



Clinical trial results:

CLINICAL EFFICACY AND SAFETY OF TAZAROTENE CREAM 0.05% IN THE INITIAL AND MAINTENANCE THERAPIES OF LAMELLAR ICHTHYOSIS (LI)

Summary

EudraCT number	2010-022284-35
Trial protocol	IT SE DE FR AT
Global end of trial date	03 December 2013

Results information

Result version number	v1 (current)
This version publication date	13 August 2016
First version publication date	13 August 2016

Trial information

Trial identification

Sponsor protocol code	R00002 CR 301 (ORF)
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Orfagen
Sponsor organisation address	3, avenue Hubert Curien, Toulouse CEDEX 1, France, 31035
Public contact	Clinical project manager, Orfagen, info@orfagen.com
Scientific contact	Clinical project manager, Orfagen, info@orfagen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000510-PIP02-10
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	03 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 October 2012
Global end of trial reached?	Yes
Global end of trial date	03 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the long-term clinical efficacy and safety of Tazarotene 0.05% cream in LI patients in real-life setting conditions.

Protection of trial subjects:

- plasmatic bone markers monitoring
- IDMC/Data Safety Management Board (quarterly meeting)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Tunisia: 6
Country: Number of subjects enrolled	Algeria: 44
Worldwide total number of subjects	91
EEA total number of subjects	41

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)	10
Adolescents (12-17 years)	21
Adults (18-64 years)	59
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After a wash-out of at least 7 days (period with no application of treatment, except the standard moisturizer), patients with moderate to severe ichthyosis and who fulfilled all the inclusion criteria were enrolled in the study

Period 1

Period 1 title	Period I (84 days)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Tazarotene 0.05%

Arm description: -

Arm type	Experimental
Investigational medicinal product name	R0002 CR 0.05%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

1mg/cm² using the finger tip technique. Application every other day on lesional areas excluding face, neck, scalp, palms, soles and genital areas.

Arm title	Urea cream
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Urea cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

1mg/cm² using the finger tip technique. Application every other day on lesional areas excluding face, neck, scalp, palms, soles and genital areas.

Number of subjects in period 1	Tazarotene 0.05%	Urea cream
Started	42	49
Completed	37	47
Not completed	5	2
Consent withdrawn by subject	4	1

Lost to follow-up	1	1
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Period 2

Period 2 title	Period II (84 days)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Tazarotene 0.05%
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	R0002CR 0.05%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

1mg/cm² using the finger tip technique. Recommended frequency of application: every other day excluding genital areas

Number of subjects in period 2	Tazarotene 0.05%
Started	84
Completed	82
Not completed	2
Consent withdrawn by subject	1
Lost to follow-up	1

Period 3

Period 3 title	Period III (up to 56 days)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Tazarotene 0.05%
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	R0002 CR 0.05%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

1mg/cm² using the finger tip technique. Recommended frequency of application: every other day excluding genital areas

Arm title	Vehicle
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

1mg/cm² using the finger tip technique. Recommended frequency of application: every other day excluding genital areas

Number of subjects in period 3^[1]	Tazarotene 0.05%	Vehicle
Started	35	35
Completed	30	25
Not completed	5	10
Relapse	4	8
Consent withdrawn by subject	-	1
Lost to follow-up	1	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Patients with non persisting lesions at the end of Period II only could enter Period III.

Period 4

Period 4 title	Children Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Follow-up without treatment
Arm description:	
Post treatment follow-up for children who entered at least Period I	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 4^[2]	Follow-up without treatment
Started	22
Completed	10
Not completed	12
upon sponsor request	10
Lost to follow-up	1
Protocol deviation	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Post treatment long term safety for children who entered at least period I and who agreed to perform this follow-up.

Period 5

Period 5 title	Period IV
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Tazarotene 0.05%
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	R0002CR 0.05%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

1mg/cm² using the finger tip technique. Recommended frequency of application: every other day excluding genital areas.

Number of subjects in period 5^[3]	Tazarotene 0.05%
Started	4
Completed	0
Not completed	16
Study ended by sponsor	16
Joined	12
Extension after Period III	12

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Study extension in order to maintain an optimal follow-up procedure, following patients' request to benefit from R0002CR 0.05% cream: 4 patients after children follow-up end, 12 patients after Period III end.

Baseline characteristics

Reporting groups

Reporting group title	Tazarotene 0.05%
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Reporting group description: -

Reporting group title	Urea cream
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Reporting group description: -

Reporting group values	Tazarotene 0.05%	Urea cream	Total
Number of subjects	42	49	91
Age categorical			
Units: Subjects			
9 years and over			
Age continuous			
Units: years			
arithmetic mean	29.2	25.2	
standard deviation	± 16.9	± 13	-
Gender categorical			
Units: Subjects			
Female	22	22	44
Male	20	27	47

End points

End points reporting groups

Reporting group title	Tazarotene 0.05%
Reporting group description: -	
Reporting group title	Urea cream
Reporting group description: -	
Reporting group title	Tazarotene 0.05%
Reporting group description: -	
Reporting group title	Tazarotene 0.05%
Reporting group description: -	
Reporting group title	Vehicle
Reporting group description: -	
Reporting group title	Follow-up without treatment
Reporting group description:	
Post treatment follow-up for children who entered at least Period I	
Reporting group title	Tazarotene 0.05%
Reporting group description: -	

Primary: Response to treatment at day 84 compared to Baseline

End point title	Response to treatment at day 84 compared to Baseline
End point description:	
Response to test treatment at the end of Period I (Day 84): treatment response was defined as a score of 0 to 2 for scaling and roughness using a 5-point severity scale combined with a reduction from baseline of the score of at least 2 grades for scaling only. Patients with premature switch from Period I to Period II were classified as non-responders.	
End point type	Primary
End point timeframe:	
Baseline - End of Period I (day 84 visit)	

End point values	Tazarotene 0.05%	Urea cream		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20 ^[1]	27 ^[2]		
Units: patients	5	2		

Notes:

[1] - efficacy analysis on ITT population from centers without GCP violation

[2] - efficacy analysis on ITT population from centers without GCP violation

Statistical analyses

Statistical analysis title	Primary efficacy parameter
Comparison groups	Urea cream v Tazarotene 0.05%

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.119
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From study beginning to study end

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

Reporting group title	Urea Group
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Reporting group description:

TEAE that occurred when patients received urea treatment.

Reporting group title	Tazarotene group
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Reporting group description:

TEAE that occurred when patients received tazarotene treatment.

Reporting group title	Vehicle group
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Reporting group description:

TEAE that occurred when patients received vehicle.

Reporting group title	No treatment
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Reporting group description:

TEAE that occurred when patients did not received study treatment.

Serious adverse events	Urea Group	Tazarotene group	Vehicle group
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 49 (0.00%)	2 / 84 (2.38%)	0 / 35 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 49 (0.00%)	1 / 84 (1.19%)	0 / 35 (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
Surgical and medical procedures			
Hip surgery			
subjects affected / exposed	0 / 49 (0.00%)	1 / 84 (1.19%)	0 / 35 (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

Serious adverse events	No treatment		
Total subjects affected by serious			

adverse events			
subjects affected / exposed	0 / 21 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hip surgery			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Urea Group	Tazarotene group	Vehicle group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 49 (51.02%)	63 / 84 (75.00%)	8 / 35 (22.86%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 49 (6.12%)	2 / 84 (2.38%)	0 / 35 (0.00%)
occurrences (all)	3	2	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	8 / 49 (16.33%)	29 / 84 (34.52%)	1 / 35 (2.86%)
occurrences (all)	8	41	1
Erythema			
subjects affected / exposed	2 / 49 (4.08%)	20 / 84 (23.81%)	0 / 35 (0.00%)
occurrences (all)	2	23	0
Skin irritation			
subjects affected / exposed	0 / 49 (0.00%)	10 / 84 (11.90%)	0 / 35 (0.00%)
occurrences (all)	0	12	0
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	3 / 49 (6.12%)	7 / 84 (8.33%)	1 / 35 (2.86%)
occurrences (all)	3	9	1
Influenza			
subjects affected / exposed	3 / 49 (6.12%)	3 / 84 (3.57%)	2 / 35 (5.71%)
occurrences (all)	3	3	2

Non-serious adverse events	No treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Skin irritation			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2012	To provide recommendations concerning the allocation of the treatment units for patients who may request more amount of drug.
25 January 2012	Implementation of a Children Follow-up Period (postponement of study end: prolongation for 1 year)
22 November 2012	Implementation of the Period IV: Study extension with treatment for patient wishing to continue to apply the Tazarotene cream

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported