Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

A multicentre, randomized, controlled study of the efficacy, safety and cost effectiveness of a sequential therapy with RV4104A ointment, ciclopiroxolamine cream and ciclopirox film-forming solution compared with amorolfine nail lacquer alone for the treatment of dermatophytic onychomycosis without matrix involvement

Investigational product: RV4104 oinment

Study Design: Randomized, parallel-group, multicentre, open-labeled, active-controlled study

EudraCT number: 2009-011125-14

Protocol number: RV4104 2008 548

Phase of development: Phase IV

Date of first enrolment: 10 November 2008

Date of last completed: 29 August 2011

Coordinating Investigator: **Prof Carle PAUL, MD**
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Date of report: 16 May 2012

Study performed in compliance with Good Clinical Practice.

2. SYNOPSIS

Name of Company: Pierre Fabre Dermatologie	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: Onyster	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)*: **urea**	**Vol.: .....Page: .....**	

Title of study:	**A multicentre, randomized, controlled study of the efficacy, safety and cost effectiveness of a sequential therapy with RV4104A ointment, ciclopiroxolamine cream and ciclopirox film-forming solution compared with amorolfine nail lacquer alone for the treatment of dermatophytic onychomycosis without matrix involvement.**
Coordinating Investigator:	D Professor Carl Paul, MD.
Investigators:	Dermatologie-Vénérologie . CHU Purpan. Place Raymond Baylac. BP 74 31300 Toulouse (France).
Study centre(s):	The study was conducted in 17 investigational centers located in France and Tunisia.
Publication (reference):	Paul C, Coustou D ,Lahfa M et al. A multicenter, randomized, open-label, controlled study comparing the efficacy, safety and cost-effectiveness of a sequential therapy with RV4104A ointment, ciclopiroxolamine cream and ciclopirox film-forming solution with amorolfine nail lacquer alone in dermatophytic onychomycosis. Dermatology. 2013;227(2):157-64
Studied period : **(date of first enrolment)** **(date of last completed)**	10 November 2008 29 august 2011
Phase of development:	Phase IV
Objectives: **Primary:**	To evaluate and compare the efficacy of the sequential association RV4104A ointment followed by ciclopiroxolamine 1% cream and ciclopirox 8% film-forming solution versus amorolfine 5% nail lacquer alone in the treatment of patients with dermatophytic onychomycosis (toenail) without matrix involvement.
Secondary:	• To evaluate and compare the safety of the sequential association RV4104A ointment followed by ciclopiroxolamine 1% cream and ciclopirox 8% film-forming solution versus amorolfine 5% alone in the treatment of patients with dermatophytic onychomycosis (toenail) without matrix involvement. • To evaluate and compare the cost-effectiveness of the sequential association RV4104A ointment followed by ciclopiroxolamine 1% cream and ciclopirox 8% film-forming solution versus amorolfine 5% alone in the treatmen of patients with dermatophytic onychomycosis (toenail) without matrix involvement.
Methodology:	48-week randomized, parallel-group, multicentre, open-labeled, active-controlled study. 36 weeks of treatment and a 12-week follow up period . Group 1 received amorolfine 5% nail lacquer, Group 2 received sequential therapy with RV4104A ointment followed by ciclopiroxolamine 1% cream and ciclopirox 8% film-forming solution .Main efficacy criteria was assessed at week 48 (day 336) while secondary criteria were assessed at the end of treatment (day 252, 36 week) in each group.
Number of patients (planned and analysed):	Planned: 130 subjects - Screened : 357 - Included : 142 (71 per group) - "Per Protocol evaluable: 135
Diagnosis and main criteria for inclusion:	Subjects: • males or females aged over 18 years, • with a Clinical diagnosis of distal-lateral or lateral subungual onychomycosis of one great toenail (the target nail) without matrix involvement • with Target nail plate showing between 25% and 60% of clinically infected area), • with at least 2 mm of unaffected proximal target nail area, • with a Target nail infection due exclusively to a dermatophyte (from positive fungal culture as reported by the central mycological laboratory,
Exclusion criteria	Subjects • had received systemic antifungal therapy or any topical antifungal therapy applied to the toenails within 3 months prior to screening visit • had more than 3 affected nails • had psoriasis, lichen planus or other abnormalities that could result in clinically abnormal toenail(s) • · Patient with moccasin-type tinea pedis • For women, those who : Were pregnant or lactating, Had no efficient contraception

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Duration of treatment:	36 weeks in 3 steps - RV4104A ointment (Onyster®) for 3 weeks, Mycoster® 1% cream once daily for 8 weeks, and Mycoster® 8% film-forming solution twice weekly for 25 weeks
Test product,	*Tested compounds :* - *RV4104A ointment : Onyster : urea (40%)-lanolin-Vaseline* - *Mycoster® 1% cream (marketed in France and Tunisia)* *Mycoster® 8% film-forming solution(marketed in France and Tunisia)*
Reference therapy, **,**	Amorolfine 5% nail lacquer (Loceryl®) marketed by Galderma International The patient was instructed to clean the surface of the affected nail with the lacquer remover and to remove the softened part using the scraper provided before the application o the amorolfine nail lacquer. The application was repeated twice a week.
Criteria for evaluation:	**Efficacy:** ***Primary efficacy criterion*** - Treatment success at endpoint (D336, week 48) in each group: Treatment Success at D336 was defined as clinical and mycological cure o Clinical cure at D336 (judged by the investigator) defined as disappearance of all lesions on target nail or residual disease of no more than 10% of the original total diseased surface (the remaining diseased surface had to affect the distal portion of the nail). **o** Mycological cure at D336 defined as negative direct microscopy examination and negative fungal culture (as reported by the central mycological laboratory). ***Secondary efficacy criteria*** - Clinical cure at D77, D168, and D252 was defined as disappearance of all lesions on target nail or residual disease of no more than 10% of the original total diseased surface (the remaining diseased surface should involve only the distal third) **Safety** Safety was evaluated using the following criteria: • Continuous assessment of adverse events (AEs). • Local tolerance assessment at D21, D77, D168 and D252 using a 4 points scale (0 very good tolerability to 3 very poor tolerability) **Cost effectiveness** The pharmaco-economic evaluation was conducted from the payer's perspective in each country. Treatment success at D336 (primary efficacy criterion) was used as the effectiveness measure in the pharmaco-economic analysis. Direct costs related to the drug acquisition were solely considered (36 weeks), The mean quantity of RV4104A ointment, ciclopiroxolamine 1% cream, ciclopirox 8% film-forming solution and amorolfine 5% nail lacquer used per patients was based on the protocol indication. Local public prices of these products were considered, minimizing drug costs in case of coexistence of several packaging.

Statistical methods:

Sample size justification:

The calculation of the sample size was based on the primary efficacy criterion analysis: clinical and mycological cure of the treated great toenail after 48 weeks (36 weeks of treatment and 12 weeks of follow-up) assessed by measures and cultures.

Based on an estimated difference of 25% between treatment groups (50% in the group treated with a sequential treatment and 25% in the group treated with amorolfine) on the primary efficacy criterion, a sample size of 116 assessable patient (58 patients per treatment group) was required to achieve a 1 - b = 80% power with a type I error set to a = 5% in a two-sided condition.

Assuming 10% of non-assessable patients (premature withdrawals, major protocol deviations…), a total number of 130 included patients was required (65 patients per treatment group) Assuming 50% of patients with negative fungal culture for dermatophytes, 260 patients had to be selected to participate in the study

Analysis sets

The following analysis sets were defined:

- The Safety Set: composed of all randomized patients having received at least one dose of the study treatment between D0 and D252.
- The Local safety set composed of all who have received at least one dose of study drug D0 and D252 The and for which local tolerability can be assessed
- The Intent to Treat (ITT) composed of all randomized patients who have received at leat on dose of study drug
- The Per Protocol Set (PP) was the subset of the ITT set composed of all patients without any major protocol.

Analysis of efficacy:

The percentage of success (clinical cure and mycological cure) was compared between treatment groups using Pearson's chi-square test or Cochran-Mantel-Haenszel test (if applicable) stratified by centre using modified ridit scores on the ITT data set (all randomized patients who have received at least one dose of study drug) The same analysis was performed as a supportive analysis on the PP set.

<u>Secondary: D77, D168, D252</u>

The rates of clinical cure were compared between treatment groups (Groups 1 & 2) using Pearson's chi-square test (or Cochran-Mantel-Haenszel test if applicable stratified by centre using modified ridit scores) in the ITT data set.

Safety analysis: Between D0 and D252:

-General Safety:

The number (%) of patients with treatment emergent adverse events was tabulated by treatment group according to MedDRA 14.1 classification (system organ class).

· Local tolerability:

The global assessment by the investigator of local tolerability at D21, D77, D168 and D252 was dichotomized: 0(Very good) + 1(Good) versus 2(Poor) + 3(Very poor) and compared between treatment groups using Pearson's chi-square test or Fisher's exact test whenever required in the LS data set.

Pharmacoeconomic analysis:

Cost per patient cured (clinical and mycological cure) of the sequential association RV4104A ointment followed by ciclopiroxolamine 1% cream and ciclopirox 8% film-forming solution versus amorolfine 5% nail lacquer alone was computed in each country and converted into euros if needed using appropriate exchange rates (for example using exchange rates given by la Banque de France : see http://www.banque-france.fr).

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Statistical methods (cont'd): **Safety analysis**

The safety analysis (extent of exposure, AEs, patient's global tolerability, and previous and concomitant treatments) was performed on the Safety Set, as descriptive summary statistics by treatment group.

Summary - Conclusions:

Of the 357 subjects screened, 142 (71 per group) were included in the study, of them all received at least one dose of study treatment and were therefore included in the Safety Set. 29 patients were excluded from the PP set due to major protocol deviations with a higher incidence in the AMO group (19 patients, 26.8%) compared with the SEQ group (10 patients, 14.1%)., which thus comprised 113 patients:

Efficacy analysis

The proportion of clinically and mycological cured patients at V7 was significantly higher in the SEQ group than in the AMO group in the ITT as well as in the PP populations, respectively 36.6% versus 12.7% and 36.1 versus 11.5% ($p<0.001$ and 0.003).

The efficacy results were confirmed by the secondary criteria: the clinical cure defined as disappearance of all lesions on target nail or residual disease of no more than 10% of the original total diseased surface was significantly higher ($p<0.01$) with sequential treatment than in the AMO group at D252 (V6) (42.0% versus 11.9%).

Safety

Adverse events were coded using the MedDRA version 14.1 and classified according to their period of occurence as pretreatment, treatment emergent (TEAE) and post-treatment adverse events.

Overall, 34 patients (23.9%) experienced at least one adverse event: 22 patients (31.4%) in the AMO group and 12 patients (16.7%) in the SEQ group. There was no statistical difference between the 2 groups ($p=0.07$).

No death occured in this study. One serious adverse event, an intervertebral disc protusion, was experienced in the Loceryl® group. It was not related to the study treatment.

The local tolerability was good and very good for more than 90% of patients in each group at each visit. Assessed at W36, local tolerability was 'very good' and 'good', respectively, in 97.0 and 3.0% in the AMO group compared to 94.3 and 5.7% in the SEQ group.

Regarding local tolerability of the treatment, there was no, significant difference groups. In a global investigator assessement, the tolerability was considered good and very good more than 90% of the cases in each group and at each visit time.

Pharmacoeconomics

Cost per completely cured patient of the SEQ treatment RV4104A ointment followed by ciclopiroxolamine 1% cream and ciclopirox 8% film-forming solution versus amorolfine 5% nail lacquer alone was computed in each participating country. Quantities used were those defined according to the EPPM panel (permanent survey of the medical prescription).

Total cost per patient completely cured was shown to be about twice higher with amorolfine at EUR 76 than with SEQ treatment at EUR 33.

Conclusion

In practice, the treatment of onychomycosis comprising chemical avulsion of the pathological nail, ciclopirox cream and nail lacquer is significantly more effective than amorolfine nail lacquer with a good safety profile. Moreover this study provides arguments for a SEQ treatment strategy including chemical nail avulsion followed by topical antifungal as first-line treatment in dermatophytic onychomycosis without matrix involvement. The study results also question the value of topical treatment of onychomycosis used as monotherapy as it is associated with low cure rates and higher cost.