Pierre Fabre Médicament
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1. TITLE PAGE

ABRIDGED CLINICAL STUDY REPORT

Efficacy and safety study of the antihistamine V0114CP 2.5 mg in the treatment of perennial allergic rhinitis.

Investigational product:	V0114CP 2.5 mg.
Study Design:	Randomised, double-blind, three arm parallel group study including placebo and active control arm (levocetirizine 5 mg).
Protocol number:	V00114 CP302 2A.
EudraCT number	2007-003572-19.
Phase of development:	III
Date of first enrolment:	February 13, 2008.
Date of last completed:	August 27, 2009.
Coordinating Investigator:	Prof M. Kowalski M.D. Department of Immunology, Rheumatology and Allergy Medical University of Lödz 92-213 LÖDZ POLAND.
Sponsor Representatives for study report:	Medical study manager A. Delarue M.D. (☎ 0 534 506 188). Clinical Monitor C. Meunier (☎ 0 534 506 189). Project Statistician M. Aguilar (☎ 0 562 245 442). Medical Writer C. Touzet M.D. (☎ 0 534 506 353).

Date of report: **December 12, 2011**

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: l-mequitazine	**Vol.: .....Page: .....**	
Title of study:	Efficacy and safety study of the antihistamine V0114CP 2.5 mg in the treatment of perennial allergic rhinitis.	
Coordinating Investigator:	Professeur M. Kowalski, MD, Medical University of Lódź, POLAND.	
Investigators:	110 investigators (allergologists, ENT) in 11 countries.	
Study centres:	17 centres in Czech republic, 9 in Estonia, 20 in India, 9 in Lithuania, 13 in Poland, 10 in Romania, 12 in Spain, 10 in United Kingdom, 4 in Latvia, 4 in Finland, 2 in Austria	
Publication (reference):	Not applicable.	
Studied period:		**Phase of development: III.**
date of first enrolment:	February 13, 2008.	
adate of last completed:	August 27, 2009.	
Objectives:	The main study objective was to demonstrate the efficacy of a 6-week treatment period (Period 1) by the antihistamine V0114 2.5 mg/day versus placebo in reducing symptoms during perennial allergic rhinitis. The secondary objectives were to evaluate over 1 year of treatment (including the 3 study treatment periods): – the global improvement, the global assessment and treatment satisfaction of V0114 2.5 mg/day by both the patients and the investigators, – the safety (clinical, ECG, biology) of V0114 2.5 mg/day. The sponsor decided to prematurely stop the study because of a strategic decision related to safety concerns from a concomitant PK/PD study.	
Methodology:	Multicentre, randomised, double-blind, 3-arm parallel group prospective study, including V0114 2.5 mg, a placebo and levocetirizine 5 mg as active control as follows: - Period 1 (6 weeks in double-blind from V2 to V5): placebo, levocetirizine 5 mg/day, V0114 2.5 mg/day, - Period 2 (4.5 months in double-blind from V5 to V7): levocetirizine 5 mg/day, V0114 2.5 mg/day, placebo being replaced by V0114, - Period 3 (6 months in open from V7 to V10): V0114 2.5 mg/day, levocetirizine being replaced by V0114.	
Number of patients:	1080 patients were planned to be randomised. From the 1333 selected patients, 1041 were randomised, and 1038 were treated in Period 1, respectively 346 in the placebo group, 347 in the levocetirizine group and 345 in the V0114 group.	
Diagnosis and main criteria for inclusion:	Eligible patients met the following criteria: - over 18 year-old male or female ambulatory patient, - suffering from a perennial allergic rhinitis (dust mite, animal dander, cockroaches) defined by: . a recorded medical history of perennial rhinitis with symptoms for at least two years or assessed by the score for allergic rhinitis (SFAR), . a positive prick test and/or positive specific IgE to the concerned allergen, . with an instantaneous morning nasal symptom score (NSS) ≥ 6 during at least 4 days within the 7 days before V02 (*maximal score: 12*), . in case of associated bronchial asthma, only mild intermittent asthma not requiring corticosteroids treatment, . patient accepted to participate to the study and sign an approved Informed Consent Form.	
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Test product, dose, mode of administration, batch number:	**V0114 2.5 mg,** 1 white tablet masked in a hard brownish red capsule *per* day *p.o.*, during Periods 1 and 2: - batch SB0577, expiry date February 2010, - batch SB0592, expiry date February 2010, - batch SB0707, expiry date March 2011, - batch SB0710, expiry date March 2011, **V0114 2.5 mg, 1 tablet** *per* day *p.o.*, during Period 3: - batch SB0547, expiry date February 2010, - batch SB0629, expiry date March 2011.	
Duration of treatment:	3 periods respectively of 6 weeks, 4.5 months and 6 months.	
Reference therapies, dose, mode of administration, batch number:	**Placebo, 1** hard brownish red capsule *per* day *p.o.*, - batch SB0576, expiry date June 2010, - batch SB0607, expiry date December 2011, **Levocetirizine 5 mg,** 1 white tablet masked in a hard brownish red capsule *per* day *p.o.*, - batch SB0575, expiry date June 2009, - batch SB0582, expiry date July 2009, - batch SB0591, expiry date October 2009, - batch SB0714, expiry date March 2011.	
Criteria for evaluation:	**Efficacy** - patient's rated instantaneous and reflective NSS, instantaneous non NSS, instantaneous total scores, every morning over Period 1, - investigator rated NSS, non NSS, total scores at each visit from V2 to V10, - sleep quality at each visit from V2 to V5, then V8, - rhiniconjuntivitis quality of life at V2 and V5, - patient and investigator's global assessments at V5 and V8. **Safety** - adverse events at each visit from V2 to V10, - biological safety at V2, V5, V8, V10. - vital signs, clinical examination, concomitant treatments at each visit from the selection visit to V10. - nasal examination at the selection visit, V2, V5, V8, V10, - ECG at the selection visit, V5, V8, V10. Analyses of the abridged NSS, the success rate and the number of days of use of rescue medication were not carried out.	
Statistical methods:	All the study analyses were carried out on the FAS (none on the PP data set). – MMRM test for Patient's rated instantaneous and reflective NSS, instantaneous non NSS, instantaneous total scores (Period 1). – ANCOVA for Investigator rated NSS, non NSS, total scores (Period 1) and sleep quality. – Cochran-Mantel-Haenzel test for clinical global improvement assessment. – Sedative ("sedation", "somnolence") and anti-cholinergic ("accommodation disorder", "constipation", "dry eye", "dry mouth", "dry throat", "mucosal dryness", "nasal dryness", "tachycardia", "thirst", "vision blurred") effects were analysed by Fisher's exact test (placebo vs V0114, placebo vs levocetirizine). – Descriptive statistics for any other efficacy or safety parameters.	
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Summary - Conclusions:

