PIERRE FABRE DERMATOLOGIE
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CLINICAL STUDY REPORT

1. TITLE PAGE

EFFICACY AND SAFETY OF 0.1%, 0.5% AND 1% TAZAROTENE NAIL LACQUER FORMULATION VERSUS VEHICLE IN NAIL PSORIASIS

Phase II, international, multicentre, double-blind, randomized study of four parallel groups

Investigational drug:	0.1%, 0.5% and 1% Tazarotene
N° EudraCT	2004- 004825-87
Protocol number:	R00002 VE 201
Phase of development:	II
Date of first enrolment:	28/04/05
Date of last completed:	08/05/06
Date of final report:	01 June 2007
Author:	Christelle GOUHIER-KODAS (MEDIBRIDGE)
Co-author:	Caroline NORAY (STATITEC)
Coordinator:	Jean-Paul ORTONNE (Hôpital de l'Archet 2, Nice)

Clinical trial performed in compliance with Good Clinical Practice.

2. SYNOPSIS

<table>
<tr><td><u>Name of the Company:</u>
PIERRE FABRE DERMATOLOGIE</td><td rowspan="3"><u>Individual Study Table Referring to part:</u>
<u>of the Dossier:</u>

<u>Volume:</u>

<u>Page:</u></td><td rowspan="3">(FOR NATIONAL Authority Use only)</td></tr>
<tr><td><u>Name of Finished Product:</u>
Not applicable</td></tr>
<tr><td><u>Name of Active Ingredient:</u>
0.1%, 0.5% and 1% Tazarotene</td></tr>
<tr><td colspan="3"><u>Title of Study:</u> EFFICACY AND SAFETY OF A 0.1%, 0.5% AND 1% TAZAROTENE NAIL LACQUER FORMULATION VERSUS VEHICLE IN NAIL PSORIASIS.</td></tr>
<tr><td colspan="3"><u>Investigators:</u> Scientific Advisor: ROBERT BARAN – Nail Disease Centre - 42, rue des Serbes - 06400 Cannes – FRANCE</td></tr>
<tr><td colspan="3"><u>Coordinator:</u> JEAN-PAUL ORTONNE – Hôpital de l'Archet 2 - 151, Route Saint Antoine Ginestière - BP 3079 - 06202 Nice Cedex 3 - FRANCE</td></tr>
<tr><td colspan="3"><u>Study centres:</u> France – 4 centres, Germany – 1 centre, Belgium – 2 centres, Poland – 5 centres, Czech Republic - 3 centres, Bulgaria – 4 centres, Hungary – 1 centre</td></tr>
<tr><td colspan="3"><u>Publication:</u> None</td></tr>
<tr><td colspan="2"><u>Studied period</u> (years):
Date of first enrolment: 28th April 2005
Date of last completed: 8th May 2006</td><td><u>Phase of development:</u> Phase II</td></tr>
<tr><td colspan="3"><u>Objectives:</u>
<u>Main objective</u>:
- To assess the efficacy of a 6-month daily application of 0.1%, 0.5% and 1% tazarotene fingernail lacquer in fingernail psoriasis, using the Dynamic Expert Physician Global Assessment (Dynamic EPGA) using a 6-point scale, performed by a blinded experts' committee

<u>Secondary objectives</u>:
- To assess the efficacy every 6 weeks using Baran's Total Clinical Score and Dynamic Investigator Physician Global Assessment (Dynamic IPGA)
- To assess the efficacy of a 3-month daily application using the Dynamic EPGA performed by a blinded experts'committee
- To assess the efficacy of a 3-month and a 6-month daily application using the Static EPGA performed by a blinded experts'committee
- To assess relapse at 3 months after the end of treatment
- To perform blood safety tests at 3 and 6 months
- To assess local and general safety of the test product at each visit
- To collect the Patient Self Assessment at 3 and 6 months</td></tr>
</table>

Methodology: International, multicentre, double-blind, randomized study of four parallel groups
Number of patients (planned and analysed): planned: 184 patients included: 205 patients analysed: 193 patients in the Full Analysis Set population (FAS) and 178 in the Per Protocol (PP) population
Diagnosis and main criteria for inclusion: • Patient aged 18 years or over, • Patient with a personal history of a cutaneous psoriasis, • Patient with at least four nails with a minimal severity level defined as an onycholysis at least 25% or subungual hyperkeratosis at least 2 mm, • Patient with a negative urine pregnancy test at inclusion for women of childbearing potential and using an efficient contraceptive (oral contraceptive, IUD, or tubal surgery), • Patient accepting to participate in the study and to give written informed consent, • For French patients, patient registered with the French Social Security, in agreement with the French law on biomedical experimentation.

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Test product:	0.1%, 0.5% and 1% Tazarotene nail lacquer formulation
Dose:	Each affected nails was covered of lacquer once per day at bedtime using the applicator brush provided
Mode of administration:	Local application
Batch number:	
Reference product:	Vehicle (Excipients)
Dose:	Each affected nails was covered of lacquer once per day at bedtime using the applicator brush provided
Mode of administration:	Local application
Batch number:	
Co-therapy product:	Not applicable
Dose:	Not applicable
Mode of administration:	Not applicable
Batch number:	Not applicable
Duration of treatment:	6 months

Criteria for evaluation:

Efficacy:

Primary criterion

The main criterion was the Dynamic Expert Physician Global Assessment (EPGA) at 6 months assessed by blinded experts on a 6-point scale.

Secondary criteria

- Baran's Total Clinical Score at each visit,
- Dynamic Investigator Physician Global Assessment (IPGA) for each visit,
- Dynamic Expert Physician Global Assessment (EPGA) at 3 months,
- Static Expert Physician Global Assessment (EPGA) at 3 months and 6 months,
- Relapse using Baran's Total Clinical score on nails involved at inclusion after 3 months without treatment for all patients who have completed the study treatment,
- Patient self-assessment of efficacy and ease of use at 3 and 6 months.

Safety:

- Local and general safety (adverse events) at each visit,
- Blood safety tests at 3 and 6 months,
- Patient self-assessment of tolerance at 3 and 6 months.

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Statistical methods:

All statistical tests were performed at the 0.05 (two-sided) significance level on the FAS and PP populations.

Efficacy:

Demographic and baseline characteristics:
Demographic and baseline characteristics were summarized for the ITT and the PP populations. The treatment groups were compared for the main characteristics using an analysis of variance with a treatment and a centre effect for quantitative variables and using the Cochran-Mantel-Haenszel (CMH) test, adjusting for the centre for qualitative variables.

Main criterion:
Each dose of tazarotene was compared with vehicle using the Cochran-Mantel-Haenszel (CMH) test, adjusting for the centre, and the Hochberg procedure for controlling the overall Type I error rate. In addition, a global dose-effect relationship including the placebo group and the three active groups was investigated using the Jonckheere-Terpstra test.

Secondary criteria:
The same analyses as the main criterion were used to compare Dynamic Investigator PGA at 3 months, Dynamic and Static Expert PGA respectively at 3 and 6 months and Patient's self assessment between groups. Each change from baseline of the PASI and the Baran's Total Clinical scores were calculated and compared between the treatment groups by an analysis of covariance with baseline covariate and treatment factors, adjusted on centre. Dunnett's test was used to compare active treatment groups versus placebo.

Safety:

The safety population analysed included all randomized patients who applied at least one dose of study medication.

Extent of exposure:
The length of exposure and the study duration were described for each group but no test was performed.

Descriptive analysis of adverse events displayed by body system and preferred terms using the MedDRA dictionary.

Overall local tolerance:
Any sign/sensation of periungual erythema, ulceration/erosion or burning/stinging present after applications of the nail lacquer on the treated lesions were assessed. Each dose of tazarotene was compared with vehicle using the Cochran-Mantel-Haenszel (CMH) test, adjusting for the centre, and the Hochberg procedure for controlling the overall Type I error rate. In addition, a global dose-effect relationship including the placebo group and the three active groups was investigated using the Jonckheere-Terpstra test.

Laboratory data: Blood tests (transaminases, cholesterol, triglycerides dosage) were performed at inclusion, 3 months and 6 months. Patients were only classified according to laboratory normal range. No statistical analysis was performed.

Physical examination: Patients with worsening in a physical system between the inclusion and the end of the study treatment were described.

Safety and easiness to use were assessed by the patient after 3 and 6 months of treatment. Each dose of tazarotene was compared with vehicle using the Cochran-Mantel-Haenszel (CMH) test, adjusting for the centre, and the Hochberg procedure for controlling the overall Type I error rate. In addition, a global dose - effect relationship including the placebo group and the three active groups was investigated using the Jonckheere-Terpstra test.

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Summary – Conclusions:

Efficacy results

Subject disposition: A total of 205 patients were enrolled (53 randomised to the Vehicle group, 49 to the 0.1% Tazarotene group, 51 to the 0.5% Tazarotene group, 52 to the 1% Tazarotene group). Patients of the FAS population (n=193) were 61 females and 132 males with mean age of 49 ± 14 years (range: 20-79). All treatment groups were comparable concerning all baseline characteristics (demographic characteristics, general medical history, history of nail psoriasis, presence of arthropatic psoriasis).

Compliance and premature discontinuation: Among included patients, a total of 26 were withdrawn and discontinued the treatment prematurely (4 patients in the Vehicle group, 7 patients in the 0.1% Tazarotene, 6 patients in the 0.5% Tazarotene, and 9 patients in the 1% Tazarotene group.

Primary efficacy criterion: The Dynamic Physician Global Assessment evaluated on the basis of photographs by the blinded Experts after six months of treatment was not different between the four treatment groups of the FAS population. The same results were observed in the PP population.

Secondary efficacy criteria (both FAS and PP may apply):

- The Dynamic PGA evaluated by the blinded experts after 3 months of treatment.
- The Dynamic PGA evaluated by the investigator at each visit did not demonstrate any significant treatment effect in all groups.
- The Static PGA evaluated by the blinded experts after 6 months of treatment showed no significant treatment effect whatever the tested concentration of tazarotene in the lacquer.
- The changes of PASI scores between the end-of-treatment visit and the inclusion visit were comparable between the four groups of patients.
- The Total Clinical Baran's Score evaluated by the investigator at each visit: no treatment effect was highlighted by the statistical analysis.
- The Patients' self-assessment of efficacy was not different between groups: about 36% of patients were satisfied or very satisfied at V2 and about 50% of patients were satisfied or very satisfied at V4.

The same results were obtained in the PP population.

Safety results

The safety population was constituted of 203 patients.

Adverse events:
TEAE: A total of 156 TEAEs were experienced by 88 patients. The majority of these TEAEs concerned skin and subcutaneous tissue disorders (n=58) and infections and infestations (n=31). No difference between groups was observed. Among these 156 TEAE, 8 led to treatment discontinuation. The relationship with the study drug was excluded in 4 cases.
SAE: A total of 9 TEAE were serious: 3 occurred in the Vehicle group, 2 occurred in the 0.1% Tazarotene group, 3 occurred in the 0.5% Tazarotene group, 1 occurred in the 1% Tazarotene group.
Deaths: No death was reported in this study.

Local tolerance: Only a statistically significant difference for burning and stinging sensations was highlighted at V3 between the three active groups treated with Tazarotene and the Vehicle group (p=0.002).

Patients' self assessment: The safety and the easiness to use of the treatment was found satisfactory by a majority of patients.

Conclusion:

The results of this multicentre, double-blind, randomised Phase II study show that the developed tazarotene nail lacquer with the active substance concentrated at 0.1%, 0.5% or 1% is not more efficacious than the vehicle comparator lacquer. No problem of general safety was observed. Concerning the local tolerance, only burning and stinging sensations were significantly increased at V3 in active treatment groups of patients compared to the Vehicle group.

Date of the report: 01 june 2007