 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	18	22	
Units: number of deformities per year				
least squares mean (confidence interval 95%)	1.797 (1.272 to 2.537)	1.802 (1.209 to 2.684)	1.895 (1.584 to 2.266)	

Statistical analyses

Statistical analysis title	Risk ratio for new or worsening deformities 1

Statistical analysis description:

The annualized rate for number of new or worsening deformities was estimated using an unadjusted negative binomial regression model, offsetted by log-transformed follow-up time (years) to obtain annualized rate.

Comparison groups	Palovarotene 2.5 mg v Palovarotene 5.0 mg

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8155 [10]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.951
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.623
upper limit	1.451

Notes:

[10] - The p-values were not adjusted for multiple testing due to small sample size. The correlation matrix type = compound symmetry was used.

Statistical analysis title	Risk ratio for new or worsening deformities 2

Statistical analysis description:

The annualized rate for number of new or worsening deformities was estimated using an unadjusted negative binomial regression model, offsetted by log-transformed follow-up time (years) to obtain annualized rate.

Comparison groups	Palovarotene 2.5 mg v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9918 [11]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	1.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.592
upper limit	1.699

Notes:

[11] - The p-values were not adjusted for multiple testing due to small sample size. The correlation matrix type = compound symmetry was used.

Statistical analysis title	Risk ratio for new or worsening deformities 3

Statistical analysis description:

The annualized rate for number of new or worsening deformities was estimated using an unadjusted negative binomial regression model, offsetted by log-transformed follow-up time (years) to obtain annualized rate.

Comparison groups	Palovarotene 5.0 mg v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7997 [12]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	1.055

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.589

Notes:

[12] - The p-values were not adjusted for multiple testing due to small sample size. The correlation matrix type = compound symmetry was used.

Secondary: Annualized Rate of MO-Related Surgeries

End point title	Annualized Rate of MO-Related Surgeries

End point description:

The MO-related surgeries included any procedure indicated for the treatment of MO, such as an excision of a symptomatic OC or correction of a limb deformity. The FAS included randomized participants who received at least 1 dose of study drug. Participants with planned surgeries within 6 months of enrollment to remove symptomatic OCs or to correct deformities present at baseline, and/or had surgical procedures that were a continuation of a previous procedure were excluded in the analysis.

End point type	Secondary

End point timeframe:

Month 12

End point values	Placebo	Palovarotene 2.5 mg	Palovarotene 5.0 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	8	7	
Units: number of MO-related surgeries per year				
least squares mean (confidence interval 95%)	2.087 (1.099 to 3.964)	3.454 (1.850 to 6.451)	2.231 (1.638 to 3.038)	

Statistical analyses

Statistical analysis title	Risk ratio for MO-Related Surgeries 1

Statistical analysis description:

The annualized rate for number of MO-related surgeries was estimated using an unadjusted poisson regression model, offsetted by log-transformed follow-up time (years) to obtain annualized rate.

Comparison groups	Palovarotene 2.5 mg v Palovarotene 5.0 mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2186 [13]
Method	Poisson regression model
Parameter estimate	Risk ratio (RR)
Point estimate	1.548
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.772
upper limit	3.108

Notes:

[13] - The p-values were not adjusted for multiple testing due to small sample size. The correlation matrix type = independent was used.

Statistical analysis title	Risk ratio for MO-Related Surgeries 2

Statistical analysis description:

The annualized rate for number of MO-related surgeries was estimated using an unadjusted poisson regression model, offsetted by log-transformed follow-up time (years) to obtain annualized rate.

Comparison groups	Palovarotene 2.5 mg v Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.27 [14]
Method	Poisson regression model
Parameter estimate	Risk ratio (RR)
Point estimate	1.655
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.676
upper limit	4.052

Notes:

[14] - The p-values were not adjusted for multiple testing due to small sample size. The correlation matrix type = independent was used.

Statistical analysis title	Risk ratio for MO-Related Surgeries 3

Statistical analysis description:

The annualized rate for number of MO-related surgeries was estimated using an unadjusted poisson regression model, offsetted by log-transformed follow-up time (years) to obtain annualized rate.

Comparison groups	Palovarotene 5.0 mg v Placebo
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8546 [15]
Method	Poisson regression model
Parameter estimate	Risk ratio (RR)
Point estimate	1.069
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.524
upper limit	2.178

Notes:

[15] - The p-values were not adjusted for multiple testing due to small sample size. The correlation matrix type = independent was used.

Secondary: Maximum Observed Plasma Drug Concentrations at Steady State (Cmax,ss) of Palovarotene

End point title	Maximum Observed Plasma Drug Concentrations at Steady State (Cmax,ss) of Palovarotene[16]

End point description:

The Cmax,ss of palovarotene was evaluated. The pharmacokinetic (PK) sampling was performed at Month 1. If samples could not be obtained at Month 1, then one additional attempt was made at a subsequent visit. The Pharmacokinetic Set (PKS) included participants receiving treatment with palovarotene and with evaluable PK data.

