Pierre Fabre Dermatologie
Represented by: Institut de Recherche Pierre Fabre (IRPF)
45, Place Abel Gance
92100 Boulogne, France

1. TITLE PAGE

CLINICAL STUDY REPORT

NON-INFERIORITY STUDY OF A METRONIDAZOLE 0.75% CREAM *VERSUS* REFERENCE THERAPY IN THE LOCAL TREATMENT OF PAPULOPUSTULAR ROSACEA

Investigational Product:	Rosiced® cream / metronidazole 0.75% cream
Study Design:	European, multicentre, randomised, Investigator-masked, active- and vehicle-controlled, 3-parallel group study
EudraCT Number:	2006-007029-29
Protocol Number:	DC0034 CR 3 01
Phase of Development:	IIIb
Date of First Enrolment:	25 July 2007
Date of Last Completed:	13 May 2008
Coordinating Investigator:	Prof Olivier Chosidow, MD *Service de Dermatologie et d'Allergie - Hôpital Tenon* *4 rue de la Chine* *75020 Paris*, France Phone: +33 (0)1.56.01.76.70
Sponsor Representative for Study Report:	Head of Therapeutic Area: Alain Delarue, MD *IRPF, Centre de Recherche et de Développement Pierre Fabre,* *3 avenue Hubert Curien,* *31100 Toulouse*, France Phone +33 (0)5 34 50 61 88
Date of Report:	31 May 2012

Study performed in compliance with Good Clinical Practice.

2. SYNOPSIS

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

Title of study:	**Non-Inferiority Study of a Metronidazole 0.75% Cream *versus* Reference Therapy in the Local Treatment of Papulopustular Rosacea**	
Coordinating Investigator:	**Prof Olivier Chosidow**, MD - Service de Dermatologie et d'Allergie - Hôpital Tenon - 4 rue de la Chine - F-75020 Paris - Phone: +33 (0)1.56.01.76.70	
Investigators:	Dermatologists (public or private practice) from 7 European countries: Austria, Estonia, France, Germany, Latvia, Poland, and Sweden.	
Study centres:	20 recruiting centres: 5 in Germany, 4 in Estonia, 4 in France, 3 in Poland, 2 in Latvia, 1 in Austria, and 1 in Sweden.	
Publication (reference):	Not written to date	
Study period **(date of first enrolment)** **(date of last completed)**	10 months 25 July 2007 13 May 2008	**Phase of development:** IIIb
Objectives: **Primary:**	To demonstrate the non-inferiority of a metronidazole 0.75% cream (Rosiced®) to the reference metronidazole 0.75% cream (Rozex®) in the topical treatment of rosacea.	
Secondary:	- To demonstrate the superiority of Rosiced® cream to its vehicle in the topical treatment of rosacea; - To assess the safety of Rosiced® cream and that of Rozex® cream.	
Methodology:	Multicentre, randomised, Investigator-masked, active- and vehicle-controlled, 3-parallel-group study.	
Number of patients:	337 randomised and treated patients (156, 147, and 34 in the Rosiced®, Rozex®, and Vehicle groups, respectively)	
Diagnosis and main criteria for inclusion:	- Men or women aged ≥18 years; - With papulopustular rosacea (*i.e.*, subtype 2 according to the National Rosacea Society Expert Committee classification) only requiring topical treatment; - With 8 to 30 inflammatory lesions (papules and pustules).	
Test product, **Dose and mode of administration**, **Batch numbe**r: **Associated products, batch numbers:**	Rosiced® cream (metronidazole 0.75% cream); 30 g tube draped in a silver wrap (one tube per month). Topical bid (morning and evening) self-application (without occlusion) of a thin layer on a dry skin after face cleansing with the dermatological soap bar. Precaution: avoiding sunlight and using the SPF40 sunscreen in case of sun exposure. M608B, expiry (exp.) November 2008. - Ictyane dermatological soap bar (one bar per month): T188, exp. February 2012; T187, exp. November 2011 - 50 ml tube of Avène SPF 40 sunscreen (one tube per month): AV208, exp. January 2010; AV205, exp. August 2009.	
Duration of treatment:	12 weeks	

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

Reference therapy 1, **Dose and mode of administration,** **Batch number:**	Rozex® cream (metronidazole 0.75% cream); 30 g tube draped in a silver wrap (one tube per month). See 'Test Product'. 6075045, exp. August 2009.
Reference therapy 2, **Dose and mode of administration,** **Batch number:**	Vehicle of Rosiced® cream; 30 g tube draped in a silver wrap (one tube per month). See 'Test Product'. SB0565, exp. August 2008.
Criteria for evaluation: **:**	**Efficacy**: **- Primary criterion: %-Change in the number of inflammatory lesions (papules and pustules) from baseline to Week 12**. **- Secondary criteria**: ⇨ %-Change in the number of inflammatory lesions (papules and pustules) from baseline to Week 6; ⇨ Improvement (≥ 1-point reduction from baseline) at Week 6 and Week 12 in the Erythema score rated on a 4-point scale (0/ None to 3/ Severe), ⇨ Improvement (≥ 1-point reduction from baseline) at Week 6 and Week 12 in the Telangiectasia score rated on a 4-point scale (0/ None to 3/ Severe), ⇨ Improvement (≥ 1-point reduction from baseline) at Week 6 and Week 12 in the Investigator Global Assessment (IGA) score rated on a 7-point scale (0/ Clear to 6/ Severe) ⇨ Change (improvement/no change/worsening) at Week 6 and Week 12 in the score of each rosacea symptom (Burning, Stinging, and Skin Dryness), each symptom score being rated on a 4-point scale (0/ None to 3/ Severe) ⇨ Patient Overall Improvement score at Week 12 as rated on a 4-point scale of comparison with prior to treatment (1/ Much better to 4/ Worse) ⇨ Patient Cosmetic Agreement score at Week 12 on a 4-point scale (1/ Very good to 4/ Poor). **Safety:** Only local or systemic adverse events (AEs) since the last visit recorded either from Patient's spontaneous reporting or the Investigator clinical evaluation (including local and general physical exam).
Statistical methods (1/2):	**Data sets analysed:** - Intent-To-Treat (ITT) data set: from all randomised and treated patients, - Per-protocol (PP) data set: from all ITT patients without any major protocol deviation. **Efficacy (1/2):** **- Primary criterion (1/2):** ⇨ ***Primary analysis****:* • Step 1, Rosiced® *versus* (*vs.*) Vehicle: Covariance analysis with Treatment effect, Country* effect, and the Baseline number of inflammatory lesions as a covariate on the ITT data set without the Rozex® group. • Step 2 (only if Rosiced® is significantly superior to Vehicle), Rosiced® *vs.* Rozex®: Analysis of variance with Treatment effect and Country* effect on the PP sample without Vehicle group. Rosiced® was considered non-inferior to Rozex® at Week 12 if the upper limit of the confidence interval of the difference between LS means was below 15%. **As Austria and Sweden included only 5 patients each, Austrian and Swedish patients were respectively included in the German and Estonian groups.*

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

Statistical methods (2/2):

Efficacy (2/2):

- Primary criterion (2/2):

⇨ ***Supportive analyses*:**

- Primary analysis repeated on the ITT data set;
- Non-parametric strategy: if the normality of residuals of the non-inferiority analysis checked *via* the Shapiro-Wilk test was rejected (at level 1%):
  - Step 1, Rosiced® *vs.* Vehicle: Cochran-Mantel-Haenszel [CMH] test stratifying for country, on the ITT data set without the Rozex® group;
  - Step 2 (only if Rosiced® is significantly superior to Vehicle), Rosiced® *vs.* Rozex®): Hodges-Lehmann method adjusted on country, first on the PP sample and then on the ITT data set without Vehicle group.

- Secondary criteria:

⇨ **Primary variable at Week 6:** same parametric and non-parametric strategies;

⇨ **Other secondary criteria** (all categorical variables): CMH test stratified by country with modified ridit scores (CMH_mr) on the ITT data set. Rosiced® compared separately with Rozex® and with Vehicle.

Safety:

- On the ITT data set.

- AEs: tabulations by treatment group, according to MedDRA classification (body system and preferred term [PT]) of N (%) of patients with at least one:
  - Treatment-emergent AE (TEAE),
  - Moderate or severe TEAE,
  - Drug-related (non assessable or non excluded relationship with the study product) TEAE.
  - Serious AE (SAE),
  - AE leading to the study treatment definitive discontinuation.

- Physical exam: normal/abnormal general and dermatological physical findings.

Summary – Conclusions (1/3):

Patients' Disposition

A total of 337 patients were randomised (156 in the Rosiced Group, 147 in the Rozex Group, and 34 in the Vehicle group), of whom 24 (7.1%) prematurely withdrawn (12 in each *verum* group: 7.7% and 8.2% in the Rosiced and Rozex groups, respectively). Of the 24 premature withdrawals, 20 (10 in each *verum* group) can be attributed to a therapeutic failure and 2 (1 in each *verum* group) were losses to follow-up.

The 337 randomised patients were treated (ITT) and analysed for safety and efficacy.

Data sets for primary efficacy analysis:

- Step 1: 156/ITT-Rosiced *vs.*. 34/ITT-Vehicle,
- Step 2: 135/PP-Rosiced *vs.*. 122/PP-Rozex.

Efficacy Results (1/2)

According to the parametric analysis of the primary criterion (%-change in the inflammatory lesion count at Week 12), Rosiced® was shown to be superior to its vehicle in the ITT sample (-51.32%/Rosiced® *vs.* -32.98%/vehicle; ANCOVA, p=0.021)). The non-inferiority of Rosiced® to Rozex® was not demonstrated by the primary comparison in the PP sample (mean change of -66.83%/Rozex® *vs.* -57.97%/Rosiced®; ANOVA, p=0.023; 95%CI: [1.21%;16.40%] including the 15% limit of non-inferiority), whereas the supportive comparison in the ITT sample showed similar results between the *verum* groups (-53.73%/Rozex® and -51.32%/Rosiced®; ANOVA, p=0.693; 95%CI: [-8.76%;13.16%]), which supports a non-inferiority of Rosiced® to Rozex® in this sample.

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

Summary – Conclusions (2/3):

Efficacy Results (2/2)

A significant Country effect was seen for both comparisons between the *verum* treatments: in terms of mean values, Latvia and France systematically showed results in favour of Rosiced®, Poland systematically showed results in favour of Rozex®, Estonia-Sweden systematically showed similar results on both treatments, and Germany-Austria showed results in favour of Rozex® in the PP sample and in favour of Rosiced® in the ITT sample.

The non parametric analysis of the primary criterion did not show that Rosiced® was superior to its vehicle in the ITT sample (CMH stratified by country, p=0.122). This should not allow to test the non-inferiority of Rosiced® to Rozex® according to the non-parametric approach; however, this test was performed to check the consistence of results between both approaches. Indeed, corresponding results confirmed those of the parametric analyses (*i.e.*, non-inferiority not supported on the PP data set and supported on the ITT data set).

According to both parametric and non parametric analyses of the primary variable at Week 6, Rosiced® was not shown to be superior to its vehicle (-33.20%/Rosiced® and -23.81%/vehicle), which does not allow to test the non-inferiority of Rosiced® to Rozex® according to both strategies.

The table below summarizes all efficacy results at Week 12 endpoint (mean values by treatment group and p-values of corresponding tests). The superiority of Rosiced® over its vehicle ($p < 0.05$) was seen for the improvement in the Investigator's Global Assessment (IGA), the change in the Burning Symptom of Rosacea, and the Patient's Cosmetic Agreement. A borderline significant difference in favour of Rosiced® as compared to its vehicle was also observed for erythema and telangiectasia scores (p=0.052 and 0.051, respectively). For all efficacy parameters, ITT analyses showed non-significant differences between the *verum* groups (minimum p-value: 0.113).

Parameter		**Data Set**	**Rosiced**	**Rozex**	**Vehicle**	**Vehicle *vs.* Rosiced**	**Rozex *vs.* Rosiced**
			N=156	**N=147**	**N=34**		
		PP	**N=135**	**N=122**	**N=34**		
%-Change in the inflammatory lesion count		**ITT**	**-51.32**	-53.73	**-32.98**	**ANCOVA, p=0.021**	ANOVA, p=0.693
						CMH, p=0.122	HL: N/A
		PP	**-57.97**	**-66.83**	N/A	N/A	**ANOVA, p=0.023**
							HL: N/A
Erythema Score Improvement		**ITT**	56.9%	65.0%	38.2%	CMH_mr, p=0.052	CMH_mr, p=0.143
Telangiectasia Score Improvement			27.1%	22.6%	11.8%	CMH_mr, p=0.051	CMH_mr, p=0.336
IGA Improvement			74.7%	75.2%	47.1%	CMH_mr, p<0.001	CMH_mr, p=0.935
Burning:	**Improvement**		57.6%	61.3%	38.2%	CMH_mr, p=0.014	CMH_mr, p=0.725
	No Change		41.0%	32.8%	47.1%		
	Worsening		1.4%	5.8%	14.7%		
Stinging	**Improvement**		58.3%	51.1%	44.1%	CMH_mr, p=0.127	CMH_mr p=0.192
	No Change		37.5%	43.1%	47.1%		
	Worsening		4.2%	5.8%	8.8%		
Dryness	**Improvement**		59.0%	59.9%	50.0%	CMH_mr, p=0.332	CMH_mr, p=0.745
	No Change		33.3%	34.3%	41.2%		
	Worsening		7.6%	5.8%	8.8%		
Overall Change	**Much Better**		34.8%	42.1%	20.6%	CMH_mr, p=0.073	CMH_mr, p=0.113
	Slightly Better		34.8%	36.6%	38.2%		
	Same		19.4%	11.0%	14.7%		
	Worse		11.0%	10.3%	26.5%		
Cosmetic Agreement	**Very Good**		34.0%	42.0%	20.6%	CMH_mr, p=0.042	CMH_mr, p=0.142
	Much Better		51.0%	46.4%	47.1%		
	Poor		12.9%	10.1%	23.5%		
	Very Poor		2.0%	1.4%	8.8%		

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

Summary – Conclusions (3/3):

Safety Results

The overall incidence of TEAEs was not relevantly different between groups: 52.6% in the Rosiced group, 46.9% in the Rozex group and 44.1% in the Vehicle group.

The most common TEAEs (incidence > 4% in either group) were, by decreasing order of overall frequency (within brackets: incidence in the Rosiced, Rozex, and Vehicle group, respectively): *erythema* (10.3%, 6.1%, and 14.7%), *skin burning sensation* (7.1%, 5.4%, and 11.8%), *headache* (6.4%, 6.8%, and 8.8%), *skin irritation* (6.4%, 4.8%, and 0.0%), *dry skin* (5.1%, 2.7%, and 5.9%), *pain of skin* (4.5%, 3.4%, and 0.0%), *rhinitis* (1.9%, 4.1%, and 2.9%), and *influenza* (4.5%, 0.7%, and 0.0%).

Overall, a moderate or severe intensity was reported for 55.3% of TEAE(s)[1]. With respect to most common TEAEs, this proportion was exceeded: in the Rosiced group for *erythema* (75%), *skin burning sensation* (63.6%), and *dry skin* (75%); in the Rozex group for *erythema* (77.8%), *skin irritation* (57.1%), and *dry skin* (100%); and, in the Vehicle group for *headache* (75%).

The incidence of drug-related TEAEs was non relevantly different between groups: 29.5%, 23.1%, and 29.4% in the Rosiced, Rozex, and Vehicle groups, respectively. Almost all drug-related TEAEs were skin disorders (95.9%). Drug-related TEAEs outside this SOC were: a *burning sensation*, a *pustular rash*, and an *eye swelling* in the Rosiced group; a *nasopharyngitis* and a *conjunctivitis* in the Rozex group. *Skin irritation* and *pain of skin*, only reported in the *verum* groups, may have been caused or aggravated by the active principle, whereas related *erythema* and *skin burning sensation*, more frequent in the Vehicle group (respectively: 14.7% and 11.8% as compared to 10.3% and 7.1% in the Rosiced group and 5.4% and 5.4% in the Rozex group) may have been improved by the active principle.

No deaths occurred during the study course. Four SAEs were reported in 4 patients, all from the Rosiced group: 1 case of *breast cancer*, 1 case of *joint ligament rupture*, 1 case of *appendectomy*, and 1 case of (planned) *nasal septal operation*. All SAEs were considered unrelated to the study treatment (by both the Investigator and the Sponsor) and resolved after corrective therapy.

Fifteen AEs led to definitive study treatment discontinuation and were reported in 15 patients, all from the *verum* groups: 6 in the Rosiced group and 9 in the Rozex group. Except a non-related case of *osteoarthritis* in the Rosiced group, all were drug-related skin disorders (2 AEs of *rosacea worsening* and 3 of *skin irritation* in the Rosiced group; 3 AEs of *rosacea worsening*, 3 of *skin irritation*, 2 of *contact dermatitis*, and 1 of *dry skin* in the Rozex group). All were on-going at study end except 2 of them: a *rosacea worsening* in the Rosiced group that resolved on the day of study treatment discontinuation and after 6 days of oral tetracycline treatment, and a *skin irritation* in the Rozex group that resolved 3 days after the study treatment discontinuation and after 2 days of topical dermatological treatment.

Of the 14 treatment-emergent abnormal general and dermatological physical findings reported in 13 patients (5, 7 , and 1 patients in the Rosiced, Rozex and Vehicle groups, respectively), only the 4 abnormalities of *contact dermatitis* (3 in the Rozex group and 1 in the Vehicle group) were reported as drug-related AEs.

Conclusion

This 12-week, randomised, Investigator-masked, active reference- and vehicle-controlled study failed to fully demonstrate the non-inferiority of Rosiced® cream to Rozex® cream in the topical treatment of rosacea (supported on the ITT data set but not on the primary PP data set), a result to be linked to a significant Country effect and to a contradictory effect between both data sets in a Country group. The equivalent tolerability profiles of both *verum* creams with prevailing skin disorders were in accordance with that usually described with metronidazole topical formulations' use.

Date of report: 31 May 2012

***DC0034 CR 3 01* – synopsis page 5/5**

[1] In a given patient: TEAEs of same PT counted once and highest severity considered.