# Clinical trial results:
# Efficacy and tolerance of the emollient cream V0034 CR in the symptomatic treatment of ichthyosis in children. International, multicentric, randomised, controlled, double blind study, in parallel groups V0034 CR versus vehicle.

## Summary

| | |
|---|---|
| EudraCT number | 2006-003369-14 |
| Trial protocol | FI EE CZ NL DE LT FR LV IT ES |
| Global end of trial date | 01 November 2007 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 10 December 2016 |
| First version publication date | 10 December 2016 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | V00034 CR 309 1B |

### Additional study identifiers

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

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Pierre Fabre Medicament |
| Sponsor organisation address | 45, Place Abel Gance, Boulogne, France, 92100 |
| Public contact | Elisabeth COPPEL, Centre de Recherche et Développement<br>Clinique Pierre Fabre<br>3, Avenue Hubert CURIEN<br>31100 TOULOUSE, elisabeth.coppel@pierre-fabre.com |
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Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| 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 | 25 June 2008 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 November 2007 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 November 2007 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the efficacy of a 4-week treatment by the emollient V0034CR in reducing the disease severity assessed by a specified symptom sum score (SRRC: Scales Roughness Redness Cracks fissures score) on both legs.

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki and subsequent amendments thereto, the Good Clinical Practices (CPMP/ICH/135/95) and local legal régulations.

Patient underwent a health assessment at the start of the study and remaines under regular Medical control during the whole study

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 05 February 2007 |
| 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 | Czech Republic: 28 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | Estonia: 50 |
| Country: Number of subjects enrolled | Finland: 16 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Germany: 26 |
| Country: Number of subjects enrolled | Italy: 3 |
| Country: Number of subjects enrolled | Latvia: 38 |
| Country: Number of subjects enrolled | Lithuania: 30 |
| Country: Number of subjects enrolled | Poland: 40 |
| Country: Number of subjects enrolled | Tunisia: 30 |
| Worldwide total number of subjects | 265 |
| EEA total number of subjects | 235 |

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) | 36 |
| Children (2-11 years) | 146 |
| Adolescents (12-17 years) | 83 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 265 patients were included in the study and randomized in the two treatment groups. The study was performed in 12 countries and involved 21 centres. Among randomized patients, a total of 9 patients (3.4%) did not complete the study  3 (2.3%) in Vehicle group and 6 (4.5%) in V0034CR group. The main reason was lost to follow-up

### Pre-assignment

Screening details:

Patients under 18 years suffering from a non-bullous form of ichthyosis with SRRC global score >=4 and scaling SRRC >=2 on both external faces of the legs.

A double-blind period (V0034CR  or vehicle) during 4 weeks followed by an open label period with all patients treated by V0034 CR  for 8 weeks.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | V0034 |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | V0034 |
| Investigational medicinal product code | V0034 CR |
| Other name | Dexeryl |
| Pharmaceutical forms | Cream |
| Routes of administration | Topical use |

Dosage and administration details:

Twice a day on the whole body, in the morning and the evening for 4 weeks

| | |
|---|---|
| **Arm title** | Vehicle |

Arm description: -

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

Dosage and administration details:

Twice a day on the whole body in the morning and in the evening during 4 weeks

| Number of subjects in period 1[1] | V0034 | Vehicle |
|---|---|---|
| Started | 131 | 130 |
| Completed | 131 | 130 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: of the 265 enrolled and randomized patients worlwide, 9 patients ( 3.4%) did not complete the study; Mean reason for non completion was lost of follow up

## Period 2

| | |
|---|---|
| Period 2 title | Open - label period |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| **Arm title** | V0034-8 weeks |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | V0034 |
| Investigational medicinal product code | V0034 CR |
| Other name | Dexeryl |
| Pharmaceutical forms | Cream |
| Routes of administration | Topical use |

Dosage and administration details:

Twice a day on the whole body, in the morning and the evening for 4 weeks

| Number of subjects in period 2[2] | V0034-8 weeks |
|---|---|
| Started | 258 |
| Completed | 258 |

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: only subjects treated by V0034 CR were enrolled in the open label 4week follow up period