End point type	Secondary

End point timeframe:

Month 1: pre-dose and 3, 6, 10 and 24 hours post-dose

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only reporting groups in which participants received palovarotene were evaluated for this PK endpoint.

End point values	Palovarotene 2.5 mg	Palovarotene 5.0 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	52		
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	18.0 (± 50.2)	34.9 (± 63.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Plasma Drug Concentrations at Steady State (Cmin,ss) of Palovarotene

End point title	Minimum Observed Plasma Drug Concentrations at Steady State (Cmin,ss) of Palovarotene[17]

End point description:

The Cmin,ss of palovarotene was evaluated. The PK sampling was performed at Month 1. If samples could not be obtained at Month 1, then one additional attempt was made at a subsequent visit. The PKS included participants receiving treatment with palovarotene and with evaluable PK data.

End point type	Secondary

End point timeframe:

Month 1: pre-dose and 3, 6, 10 and 24 hours post-dose

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only reporting groups in which participants received palovarotene were evaluated for this PK endpoint.

End point values	Palovarotene 2.5 mg	Palovarotene 5.0 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	53		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	0.314 (± 86.1)	0.674 (± 83.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Drug Concentration at Steady State (Tmax,ss) of Palovarotene

End point title	Time to Maximum Observed Drug Concentration at Steady State (Tmax,ss) of Palovarotene[18]

End point description:

The Tmax,ss of palovarotene was evaluated. The PK sampling was performed at Month 1. If samples could not be obtained at Month 1, then one additional attempt was made at a subsequent visit. The PKS included participants receiving treatment with palovarotene and with evaluable PK data.

End point type	Secondary

End point timeframe:

Month 1: pre-dose and 3, 6, 10 and 24 hours post-dose

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only reporting groups in which participants received palovarotene were evaluated for this PK endpoint.

End point values	Palovarotene 2.5 mg	Palovarotene 5.0 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	52		
Units: hour				
median (full range (min-max))	3.00 (2.47 to 10.00)	3.01 (2.42 to 24.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve at Steady State From Time 0 to 24 Hours After Dosing (AUC0-24,ss) of Palovarotene

End point title	Area Under the Plasma Concentration-Time Curve at Steady State From Time 0 to 24 Hours After Dosing (AUC0-24,ss) of Palovarotene[19]

End point description:

The AUC0-24,ss of palovarotene was evaluated. The PK sampling was performed at Month 1. If samples could not be obtained at Month 1, then one additional attempt was made at a subsequent visit. The PKS included participants receiving treatment with palovarotene and with evaluable PK data.

End point type	Secondary

End point timeframe:

Month 1: pre-dose and 3, 6, 10 and 24 hours post-dose

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only reporting groups in which participants received palovarotene were evaluated for this PK endpoint.

End point values	Palovarotene 2.5 mg	Palovarotene 5.0 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	46		
Units: hour*ng/mL				
geometric mean (geometric coefficient of variation)	112 (± 29.1)	241 (± 42.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Palatability of Sprinkled Palovarotene and Placebo

End point title	Number of Participants With Palatability of Sprinkled Palovarotene and Placebo

End point description:

Palatability of palovarotene and placebo when sprinkled on specific foods as assessed with a 5-point hedonic face scale at the first dose (Day 1) and at Month 1 in all participants (including <4 years old) who sprinkled the palovarotene or placebo onto a spoonful of specific foods. The hedonic face scale ranges from 1 to 5 where, 1= dislike very much, 2= dislike slightly, 3= neither like nor dislike, 4= like slightly, 5= like very much. Higher scores indicate positive outcome. The Safety set included randomized participants who received at least 1 dose of study drug. Only data from the participants analyzed at Day 1 and Month 1 were included in the analysis.

End point type	Secondary

End point timeframe:

Day 1 and Month 1

End point values	Placebo	Palovarotene 2.5 mg	Palovarotene 5.0 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	15	11	
Units: participants				
Day 1: Dislike very much	0	1	0	
Day 1: Dislike a little	1	1	0	
Day 1: Not sure	6	3	3	
Day 1: Like a little	3	5	3	
Day 1: Like very much	11	5	5	
Month 1: Dislike very much	1	0	0	
Month 1: Dislike a little	1	1	1	
Month 1: Not sure	5	1	3	
Month 1: Like a little	8	5	1	
Month 1: Like very much	6	8	6	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were collected from the start of the first study drug (Day 1) up to 7 days after last study drug intake, assessed until data cut-off for study termination (maximum of 595 days).

Adverse event reporting additional description:

The Safety set included randomized participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants were to receive placebo matching with palovarotene capsules orally once daily, for up to 24 months.

Reporting group title	Palovarotene 5.0 mg

Reporting group description:

Participants were to receive weight-adjusted dose equivalent of palovarotene 5.0 mg capsules orally once daily, for up to 24 months.

Reporting group title	Palovarotene 2.5 mg

Reporting group description:

Participants were to receive weight-adjusted dose equivalent of palovarotene 2.5 mg capsules orally once daily, for up to 24 months.

Serious adverse events	Placebo	Palovarotene 5.0 mg	Palovarotene 2.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 62 (0.00%)	2 / 65 (3.08%)	2 / 66 (3.03%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Radius Fracture			
subjects affected / exposed	0 / 62 (0.00%)	0 / 65 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna Fracture			
subjects affected / exposed	0 / 62 (0.00%)	0 / 65 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Status Epilepticus			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Blood Loss Anaemia			
subjects affected / exposed	0 / 62 (0.00%)	1 / 65 (1.54%)	0 / 66 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 62 (0.00%)	0 / 65 (0.00%)	1 / 66 (1.52%)
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	Placebo	Palovarotene 5.0 mg	Palovarotene 2.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 62 (66.13%)	56 / 65 (86.15%)	56 / 66 (84.85%)
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 62 (9.68%)	3 / 65 (4.62%)	4 / 66 (6.06%)
occurrences (all)	8	4	4
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 62 (0.00%)	9 / 65 (13.85%)	3 / 66 (4.55%)
occurrences (all)	0	9	3
Gastrointestinal disorders			
Lip Dry			
subjects affected / exposed	3 / 62 (4.84%)	11 / 65 (16.92%)	6 / 66 (9.09%)
occurrences (all)	3	11	6
Vomiting			
subjects affected / exposed	2 / 62 (3.23%)	7 / 65 (10.77%)	3 / 66 (4.55%)
occurrences (all)	2	9	4
Dry Mouth			

subjects affected / exposed	3 / 62 (4.84%)	4 / 65 (6.15%)	4 / 66 (6.06%)
occurrences (all)	3	4	4
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	7 / 62 (11.29%)	25 / 65 (38.46%)	17 / 66 (25.76%)
occurrences (all)	12	50	31
Dry Skin			
subjects affected / exposed	7 / 62 (11.29%)	19 / 65 (29.23%)	16 / 66 (24.24%)
occurrences (all)	9	23	19
Pruritus			
subjects affected / exposed	6 / 62 (9.68%)	7 / 65 (10.77%)	8 / 66 (12.12%)
occurrences (all)	7	9	9
Rash Generalised			
subjects affected / exposed	2 / 62 (3.23%)	5 / 65 (7.69%)	3 / 66 (4.55%)
occurrences (all)	4	5	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 62 (11.29%)	1 / 65 (1.54%)	3 / 66 (4.55%)
occurrences (all)	10	1	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 62 (4.84%)	5 / 65 (7.69%)	3 / 66 (4.55%)
occurrences (all)	3	6	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 July 2018	Increased screening period from 28 to 35 days to accommodate time required for genetic testing. Added a safety follow-up visit 6 months after end of treatment (EOT) for participants who did not participate in the open-label extension study, as requested by regulatory authorities. Added that additional safety follow-up could be required to ensure that ongoing adverse events were resolved or stabilized. Modified inclusion criteria to require ≥5 clinically evident OCs with one new/enlarging OC in preceding 12 months and one painful OC and to specify disease-causing EXT1 or EXT2 gene mutations. Added the following endpoints as requested by regulatory authorities: proportion of participants with no new OCs as assessed by whole-body MRI at Months 12 and 24; palatability of sprinkled drug product; and OC cartilage cap volume. Added skeletal deformity and long bone length assessments and safety assessment for osteonecrosis, as requested by regulatory authorities. Amended MRI sedation to allow general anesthesia to ensure participant safety and successful image acquisition. Adjusted the timing of safety laboratory tests, dual X-ray absorptiometry (DXA), and hearing and visual acuity testing to decrease participant burden.
23 April 2019	Stipulated that only clinically significant abnormal clinical laboratory results at the EOT, including hematology parameters, would require retesting at the safety follow-up visit, rather than all abnormal clinical laboratory findings. Changed the definition of female of childbearing potential from Tanner 2+ to age >13 years or postmenarchal, whichever occurred earlier. Added 25-hydroxyl vitamin D assessments at the discretion of the Investigator to evaluate changes in bone mineral density. Amended the requirement for a confirmatory DXA scan to only those that would result in a dose modification (that is, >5% loss in spine areal bone mineral density and -1 change from baseline in height adjusted z-score in lumbar spine bone mineral density). Removed some of the age restrictions on participant enrollment for sites in the EU. Defined effective and highly effective forms of birth control. Added that the Investigator should review the participant's condition to determine whether a missed clinical laboratory test or non-evaluable test should be repeated for that time point. Stipulated that participants enrolled in Japan would have on-site clinic visits every 3 months.

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.

The Sponsor terminated the study early due to a partial clinical hold instituted by the Food and Drug Administration. Recruitment was stopped before full enrollment was reached, and study drug administration was discontinued.

Notes: