# 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) |

### 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) | 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 | 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 (quartely 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 f 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 |

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 |

| **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% |
| Reporting group description: - | |
| Reporting group title | Urea cream |
| Reporting group description: - | |

| Reporting group values | Tazarotene 0.05% | Urea cream | Total |
|---|---|---|---|
| Number of subjects | 42 | 49 | 91 |
| Age categorical<br>Units: Subjects | | | |
| 9 years and over | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 29.2 | 25.2 | |
| standard deviation | ± 16.9 | ± 13 | - |
| Gender categorical<br>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 |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 14.0 |

| Reporting groups | |
|---|---|
| Reporting group title | Urea Group |
| Reporting group description: | |
| TEAE that occured when patients received urea treatment. | |
| Reporting group title | Tazarotene group |
| Reporting group description: | |
| TEAE that occured when patients received tazarotene treatment. | |
| Reporting group title | Vehicle group |
| Reporting group description: | |
| TEAE that occured when patients received vehicle. | |
| Reporting group title | No treatment |
| Reporting group description: | |
| TEAE that occured 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 recommandations 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