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | V0034 |
| Reporting group description: - | |
| Reporting group title | Vehicle |
| Reporting group description: - | |

| Reporting group values | V0034 | Vehicle | Total |
|---|---|---|---|
| Number of subjects | 131 | 130 | 261 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 9.18 | 8.52 | |
| full range (min-max) | 0.1 to 17.9 | 0.2 to 17.9 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 43 | 48 | 91 |
| Male | 88 | 82 | 170 |
| type of ichtyosis<br>Units: Subjects | | | |
| Ichthyosis vulgaris | 78 | 81 | 159 |
| X linked recessive ichthyosis | 15 | 21 | 36 |
| Non erythrodermic ichthyosis | 22 | 15 | 37 |
| Other | 16 | 13 | 29 |
| Scaling score | | | |
| Visual evaluation of scaling syptom on a five-point scale:<br>0 Absent<br>1 Slight: small scales only, surface lightly dull in colour<br>2 Moderate: small scales in combination with larger scales (>0.05mm), surface opaque or whitish<br>3 Severe: larger and large scales (flakes >1mm) are prominent, surface whitish Scaling (visual evaluation)<br>4 Extreme: larger flakes covering almost the entire skin surface in the examination field | | | |
| Units: Subjects | | | |
| absent | 0 | 0 | 0 |
| slight | 0 | 0 | 0 |
| moderate | 48 | 43 | 91 |
| severe | 62 | 72 | 134 |
| extreme | 21 | 15 | 36 |
| SRRC score | | | |
| Four symptoms, scaling, roughness, redness and cracks on both legs were rated on a five-grade scale from 0 absent to 4 extreme The SRRC score was the sum of these four symptom grades. The maximum score was 16. | | | |
| Units: decimal | | | |
| arithmetic mean | 7.47 | 7.12 | |
| full range (min-max) | 4 to 14 | 3 to 13 | - |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | Safety data set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| All randomised patients having taken at least one dose of study treatment. | |
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| All randomised patients having taken at least one dose of study treatment and with at least one post baseline evaluation of the primary efficacy criterion. | |
| Subject analysis set title | Full Analysis Set excluding one country |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| All randomised patients having taken at least one dose of study treatment and with at least one post baseline evaluation of the primary efficacy criterion, excluding patients from Tunisia (because unexpected results in this country- 100% responders in both groups). | |

| Reporting group values | Safety data set | Full analysis set | Full Analysis Set excluding one country |
|---|---|---|---|
| Number of subjects | 262 | 261 | 231 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 8.84 | 8.85 | 8.68 |
| full range (min-max) | 0.1 to 17.9 | 0.1 to 17.9 | 0.1 to 17.9 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 91 | 91 | 79 |
| Male | 171 | 170 | 152 |
| type of ichtyosis | | | |
| Units: Subjects | | | |
| Ichthyosis vulgaris | | 159 | |
| X linked recessive ichthyosis | | 36 | |
| Non erythrodermic ichthyosis | | 37 | |
| Other | | 29 | |
| Scaling score | | | |
| Visual evaluation of scaling syptom on a five-point scale:<br>0 Absent<br>1 Slight: small scales only, surface lightly dull in colour<br>2 Moderate: small scales in combination with larger scales (>0.05mm), surface opaque or whitish<br>3 Severe: larger and large scales (flakes >1mm) are prominent, surface whitish Scaling (visual evaluation)<br>4 Extreme: larger flakes covering almost the entire skin surface in the examination field | | | |
| Units: Subjects | | | |
| absent | | 0 | |
| slight | | 0 | |
| moderate | | 91 | |
| severe | | 134 | |
| extreme | | 36 | |

| SRRC score | | | |
|---|---|---|---|
| Four symptoms, scaling, roughness, redness and cracks on both legs were rated on a five-grade scale from 0 absent to 4 extreme The SRRC score was the sum of these four symptom grades. The maximum score was 16. | | | |
| Units: decimal | | | |
| arithmetic mean | | 7.3 | |
| full range (min-max) | | 3 to 14 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | V0034 |
| Reporting group description: - | |
| Reporting group title | Vehicle |
| Reporting group description: - | |
| Reporting group title | V0034-8 weeks |
| Reporting group description: - | |
| Subject analysis set title | Safety data set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| All randomised patients having taken at least one dose of study treatment. | |
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| All randomised patients having taken at least one dose of study treatment and with at least one post baseline evaluation of the primary efficacy criterion. | |
| Subject analysis set title | Full Analysis Set excluding one country |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| All randomised patients having taken at least one dose of study treatment and with at least one post baseline evaluation of the primary efficacy criterion, excluding patients from Tunisia (because unexpected results in this country- 100% responders in both groups). | |