In regard to the context of the study, the number of completers was lower than planned. The Validation Committee decided that no determination of major protocol deviations was carried out and that the statistical analyses were limited to the FAS. 1038 patients were randomised and treated, among them 944 patients completed the 6-week treatment period (Period 1), More details concerning completers and withdrawn patients over the different periods are displayed in the following table:

	Placebo	**Levocetirizine**	**V0114**	**Total**
Randomised and treated patients	346	347	345	1038
Withdrawn within Period 1 (P1)	35	23	36	94
Completers at 6 weeks (end P1)	311	324	309	944
Withdrawn at Visit 5 (Week 6)	17	10	12	39
Entered Period 2 (P2)	294	314	297	905
Withdrawn within P2	73	77	70	220
Completers at 6 months (end P2)	221	237	227	685
Withdrawn at Visit 8 (Month 6)	15	27	18	60
Enterred Period 3 (P3)	206	210	209	625
Withdrawn within P3	126	131	126	383
Completers at 1 year (end P3)	80	79	83	242

796/1038 patients withdrew prematurely from the study including 553 patients for sponsor's decision, respectively 187 on placebo, 187 on levocetirizine and 179 on V0114. 243 patients withdrew prematurely for another reason (non exclusive reasons) *e.g.* patient's decision (85/1038), lake of efficacy *i.e.* worsening or insufficient response (72/1038), lost to follow-up (49/1038) or safety (26/1038).

534/1038 patients (51.4%) were women and 504/1038 (48.6%) were men, aged 34.1 (sd = 11.8) years on average. Allergy was caused mainly by dust mites (about 67%) and the main allergic symptoms except rhinitis were conjunctivitis (about 30.5%) and asthma (about 16%). The populations were overall similar between the three treatment groups.

Efficacy results

The evolution of the decrease over time throughout the 6-week treatment period of the patient-rated instantaneous NSS, was significantly more important on V0114 than on placebo. No planned mean difference (0.8-point), considered as clinically relevant efficacy, was observed between V0114 and placebo, as well as between levocetirizine, used as active control, at any time over the 6-week period of treatment.

Similar results were observed for the patient's reflective NSS, instantaneous non NSS and total symptom scores. The differences versus placebo (adjusted data) were statistically significant apart from Investigator's rated NSS (p = 0.08), non NSS (p = 0.92) and total symptom score (p = 0.33) between V0114 and placebo.The main efficacy results (adjusted data) observed on Day 42 are displayed hereafter.

	Placebo n = 346	V0114 n = 345	
Patient's rated instantaneous NSS	Δ = -1.98 (se = 0.10)	Δ = -2.34 (se = 0.10)	p = 0.001
Patient's rated reflective NSS	Δ = -2.00 (se = 0.10)	Δ = -2.34 (se =0.10)	p = 0.002
Patient's rated instantaneous non NSS	Δ = -1.33 (se = 0.10)	Δ = -1.56 (se = 0.10)	p = 0.026
Patient's rated instantaneous total symptom score	Δ = -3.29 (se = 0.18)	Δ = -3.85 (se = 0.19)	p = 0.005
Investigator's rated NSS	Δ = -2.76 (se = 0.16)	Δ = -3.09 (se = 0.16)	p = 0.08
Investigator's rated non NSS	Δ = -1.90 (se = 0.15)	Δ = -1.88 (se = 0.15)	p = 0.92
Investigator's rated total symptom score	Δ = -4.60 (se = 0.28)	Δ = -4.92 (se = 0.29)	p = 0.33

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Safety results

Six hundred and thirty-nine (639) TEAE were reported over the whole treatment period in 393 patients, distributed as follows:

- within the first 6 weeks (P1), 85 TEAE (19 drug relationship not excluded or unassessable) in 62/346 (17.9 %) patients on placebo, 86 TEAE (31 drug relationship not excluded or unassessable) in 64/347 (18.4 %) patients on levocetirizine and 77 TEAE (23 drug relationship not excluded or unassessable) in 55/345 (15.9 %) patients on V0114,
- within the first 6 months (P1 + P2), 170 TEAE (44 drug relationship not excluded or unassessable) in 116/347 (33.4 %) patients on levocetirizine, 191 TEAE (44 drug relationship not excluded or unassessable) in 120/345 (34.8 %) patients on V0114 and 88 TEAE (14 drug relationship not excluded or unassessable) in 54/294 (18.4 %) patients on V0114 previously treated with placebo,
- within the whole treatment period of 1 year (P1+P2+P3), 222 TEAE (50 drug relationship not excluded or unassessable) in 135/345 (39.1 %) patients on V0114 were notified, 123 TEAE (19 drug relationship not excluded or unassessable) in 79/294 (26.9 %) patients on V0114 previously treated with placebo and 39 TEAE (9 drug relationship not excluded or unassessable) in 33/210 (15.7 %) patients on V0114 previously treated with levocetirizine.

The most relevant TEAE occurred over the whole treatment period and considered by the investigator with a relationship not excluded or unassessable were "somnolence" (9 cases) , "headache" (8 cases), "pharyngolaryngeal pain" (5 cases), "rhinitis" (5 cases), "abdominal pain upper" (3 cases), "epistaxis" (3 cases) on V0114 and, "somnolence" (8 cases) and "pharyngitis" (3 cases) on levocetirizine.

Eleven (11) serious adverse events were notified over the whole study period in 11 patients, in all of them, the relationship with the study drug was excluded, respectively 2 during the selection period (1 "pyelonephritis acute", 1 "hospitalisation") and 9 on study treatment, *i.e.* 1 on placebo ("depression"), 3 on levocetirizine '(1 "urethrostenosis", 2 "appendicitis") and 5 on V0114 (1 "supraventricular tachycardia", 1 "phlegmon", 1 "bipolar I disorder", 2 "pregnancies").

Twenty-five patients prematurely discontinued the study treatment due to an AE and are distributed as follows:

- within Period 1, 7 patients on placebo, 5 on levocetirizine and 3 on V0114,
- within Period 2, 1 patient on levocetirizine and 4 patients on V0114 including 1 patient previously treated with placebo,
- within Period 3, 5 patients on V0114 including 4 patients previously treated with levocetirizine.

The sedative effects and the anticholinergic effects were assessed over the 1st period of treatment (placebo versus V0114) respectively on "sedation" and "somnolence" and on "constipation", "dry eye", "dry mouth", "dry throat", "mucosal dryness", "nasal dryness", "tachycardia" and "thirst". V0114 did not show any statistically significant sedative effects (p = 0.51) nor anticholinergic effects (p = 0.29) versus placebo.

Eighty (80) laboratory abnormalities, considered as significant by the investigators, were detected over the whole treatment period, respectively 40 in 12/346 (3.5 %) patients on placebo, 19 in 10/347 (2.9 %) patients on levocetirizine and 21 in 9/1038 (0.9 %) patients on V0114. The abnormalities observed on V0114 concerned haematologic parameters (4 in 3 patients, 3 eosiniphilies already present at baseline) and hepatic parameters (17 in 6 patients, 5 of them were notified by the investigator as adverse events, AST +1.1 to 2.5 N, .ALT +1.7 to 2.4, γ-GT +4.4 N, bilirubine increased +1.2 N).

Over the 1038 patients, no patient on V0114 had a QT_{cF} longer than 500 ms and 2 patients an increase in the QT_{cF} duration longer than 60 ms. Patients with an increase in the QT_{cF} duration longer than +30 ms were distributed as follows:

- within Period 1: 3 patients on placebo, 7 patients on levocetirizine and 8 patients on V0114,
- within Period 2: 7 patients previously treated with placebo, including 1 patient with an increase up to +69 ms at Week 26 following a decrease of -68 ms from baseline, 9 patients on levocetirizine, including 1 patient with an increase up to +61 ms at Week 26 and 6 patients always on V0114,
- within Period 3: 8 patients previously treated with placebo, 4 patients previously treated with levocetirizine and 6 patients always on V0114.

In patients always treated with V0114, this increase duration was carried out over a period of 6 weeks to 1 year. In 2 patients this increase (+44 and +52 ms respectively) was notified by the investigator as an adverse event.

Conclusion

This study was prematurely discontinued upon the sponsor's decision. This study showed the efficacy of V0114 at the dosage of 2.5 mg daily versus placebo over a period of 6 weeks. The safety profile of V0114 in this study is in line with the safety profile previously observed with this drug.

Date of report: December 12, 2011