**Pierre Fabre Médicament**
**Represented by: Institut de Recherche Pierre Fabre**
**45, Place Abel Gance**
**F-92654 Boulogne Cedex**

# 1. TITLE PAGE

# CLINICAL STUDY REPORT

**IMPACT OF THE V0034 CR 01B EMOLLIENT ON ATOPIC DERMATITIS SYMPTOMS IN CHILDREN**
**A randomised, placebo-controlled, parallel-groups, double-blind study**

**Investigational product**: Product V0034 CR 01B

**Protocol number**: V00034 CR 402 1B

**Phase of development**: Phase III (Czech Republic, Italy) – Phase IV (Estonia, France, Germany, Latvia, Lithuania, Poland and Romania)

**Date of first enrolment**: October 30th 2008

**Date of last completed**: May 23th 2009

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**Date of report**: Version 1 – 22/01/2010

Study performed in compliance with Good Clinical Practice.

# 2. SYNOPSIS

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|---|---|---|
| **Name of Company: Pierre Fabre Médicament** | **Individual Study Table Referring to Module 5 of the Dossier Vol.: .....Page: .....** | **(For National Authority Use Only)** |
| **Name of finished product: V0034 CR 01B** | | |
| **Name of active substances:** Glycerol + Paraffin (liquid paraffin + soft paraffin) | | |

**Title of study:**
Impact of the V0034 CR 01B emollient on atopic dermatitis symptoms in children. A randomised, placebo-controlled, parallel-group, double-blind study.

**Coordinating Investigator:**
Prof. Thomas Bieber, M.D., Ph.D.

**Study centre(s):**
Paediatricians and/or dermatologists and/or allergologists and/or general practitioners.

| **Studied period:** | **Phase of development:** |
|---|---|
| - date of first enrolment: 30th October 2008<br>- date of last completed: 23th May 2009 | Phase III (Czech Republic, Italy)<br>Phase IV(Estonia, France, Germany, Latvia, Lithuania, Poland, Romania) |

**Objectives:**

**<u>Main objective</u> :**
- To evaluate, in children presenting with atopic dermatitis, the impact of a daily treatment by the emollient V0034CR01B on the disease symptoms: evolution of the POEM (Patient-Oriented Eczema Measure) score.

**<u>Secondary objectives</u>:**
- To evaluate the impact of the treatment on xerosis: evolution of the SRRC (Scaling, Roughness, Redness, Cracks/Fissures) score,
- To evaluate the impact of the treatment on the topical corticosteroid use,
- To assess the overall efficacy of the treatment by the parents and the investigator,
- To document the clinical, local and systemic, safety of the treatment over the study duration.

**Methodology:**
International multicentric, randomized, double-blind, parallel-groups (V0034CR01B cream versus vehicle) study.

**Number of patients (planned and analysed):**
Based on the results of a previous study, a difference of 1 in the POEM score was expected between active and vehicle group with a standard-deviation of 4. To conclude to a statistically significant difference with a Type I error rate of 0.05 two-sided and a power of 80%, 253 patients per group were required. Taking into account a previous observed rate of 8% of premature drop-out or withdrawal, 275 patients per group were required.

591 patients were screened and 588 randomized and included.
The APT safety population was made of 586 patients (292 in the Vehicle group and 294 in the V0034CR group).
The APT efficacy population was made of 573 patients (286 in the Vehicle group and 287 in the V0034CR group).
The PP population was made of 472 patients (233 in the Vehicle group and 239 in the V0034CR group).

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**Diagnosis and main criteria for inclusion:**

**<u>Inclusion criteria</u>:**
Will be eligible patients who met the following criteria:
- Age between 2 and 7 years,
- Presenting with atopic dermatitis according to the diagnostic criteria of the UK Working Party,
- Whose IGA score is ≤ 1 at inclusion,
- Whose parent(s) or guardian(s) had given his/her (their) written consent for their child's participation in the study,
- Whose parent(s) or guardian(s) was (were) cooperative with regard to compliance with study-related constraints,
- If required by national regulations, registered with a social security or health insurance system.

**<u>Non-inclusion criteria</u>:**
Will not be included patients who met one of the following criteria:

* *Criteria related to pathologies*
- Acute phase of atopic dermatitis with mild/moderate/severe erythema, excoriation, crust, oozing, exudation,
- Severe form of atopic dermatitis requiring either systemic corticosteroid treatment and/or antibiotic or antiviral treatment and/or hospitalisation,
- Primary bacterial, viral, fungal or parasitic infection,
- Ulcerated lesions, acne or rosacea,
- Dermatological disease other than atopic dermatitis liable to interfere with the assessment,
- History of serious disease considered by the investigator hazardous for the patient or incompatible with the study,
- Immunosuppression,
- History of hypersensitivity or intolerance to one of the substances of content of the study drug or Locapred, or to cosmetics.

* *Criteria related to treatments*
- Use of oral corticosteroids or immunosuppressants during the last month,
- Use of antibiotics or topical corticosteroids during the last week,
- Use of non-steroid anti-inflammatory drugs or antihistamines during the last week,
- Use of homeopathic treatment during the last 2 months,
- Regular use of food supplements that could, in the opinion of the investigator, modify skin properties.

* *Criteria related to the population*
- Child with a brother or sister already included in this study,
- Patient and/or parent(s) or guardian(s) linguistically or psychologically unable to understand the information given or give his/her (their) informed consent or who refused to give his/her (their) consent in writing,
- Parent(s) or guardian(s) subject to an administrative or court order or subject to guardianship or wardship,
- Parent(s) or guardian(s) who cannot be contacted by telephone in an emergency,
- Participation to another clinical trial or being in the exclusion period of another clinical trial.

**Test product:**
V0034 CR 01B cream for local application.
**Dose:**
1 application bid (morning and evening) on the whole body including face.
**Mode of administration:**
Topical applications will be done in thin layers by massage until complete penetration.

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**Reference therapy:**
Vehicle cream (same aspect as the verum).
**Dose:**
1 application bid (morning and evening) on the whole body including face.
**Mode of administration:**
Topical applications will be done in thin layers by massage until complete penetration.

**Duration of treatment:**
12 weeks

**Associated product:**
* During disease exacerbation phases (presence of inflammatory lesions), a moderately potent corticosteroid cream (Locapred®, desonide 0.1%) was allowed, used as follows:
- Locapred®: once a day (preferably in the evening) only on the lesions of the body and the face,
- V0034CR 01B cream or vehicle: once a day (preferably in the morning) on the whole body including face.
Locapred® was used until complete resolution of the inflammatory signs. Conditions of use of Locapred® were explained to the parents.
* When necessary, other treatments of atopic dermatitis signs/symptoms (antihistamines, antiseptics, zinc creams / ointments) were allowed and carefully notified.
* Foaming gel Klorane® provided by the sponsor was allowed for children washing/cleansing.

**Prohibited products during the study:**
* Oral steroids, moderately potent topical corticosteroids other than the study corticosteroid, potent or very potent topical corticosteroids, immunosuppressants, emollients or moisturizers other than the study emollient, body hygiene product (milk, soap, lotion) other than the foaming gel provided by the sponsor.
* Homeopathic treatment.
* Food supplements that could, in the opinion of the investigator, modify skin properties.

**Criteria for evaluation:**

**Primary criterion:**
Mean POEM score measured weekly, over the 12 weeks of treatment.

**Secondary criteria:**
* Mean SRRC score at the 2 visits on treatment (4 weeks and 12 weeks),
* Number of days of application of the moderately potent corticosteroid (weekly assessment),
* Number of patients dropped out due to lack of efficacy, adverse events or parents' decision,
* Overall assessment of treatment efficacy by the investigator,
* Overall assessment of treatment efficacy by the parents,

**Safety:**
* Assessment of the local tolerability (examination of the skin) and the systemic safety (general clinical examination),
* Reported adverse events.

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**Statistical methods:**

**Efficacy:**
- Analysis of variance for the POEM score (main criterion) using a mixed model for repeated measures with treatment, country and visit as fixed effects and subject as random effect,
- Analysis of covariance for the SRRC score usning a mixed model for repeated measures with treatment, country and visit as fixed effects, subject as random effect and baseline score as a covariate,
- The number of days of application of corticosteroid was expressed as a percentage of the total number of days in the study. This percentage was compared between treatment groups using Cochran-Mantel-Haenszel test with modified ridit scores, adjusting for country, using pre-defined classes (0%, ]0% ; 10%], ]10%-20%], ]20%-30%], ]30%-40%], > 40%),
- Logrank test for the number of subjects dropped out due to lack of efficacy, adverse events or parents' decision,
- Cochran-Mantel-Haenszel test adjusting for country and using modified ridit scores for the assessment of treatment efficacy by the investigator and by the the parents.

**Safety:**
Descriptive analysis.

**Efficacy results:**

The mean age was 52.1±19.0 months in the Vehicle group versus 50.4±17.9 months in the V0034CR group (p=0.389) and 48.3% of the patients of the Vehicle group were males while they were 50.7% in the VR0034CR group (p=0.562). There were no statistically significant differences between both treatment groups regarding demographic characteristics. Family history of atopy was present in 75.2% of patients and the age of first cutaneous clinic lesion was 9.1 months, without differences between groups. There was no difference between groups, neither for the number of consultations in the last 6 months (0.9), nor for the time of consultation motivated by the last flare (10.4 months).

The initial POEM score was around 5.3/28 in both groups, which corresponds to atopic dermatitis of mild severity. Despite this low severity at Week 1, we noticed a dramatic decrease in POEM score over the 12 weeks of the study : -57% in the V0034CR group ( from 5.3 to 2.3) versus -48% in the Vehicule group (5.4 to 2.8). Every week, there was a constant trend for a difference in favour of V0034CR. However, even if the results of the primary analysis (MMRM) exhibited a difference in favour of the study drug (-0.34), the difference was not statistically significant (p=0.2343).
The SRRC score was quite small at baseline (2.6 /16). However, there was a great decrease over the whole duration of the study, in both groups: -69% in the V0034CR group (from 2.6 to 0.8) versus -62% in the Vehicule group (from 2.6 to 0.9). Even if this difference was not statistically significant, the p value was of 0.0743, at the limit of significance.
A post hoc analysis was conducted on the sub scores of SRRC. The difference between groups regarding roughness was statistically significant (p = 0.005), in favour of V0034CR, which reflects the important emollient properties of the study product.
The consumption of corticosteroids was very low over all the duration of the study (more than half of patients did not take any corticosteroids and near of 20% were in the class ]0% ; 20%]) and there was no difference between groups (p=0.725).
As a whole, treatment efficacy was considered as good or very good in 97.4% of investigators for V0034CR and 91.7% for vehicle. The difference between groups was statistically significant (p = 0.029).
96.4% of patients juged V0034CR as good or very good, versus 93.2% for the vehicle. The difference between groups was statistically significant (p = 0.045).
The judgement of parents regarding hydration was in favor of V0034CR, with 96.4% of good or very good opinion versus 91.4% for vehicle (p = 0.053).
There was no difference between groups regarding the number of patients dropped out due to lack of efficacy, adverse events or parents' decision (p=0.8383).

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**Safety results:**

52.4% of the patients of the Vehicle group presented at least one treatment emergent adverse event while they were 54.1% in this case in the V0034CR group. 4.1% of the patients of the Vehicle group presented at least one possibly related treatment emergent adverse event while they were 3.1% in this case in the V0034CR group. Only 2.2% of patients presented at least one severe treatment emergent adverse event (2.1% for vehicule and 2.4% for V0034CR).

14 SAEs occurred in 12 patients (4 SAEs for 3 patients (1.0%) in the V0034CR group and 10 SAEs for 9 patients (3.1%) in the vehicle groups). None of these SAEs were related to the study drug. None of these SAEs led to definitive study discontinuation. All were resolved until the end of the study.

Tventy-five non serious adverse events led to definitive study drug discontinuation: 13 events in V0034CR group (7 were considered related to the drug: skin irritations or dermatitis) and 12 events in vehicle group (10 were considered related to the vehicle: irritations, dermatitis, redness or flares).

Analyses of adverse event did not show any differences between treatment groups.

Finally, this analysis confirmed the safety of V0034CR in the management of atopic dermatitis.

**Conclusions:**

The study evidenced a trend in favour of the study product, even if there was no statistically significant difference between V0034CR and the vehicle on the primary efficacy outcome. Methodological pitfalls could explain the lack of demonstration on main parameter.

First, we must emphasize that patients included were presenting with AD of mild severity and with low evolutive potential:

Children in the late stage of evolution of disease (51.2 months at inclusion),

Few flares (last flare 10.4 months before inclusion overall),

Few corticosteroids (about 37% of the patients never had topical corticosteroids before inclusion, and only about 10% had a regular use),

Small POEM at the first week (around 5.3/28 in both groups).

Thus, insufficiency of effect on POEM or corticosteroids consumption is probably linked, at least in part, to the selection of the population: AD was not severe and of low evolutive potential, so few flares were observed and therefore consumption of corticosteroids was very small.

However, even if poor, corticosteroids consumption may have lead to control of the flares, leading to a minimization of the difference between the two groups of treatment.

Second, it is important to note that the POEM score takes into account the xerosis present in AD but also the inflammatory aspects of the disease. V0034CR is an emollient and its effect could have been drowned. Thus, it is possible that the POEM score was not well adapted to the evaluation of such an emollient product. This seems to be supported by the results observed with the SRRC score (p=0.07), which is more specific of the xerosis, and in particular with its roughness sub-score (p=0.005).

Third, in order to conduct a true double-blind trial, the placebo used in the study was made with the excipient of V0034CR, and probably this excipient has a real beneficial effect. Indeed, whereas we expected a delta of at least 1 point between V0034CR and placebo, we obtained a difference of 0.4 between the 2 products. The decrease in the vehicle group cannot be the result of the natural history of the disease, and is in favour of a therapeutic effect of this vehicle.

But, despite a low severity at Week 1 (POEM score was around 5.3/28 in both groups), there was a dramatic decrease in POEM score over the 12 weeks of the study: -57% in the V0034CR group versus -48% in the Vehicule group.

Moreover, even if the difference for SRRC score was not statistically significant, there was a good trend (p=0.0743), and a sub-score post-hoc analysis evidenced a statistically significant difference for roughness (p = 0.005).

Parents and investigators judgment corroborated these results: V0034CR was more appreciated by the parent(s) than the Vehicle (p=0.045 for global opinion and p=0.053 for hydration effect) and overall efficacy is judged better by investigators (p =0.029).

Thus, all these data reflects the high emollient properties of V0034CR.

Regarding safety, few patients (about 4%) presented with possibly related treatment emergent adverse events and most of them were not severe. Only 9 patients (3.1%) of the vehicle group and 3 patients (1%) of the V0034CR group presented at least one serious treatment emergent adverse event. Analyses of adverse event did not show any differences between treatment groups.

So, this study confirmed the safety of V0034CR in the management of atopic dermatitis.