### Primary: Patients having a 50% reduction of the SRRC score (Scaling, Roughness, Redness, Cracks fissures score) on FAS including all countries

| | |
|---|---|
| End point title | Patients having a 50% reduction of the SRRC score (Scaling, Roughness, Redness, Cracks fissures score) on FAS including all countries |
| End point description: | |
| The primary efficacy criterion was the response to treatment defined by a decrease of at least 50% of the SRRC score on the external face of legs (mean of the 2 legs) between baseline and Day 28.<br><br>The main analysis of the primary efficacy criterion was performed on the FAS population (All countries) using the Cochran Mantel Haenszel test stratified by centre. | |
| End point type | Primary |
| End point timeframe: | |
| From baseline to Day 28 | |

| End point values | V0034 | Vehicle | Full analysis set | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 131 | 130 | 261 | |
| Units: Patient | 85 | 65 | 150 | |

## Statistical analyses

| Statistical analysis title | Primary efficacy analysis |
|---|---|

Statistical analysis description:

Responses to treatment defined by a decrease of at least 50% of the SRRC score (mean of the 2 legs) between the 2 arms were compared using the Cochran-Mantel-Haenszel (CMH) test stratified by type of ichtyosis

| | |
|---|---|
| Comparison groups | Vehicle v V0034 |
| Number of subjects included in analysis | 261 |
| Analysis specification | Pre-specified |
| Analysis type | other[1] |
| P-value | = 0.008 [2] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[1] - The CMH test was performed on the FAS including all countries to assess whether the response (i. e. decrease in the SRRC score by at least 50% on Day 28) was independent of treatment (explanatory variable) when adjusting for group of countries.
[2] - The difference between the two treatment groups was statistically significant (p=0.008) adjusted for pooled centres.

## Primary: Patients having a 50% reduction of the SRRC score (Scaling, Roughness, Redness, Cracks fissures score) on FAS excluding one country

| | |
|---|---|
| End point title | Patients having a 50% reduction of the SRRC score (Scaling, Roughness, Redness, Cracks fissures score) on FAS excluding one country[3] |

End point description:

The main analysis of the primary efficacy criterion was performed also on the FAS excluding Tunisia, using the Cochran Mantel Haenszel test stratified by centre.
(Thirty patients from two centres were excluded from FAS analysis because of doubtful drug administration and results, with a 100% of responders in both groups.)

| | |
|---|---|
| End point type | Primary |

End point timeframe:

From Baseline to Day 28

Notes:

[3] - 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: No analysis has been performed

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During the whole study period

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 8.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Vehicle group |
| Reporting group description: - | |
| Reporting group title | Experimental Group |

Reporting group description: -

| Serious adverse events | Vehicle group | Experimental Group | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 130 (2.31%) | 2 / 132 (1.52%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Congenital, familial and genetic disorders | | | |
| Ichthyosis | Additional description: Exacerbation of known ichtyosis (post-study ). | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Talipes correction | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 130 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 130 (0.77%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Vehicle group | Experimental Group | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 26 / 130 (20.00%) | 30 / 132 (22.73%) | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 9 / 130 (6.92%) | 9 / 132 (6.82%) | |
| occurrences (all) | 9 | 12 | |
| Rhinitis | | | |
| subjects affected / exposed | 12 / 130 (9.23%) | 6 / 132 (4.55%) | |
| occurrences (all) | 13 | 6 | |
| Pharyngitis | | | |
| subjects affected / exposed | 7 / 130 (5.38%) | 2 / 132 (1.52%) | |
| occurrences (all) | 8 | 2 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 17 November 2006 | Substantial-general - all countries:<br>Life style change in the information consent form following a discrepansy between protocol and Information consent. |
| 11 December 2006 | Substantial-local amendment (Czech Republic):<br>Precision of one non inclusion criteria and modification of Inform consent Form .<br>The protocol was modified with the addition of "pregnancy test" where appropriate. |
| 14 March 2007 | Substantial-general - all countries:<br>Modification of the dates of study schedule |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/22118417