PIERRE FABRE DERMATOLOGIE,
represented by Institut de Recherche Pierre Fabre
45, Place Abel Gance
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CLINICAL STUDY REPORT

1. TITLE PAGE

ASSESSMENT OF THE ACTIVITY OF A NEW CREAM CONTAINING BETAMETHASONE DIPROPIONATE AT 0.010%, 0.025% AND 0.050% VERSUS REFERENCE PRODUCTS USING VASOCONSTRICTION ASSAY IN HEALTHY SUBJECTS

Single centre, investigator blinded, active and vehicle-controlled, intra-individual comparison, phase IIa study

Investigational drug:	0.010, 0.025 and 0.050% betamethasone dipropionate cream (V0071 CR 03A, V0071 CR 02A and V0071 CR 01B)
Marketed drug name:	DERMOVAL® cream DIPROSONE® cream EUMOVATE™ cream
Protocol number:	V00071 CR 202
Phase of development:	Phase IIa
Date of first enrolment:	12-Mar-2009
Date of last subject completed:	16-Apr-2009
Date of signature:	
Date of approval:	
Author:	Anne-Claire CATHELINEAU
Co-author:	Magali PROCACCI-BABLED
Coordinator:	Catherine QUEILLE-ROUSSEL

Clinical trial performed in compliance with Good Clinical Practice

2. SYNOPSIS

Name of the Company: Pierre Fabre Dermatologie	**Individual Study Table Referring to part: of the Dossier:** **Volume:** **Page:**	(FOR NATIONAL Authority Use only)
Name of finished product: Not applicable		
Name of Active Ingredient: 0.010, 0.025 and 0.050% betamethasone dipropionate cream (V0071 CR 03A, V0071 CR 02A, V0071 CR 01B)		

Title of Study: "Assessment of the activity of a new cream containing betamethasone dipropionate at 0.010%, 0.025% and 0.050% versus reference products using a vasoconstriction assay in healthy subjects."

Coordinating Investigator: Dr Catherine QUEILLE-ROUSSEL

Study centre:

CPCAD – Centre de Pharmacologie Clinique Appliquée à la Dermatologie
Hôpital L'Archet 2 – 151 route de Saint Antoine de Ginestière – BP 3079 – 06202 NICE Cedex 3 - France

Publication (reference):

Studied period (years): *Date of first enrolment*: 12-Mar-2009 *Date of last completed*: 16-Apr-2009	**Phase of development:** Phase IIa (pharmacodynamic)

Objectives:

The preferred method for rank-ordering the potency of topical corticosteroids is the clinical vasoconstriction test (human skin blanching assay) described by McKenzie and Stoughton (MCKENZIE and STOUGHTON, 1962).

Vasoconstriction tests using new formulations must be compared with the effects of established corticosteroid preparations, not only with those of approximately equal activity, but also with stronger and weaker preparations.

Main objective:

This study was a pharmacodynamic study based on the corticosteroid induced skin vasoconstriction in healthy human skin. The main objective was to determine the place of new betamethasone dipropionate creams (V0071 CR) within the spectrum of topical corticosteroid formulations using as main criterion the skin colour measured by the chromameter (ChromaMeter Minolta).

This study was a ranking study. This was not a bioequivalence study.

Secondary objective:

The secondary objective was to determine the place of new betamethasone dipropionate creams (V0071 CR) within the spectrum of topical corticosteroid formulations by means of a visual assessment of the skin blanching response.

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Methodology:

This study was conducted as a single centre, investigator blinded, active and vehicle-controlled, intra-individual comparison, phase IIa study involving 40 healthy subjects meeting specific inclusion/exclusion criteria.

The tested products were randomly allocated to delineated 2.2 cm diameter sites on the volar part of the forearms. To avoid any overlap, each site was kept at least 2 cm apart from the other.

