Clinical trial results:
Efficacy and tolerance of Tazarotene cream in lamellar ichthyosis (LI): a dose-finding study.

Summary

EudraCT number	2006-006878-22
Trial protocol	FR DE
Global end of trial date	20 April 2009

Results information

Result version number	v2 (current)
This version publication date	05 August 2016
First version publication date	18 June 2015
Version creation reason	• New data added to full data set As the study was linked to a PIP, and despite PIP removal, replacement of the clinical study report synopsis by the study data sets.

Trial information

Trial identification

Sponsor protocol code	R00002 CR 201 (ORF)

Additional study identifiers

ISRCTN number	ISRCTN86666250
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)	EMEA-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	13 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 April 2009
Global end of trial reached?	Yes
Global end of trial date	20 April 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To assess and compare the short-term efficacy of Tazarotene 0.05% and 0.1% vehicled in an emollient cream in LI patients.

Protection of trial subjects:

Included patients benefited from close management of their disease, with weekly visits during the treatment period and fortnightly visits during the treatment free follow-up period. During visits, a thorough clinical examination, as well as a paraclinical examination at baseline and on Day 28, were performed. Local and systemic adverse effects were searched and monitored throughout the study. Blood samplings for routine laboratory tests and for plasmatic dosage of tazarotenic acid were performed only at baseline and on Day 28, sampling about 33 mL of blood in adults and about 20 mL in children. Blood samples were repeated for follow-up only when clinically significant abnormal values were observed.
A standard moisturizer was applied at least once a day on all sites at distance from the test products application.
In order to avoid any risk of teratogenicity inherent to retinoid exposure, women of childbearing potential had to stay under reliable contraception and to use condom in addition, up to at least 8 weeks after their last test product application. Women of childbearing potential with no reliable contraception were excluded from the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 February 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 19
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	7
Adolescents (12-17 years)	2
Adults (18-64 years)	20
From 65 to 84 years	0
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Selected patients performed a wash-out period of 7 to 28 days, during which patients were treated only with a standard moisturizer provided by the sponsor, before assessment of their inclusion/exclusion criteria and enrollment in the study period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	R0002CR 0.05% / Placebo

Arm description:

Patients who applied the active R0002CR 0.05% and Vehicle cream on two randomly designated test sides (left and right side of the body).

Arm type	Experimental lower dosage / placebo
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:

Application of R0002CR 0.05% on one randomly allocated sides (left side or right side of the body) once daily for 4 weeks (e.g. every evening).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

Application of vehicle cream on the other randomly allocated side (left side or right side of the body) once daily for 4 weeks (e.g. every evening).

Arm title	R0002CR 0.1% / Placebo

Arm description:

Patients who applied the active R0002CR 0.1% and Vehicle cream on two randomly designated test sides (left and right side of the body).

Arm type	Experimental higher dosage / placebo
Investigational medicinal product name	R0002CR 0.1%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

Application of R0002CR 0.1% on one randomly allocated sides (left side or right side of the body) once daily for 4 weeks (e.g. every evening).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

Application of vehicle cream on the other randomly allocated side (left side or right side of the body) once daily for 4 weeks (e.g. every evening).

Number of subjects in period 1	R0002CR 0.05% / Placebo	R0002CR 0.1% / Placebo
Started	15	15
Completed	15	15

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	R0002CR 0.05% / Treatment free

Arm description:

Treatment-free follow-up of remitting lesions at Period II entry (lesions treated with R0002CR 0.05% during period I).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	R0002CR 0.1% / Treatment free

Arm description:

Treatment-free follow-up of remitting lesions at Period II entry (lesions treated with R0002CR 0.1% during period I).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo / Treatment free

Arm description:

Treatment-free follow-up of remitting lesions at Period II entry (lesions treated with vehicle during period I).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[1]	R0002CR 0.05% / Treatment free	R0002CR 0.1% / Treatment free	Placebo / Treatment free
Started	8	9	4
Completed	7	9	4
Not completed	1	0	0
Consent withdrawn by subject	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: Treatment free Period II: body sides with remitting lesions only entered the Period II.

Baseline characteristics

Reporting groups	
Reporting group title	R0002CR 0.05% / Placebo

Reporting group description:

Patients who applied the active R0002CR 0.05% and Vehicle cream on two randomly designated test sides (left and right side of the body).

Reporting group title	R0002CR 0.1% / Placebo

Reporting group description:

Patients who applied the active R0002CR 0.1% and Vehicle cream on two randomly designated test sides (left and right side of the body).

Reporting group values	R0002CR 0.05% / Placebo	R0002CR 0.1% / Placebo	Total
Number of subjects	15	15	30
Age categorical Units: Subjects			
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	26.1	33.5	
standard deviation	± 12.6	± 23.5	-
Gender categorical Units: Subjects			
Female	8	5	13
Male	7	10	17

End points

End points reporting groups

Reporting group title	R0002CR 0.05% / Placebo

Reporting group description:

Patients who applied the active R0002CR 0.05% and Vehicle cream on two randomly designated test sides (left and right side of the body).

Reporting group title	R0002CR 0.1% / Placebo

Reporting group description:

Patients who applied the active R0002CR 0.1% and Vehicle cream on two randomly designated test sides (left and right side of the body).

Reporting group title	R0002CR 0.05% / Treatment free

Reporting group description:

Treatment-free follow-up of remitting lesions at Period II entry (lesions treated with R0002CR 0.05% during period I).