All the tested products (the 3 new cream formulations, the matching cream vehicle, DERMOVAL® cream (as reference product for the very potent group) , DIPROSONE® cream (as reference product for the target class, potent group) and EUMOVATE™ cream (as reference product for the moderately: potent group) were topically applied on the allocated areas without occlusion during six hours.

Visual and chromametric evaluation of the skin blanching were performed before any product application (within 30 minutes before T0), then 6 hours (T_{6h}), 8 hours (T_{8h}), 10 hours (T_{10h}), 12 hours (T_{12h}), 14 hours (T_{14h}), 24 hours (T_{24h}) and 30 hours ($T30_h$) after T0 (product application time).

Visual scoring was performed by two independent trained evaluators.

Number of subjects (planned and analysed):

In total 40 subjects planned, 40 enrolled and 40 analyzed.

Diagnosis and main criteria for inclusion:

Female and male healthy subjects, aged between 18 and 50 years old with skin type II to IV on the Fitzpatrick scale (FITZPATRICK, 1988) and demonstrating adequate vasoconstriction response to topical corticosteroids DIPROSONE® cream.

Tested product:
Name: NA
Code: V0071 CR 01B for 0.050%
V0071 CR 02A for 0.025%
V0071 CR 03A for 0.010%
Form: Cream
Dose or Strength: Betamethasone dipropionate 0.010, 0.025 and 0.050%
Dosage: 10 µL
Route of Administration: Topical application on the forearm under non-occlusive conditions
Frequency of Administration: Single application
Application Duration: 6 hours

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Matching vehicle control:

Name: NA
Form: Cream
Dose or Strength: 0%
Dosage: 10 µL
Route of Administration: Topical application on the forearm under non-occlusive conditions
Frequency of Administration: Single application
Application Duration: 6 hours

Reference product n°1:

Name: DERMOVAL® 0.05%
Form: Cream
Dose or Strength: Clobetasol propionate 0.05% (very potent, D07AD (group IV))
Dosage: 10 µL
Route of Administration: Topical application on the forearm under non-occlusive conditions
Frequency of Administration: Single application
Application Duration: 6 hours

Reference product n°2:

Name: DIPROSONE® 0.05%
Form: Cream
Dose or strength: Betamethasone dipropionate 0.05% (potent, D07AC (group II))
Dosage: 10 µL
Route of Administration: Topical application on the forearm under non-occlusive conditions
Frequency of Administration: Single application
Application Duration: 6 hours

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Reference product n°3:

Name: EUMOVATE™
Form: Cream
Dose or strength: Clobetasone butyrate 0.05% (moderately potent, D07AB (group II))
Dosage: 10 µL
Route of Administration: Topical application on the forearm under non-occlusive conditions
Frequency of Administration: Single application
Application Duration: 6 hours

Evaluation criteria:

Visual and chromametric evaluation of vasoconstriction were made before any product application (within 30 minutes before T0) then 6 hours (T6h), 8 hours (T8h), 10 hours (T10h), 12 hours (T12h), 14 hours (T12h), 24 hours (T24h) and 30 hours (T30h) after T0 (product application time).

Criteria for Evaluation:

Main criterion:

Skin colour measured by the chromameter (ChromaMeter Minolta): colorimetric parameter a* (a*=value represents the balance between red and green values). The results were adjusted to baseline value (Δa*). At each time, two successive series of measures were performed on each test site. For analyses, the mean of the two values was calculated. The results were expressed as adjusted means per time and by the mean AUC (Δa*) per product/site.

Secondary criteria:

- Visual skin blanching response (visual score (VS)) according to a multiple unit (five points) scale:

0 = no change in skin colour,
1 = slight (barely visible) blanching,
2 = obvious blanching,
3 = intense blanching,
4 = blanching judged to be maximal.
Intermediate scores (of half unit) could have been used when needed.
The analyzed variable was the mean between the two readers at each evaluation time.

The results were expressed by the mean values obtained at each assessment time and by the mean AUC (VS) by product/site.

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- Skin colour measured by the chromameter (ChromaMeter Minolta): colorimetric parameter L*

(L*=value gives the relative brightness). The results were adjusted to baseline value (ΔL*). At each time, two successive series of measures were performed on each test site. The results were expressed as adjusted means per time and by the mean AUC (ΔL*) per product/site.

Safety:
Adverse events (AE) were assessed at each visit and reported on the AE pages of the CRF.

Study schedule:
The methodology used was a methodology adapted from original human skin blanching assay described by Mc Kenzie and Stoughton (MCKENZIE and STOUGHTON, 1962).

The study schedule was the following:

- Screening (Day-22 to Day-1):
  - Information of the subject,
  - Consent of the subject,
  - First check of inclusion/exclusion criteria,
  - Pre-test of vasoconstriction response to topical corticosteroids
  - Screening check-up with complete clinical examination (vital signs)
- At Day 1 (randomization day):
  - At baseline (within 30 minutes before T_0) the following assessments were performed:
    - check of the inclusion/exclusion criteria,
    - urine pregnancy test (for women of childbearing potential),
    - drawing of 8 sites (on the volar part of the forearms),
    - objective colorimetric assessment (chromametry) on the 8 selected sites,

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➢ At T_0 (product application):

- application of the products according to the randomization list to 7 out of the 8 selected sites, by a study nurse or an assistant independent from the two trained evaluators,
- one test site was left untreated as a negative control,

➢ At T_{6h},

- on the test sites treated with the tested formulations and reference products (DERMOVAL® cream, DIPROSONE® cream, EUMOVATE™ cream) the excess of product was gently wiped with a disposable tissue,

➢ At T_{6h}, T_{8h}, T_{10h}, T_{12h}, T_{14h},

- visual scoring of skin blanching response (by two trained readers, blinded),
- colorimetric assessment (chromametry)

▪ At Day 2 (last study day):

➢ At T_{24h} and T_{30h}

- visual scoring of skin blanching response (by two trained readers, blinded),
- colorimetric assessment (chromametry)

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Statistical methods:

- ***Pharmacodynamic parameters:***

- **Main criterion:**

*Colorimetric parameter a**

Colorimetric measurements were always performed twice. The mean of the two values by site was calculated. The results adjusted to baseline value (Δa*) were expressed by the AUC calculated by classical trapezoidal rule. The means of AUC_{0-30} (Δa*) were presented by product.

- **Secondary criteria:**

Visual skin blanching response

The visual skin blanching response (VS) was expressed by the mean values and by the AUC_{0-30} per subject and product. The analyzed variable was the mean between two readers at each evaluation time. The graph of means values per time and per product was plotted.

*Colorimetric parameter L**

As for colorimetric parameter a*, measurements were always performed twice. The mean of the two values by site was calculated. The results adjusted to baseline value (ΔL*) were expressed by the AUC. The means of AUC_{0-30} (ΔL*) were presented by product.

- ***Statistical methods:***

Prior to any statistical analysis, the normality of each parameter was tested using the Shapiro-Wilk test. In case of normality, an analysis of variance (GLM model) was performed on the AUC_{0-30} by testing the effects subject and product. In case of significant ($p<0.05$) product effect, the products were compared using a multiple comparison test (Tukey test).

In case of non normality of one of the analyzed parameters, the analysis of variance was replaced by a Friedman two-way analysis of variance and the product comparisons were performed using a Wilcoxon signed rank test, adjusted by Tukey method.

- ***Safety analysis:***

Safety analysis was descriptive on the reported local and systemic adverse events. The adverse events were to be listed as per the MedDRA classification.

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Summary – Conclusions:

Demographics:

Fifty-two (52) subjects were screened and 40 were randomised. All the 40 randomised subjects completed the whole study. No major deviation was observed in this study. No subject entered the study without fully satisfying the entry criteria.

Pharmacodynamic results:

1. Main criterion – Colorimetric parameter a*

Lower is the value of Δa*, stronger is the skin blanching activity The skin blanching activity of the three strengths of V0071CR is stronger than those of the matching vehicle and of the untreated control site (No product) but weaker than the DERMOVAL® (very strong potency) one.
The skin blanching activity of V0071CR at 0.010% is weaker than those of V0071CR at 0.025% and 0.050%, EUMOVATE™ (moderate potency) and DIPROSONE® (strong potency).
No significant difference was detected between V0071CR at 0.025% and V0071CR at 0.050%.

No significant difference was detected between the two strengths of V0071CR (0.025% and 0.050%) and DIPROSONE® cream.

2. Secondary efficacy criteria:

- Visual skin blanching response

As for the parameter a*, the activity of the three strengths of V0071CR is stronger than those of Vehicle (except for V0071 at 0.010%, pTVS=1.0000) and No product but weaker than the DERMOVAL® one (very strong potency).
The activity of V0071CR at 0.010% is significantly weaker than that of the moderate potency EUMOVATE™.
No significant difference was detected between the two strengths of V0071CR (0.025% and 0.050%) and the moderate potency EUMOVATE™ cream.
The activity of V0071CR at 0.010% and 0.025% is significantly weaker than that of the strong potency DIPROSONE®.
By contrast, the activity of V0071CR at 0.050% is not significantly different than that of the strong potency DIPROSONE®.

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- Colorimetric parameter L*

Higher is the value of ΔL*, stronger is the skin blanching activity. The results of the comparisons show that the skin blanching activity of V0071CR at 0.025% and 0.050% is stronger than the Vehicle one. As for the two previous criteria (a* and TVS), the very strong potency, DERMOVAL®, markedly differs from the 3 strengths of V0071CR.

The activity of V0071CR at 0.010% is weaker than that of V0071CR at 0.025%.

The activity of V0071CR at 0.010% is significantly weaker than that of the moderate potency EUMOVATE™ cream. No significant difference was detected between the two strengths of V0071CR (0.025% and 0.050%) and the moderate potency EUMOVATE™ cream.

The activity of V0071CR at 0.010% and 0.025% is significantly weaker than that of the strong potency DIPROSONE® cream.
By contrast, the activity of V0071CR at 0.050% is not significantly different than that of the strong potency DIPROSONE®.

Safety results:

A total of 2 adverse events (AE) out of the 40 patients were reported during the study. None of these events was related to the study products.
There was no Serious Adverse Event and no death reported.

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Conclusion:

As expected, all the test formulations including DIPROSONE® cream and EUMOVATE™ cream are significantly less potent than the very potent one, DERMOVAL® cream.

In this study, a dose effect is detected for the main criterion (Δa*) between the lowest strength (0.010%) of the test product V0071CR and the two higher tested strengths (0.025% and 0.050%) but no significant different is detected between the two higher.
For the main criterion (Δa*), these two strengths (0.025% and 0.050%) do not differ from DIPROSONE® cream, the reference formulation which contains the same molecule (betamethasone dipropionate) at 0.05% and belongs to the potent group.
However, only the 0.050% formulation does not differ significantly from DIPROSONE® cream regarding the two secondary criteria, the visual score and ΔL*. Indeed, no significant difference with DIPROSONE® cream was detected for the 0.025% formulation for these two parameters.

By contrast, no significant difference with EUMOVATE™ cream was detected for the 0.025% and 0.050% formulations for the three parameters (Δa*, visual score and ΔL*).
Despite the fact that no significant difference is detected between the highest strength of V0071CR 0.050% and the reference formulation for the moderate potency group, EUMOVATE™ cream, based on the whole study results and taking into account the numerical superiority, it can be considered that the V0071CR 0.050% formulation belongs to the strong potency group, like DIPROSONE 0.05% cream.
The V0071CR 0.010% cream is significantly weaker than EUMOVATE™ cream but stronger than the matching vehicle, and can be classified as a weak potency formulation.
The ranking of the V0071CR 0.025% formulation remains uncertain, between the moderate and the strong potency groups.
All the test formulations are well tolerated.

Date of the report: 11-Jan-2010