Reporting group title	R0002CR 0.1% / Treatment free

Reporting group description:

Treatment-free follow-up of remitting lesions at Period II entry (lesions treated with R0002CR 0.1% during period I).

Reporting group title	Placebo / Treatment free

Reporting group description:

Treatment-free follow-up of remitting lesions at Period II entry (lesions treated with vehicle during period I).

Subject analysis set title	R0002CR 0.05% (R0002CR 0.05% / Placebo group)
Subject analysis set type	Full analysis

Subject analysis set description:

Answer on body lesions treated with R0002CR 0.05% (patients from R0002CR 0.05% / Placebo group).

Subject analysis set title	R0002CR 0.1% (R0002CR 0.1% / Placebo group)
Subject analysis set type	Full analysis

Subject analysis set description:

Answer on body lesions treated with R0002CR 0.1% (patients from R0002CR 0.1% / Placebo group).

Subject analysis set title	Placebo (R0002CR 0.05% / Placebo group)
Subject analysis set type	Full analysis

Subject analysis set description:

Answer on body lesions treated with vehicle cream (patients from R0002CR 0.05% / Placebo group).

Subject analysis set title	Placebo (R0002CR 0.1% / Placebo group)
Subject analysis set type	Full analysis

Subject analysis set description:

Answer on body lesions treated with vehicle cream (patients from R0002CR 0.1% / Placebo group).

Primary: Responder for scaling and roughness

End point title	Responder for scaling and roughness[1]

End point description:

End point type	Primary

End point timeframe:

End of Period I

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: Pairwise comparisons R0002CR 0.05% vs. Vehicle and R0002CR 0.1% vs. Vehicle: A

statistically significant difference was achieved with each R0002CR group compared to vehicle group (p = 0.025). (no possibility to enter those data in EudraCT database).

End point values	R0002CR 0.05% (R0002CR 0.05% / Placebo group)	R0002CR 0.1% (R0002CR 0.1% / Placebo group)	Placebo (R0002CR 0.05% / Placebo group)	Placebo (R0002CR 0.1% / Placebo group)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	15	15
Units: Responders	6	8	1	2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From study beginning to study end.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups	
Reporting group title	R0002CR 0.05% - Period I
Reporting group description:	
For safety analyses on Period I and Period II, a patient was considered in the two treatment groups corresponding to the two study treatments administered during the Period I on his/her left test side and on his/her right test side respectively.	
Reporting group title	R0002CR 0.1% - Period I
Reporting group description:	
For safety analyses on Period I and Period II, a patient was considered in the two treatment groups corresponding to the two study treatments administered during the Period I on his/her left test side and on his/her right test side respectively.	
Reporting group title	Placebo - Period I
Reporting group description:	
For safety analyses on Period I and Period II, a patient was considered in the two treatment groups corresponding to the two study treatments administered during the Period I on his/her left test side and on his/her right test side respectively.	
Reporting group title	R0002CR 0.05% - Period II
Reporting group description:	
For safety during Period II, patients were analyzed according to the study treatment(s) actually received during the Period I (i.e. “as treated”).	
Reporting group title	R0002CR 0.1% - Period II
Reporting group description:	
For safety during Period II, patients were analyzed according to the study treatment(s) actually received during the Period I (i.e. “as treated”).	
Reporting group title	Placebo - Period II
Reporting group description:	
For safety during Period II, patients were analyzed according to the study treatment(s) actually received during the Period I (i.e. “as treated”).	

Serious adverse events	R0002CR 0.05% - Period I	R0002CR 0.1% - Period I	Placebo - Period I
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 30 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	R0002CR 0.05% - Period II	R0002CR 0.1% - Period II	Placebo - Period II
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	R0002CR 0.05% - Period I	R0002CR 0.1% - Period I	Placebo - Period I
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 15 (80.00%)	12 / 15 (80.00%)	10 / 30 (33.33%)
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Foot fracture			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Hyperaesthesia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 15 (6.67%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Burning sensation			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	1 / 30 (3.33%)
occurrences (all)	4	2	2
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	0 / 15 (0.00%)	3 / 15 (20.00%)	3 / 30 (10.00%)
occurrences (all)	0	3	5
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Immune system disorders			

Seasonal allergy			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Skin irritation			
subjects affected / exposed	6 / 15 (40.00%)	5 / 15 (33.33%)	0 / 30 (0.00%)
occurrences (all)	9	11	0
Skin erosion			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	1 / 30 (3.33%)
occurrences (all)	1	3	1
Erythema			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Pain of skin			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Prurigo			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	1 / 30 (3.33%)
occurrences (all)	0	2	1
Pruritus			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Skin fissures			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	1 / 30 (3.33%)
occurrences (all)	1	1	1
Skin lesion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Rash			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Actinic keratosis			

subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Skin infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Superinfection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1

Non-serious adverse events	R0002CR 0.05% - Period II	R0002CR 0.1% - Period II	Placebo - Period II
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	1 / 17 (5.88%)
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Foot fracture			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Hyperaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Burning sensation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Skin irritation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Skin erosion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Pain of skin			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0

Prurigo			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Skin fissures			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Actinic keratosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Rhinitis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Superinfection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2008	- Extension of the study period . - Use of plastic gloves for test product applications. - Change in German and French co-investigators. - Addition of the ISCRTN number.
06 May 2008	- Extension of the study period. - Addition of an 11th centre. - Notify a change of German co-investigators
20 January 2009	- Extension of the study period. - Update of the Helsinki declaration.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported