Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE-EFFECT STUDY OF V0114 (2.5, 5, 7.5 AND 10 MG) *VERSUS* MEQUITAZINE 10 MG AND PLACEBO IN THE TREATMENT OF SEASONAL ALLERGIC RHINITIS.

Investigational product: **V0114 CP**

Protocol number: **V00114 CP 201**

Phase of development: **PHASE II**

EudraCT number: **2005-005975-13**

Date of first enrolment: 10 May 2006

Date of last completed: 14 August 2006

Coordinator: Professor Pascal DEMOLY, MD
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Date of report: 08 March 2010
Study performed in compliance with Good Clinical Practice.

2. SYNOPSIS

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

Title of study:	Randomised, double-blind, placebo-controlled dose-effect study of V0114 (2.5, 5, 7.5 and 10 mg) *versus* mequitazine 10 mg and placebo in the treatment of seasonal allergic rhinitis. Protocol Nr V00114 CP 201 with 5 amendments.	
Investigator coordinator:	Professor Pascal DEMOLY, Hôpital Arnaud de Villeneuve, 371 avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5 – France.	
Study centres:	66 active centres in France (41 centres included at least 1 patient), 10 active centres in Czech Republic (10 centres included at least 1 patient), 5 active centres in Estonia (3 centres included at least 1 patient), 4 active centres in Poland (4 centres included at least 1 patient).	
Publication (reference):	Not published at the date of the report.	
Studied period: **(date of first enrolment)** **(date of last completed)**	 10 May 2006 14 August 2006	**Phase of development:** **II**
Objectives: **Primary:**	To evaluate the clinical efficacy of V0114 in the treatment of seasonal allergic rhinitis: - research of a dose-range effect. - evaluation of the different doses of V0114 *versus* placebo. - evaluation of the different doses of V0114 *versus* mequitazine 10 mg.	
Secondary:	To assess the systemic and biological tolerability of V0114.	
Methodology:	Prospective, multicentre, international, randomised, double-blind trial in six parallel groups (4 doses of the test product, active control and placebo). Four study visits were planned: screening visit (from Day -30 to Day -1), inclusion visit (on Day 1), Day 7 visit (on Day 7 ± 1), and Day 14 visit (on Day 14 ± 1 or at the end of treatment in case of premature withdrawal).	
Number of patients (planned and analysed):	Planned: 600 patients (100 per group). 443 screened patients and 423 included patients (69 in the Placebo group, 68 in the V0114 2.5 mg group, 69 in the V0114 5 mg group, 70 in the V0114 7.5 mg group, 69 in the V0114 10 mg group, and 78 in the Mequitazine group).	
Diagnosis and main criteria for inclusion:	Ambulatory male and female patients aged from 18 to 65 years, suffering from a seasonal allergic rhinitis to grass pollen grain (defined by a recorded symptomatic seasonal rhinitis for at least two years, a positive skin prick test to grass pollen grains, and/or class 3 or more specific IgE within the past 6 months) and a Nasal Symptom Score (NSS) at least equal to 6 at inclusion (maximal score equal to 12).	
Test product:	V0114	
Dose:	One capsule containing either one 2.5-mg tablet (V0114 CP 02A) or one 5-mg tablet (V0114 CP 01A) or both one 2.5-mg (V0114 CP 02A) and one 5-mg (V0114 CP 01A) tablets or one 10-mg tablet (V0114 CP 03A).	
Mode of administration:	One capsule on Day 1 during or after the study visit then one capsule every morning.	
Batch number:	2.5mg: SB0458; 5mg: SB0459; 7.5mg: SB0460; 10mg:SB0461	
Reference therapy:	mequitazine 10 mg (Primalan®)	
Dose:	One capsule containing one 10-mg tablet of mequitazine (L0013 CP 02A)	
Mode of administration:	One capsule on Day 1 during or after the study visit then one capsule every morning.	
Batch number:	SB0462	
Placebo:		
Dose:	One placebo capsule	
Mode of administration:	One capsule on Day 1 during or after the study visit, then one capsule every morning.	
Batch number:	SB0457	
Duration of treatment:	14 consecutive days.	

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Criteria for evaluation:

Efficacy:

Each rhinitis symptom was graded as follow: 0 = no sign, 1 = mild (intermittent without trouble), 2 = moderate (frequent with trouble), 3 = severe (continuous with trouble at work and during sleep) by the investigator at inclusion, Day 7 and Day 14 visits.

Four global scores were computed:

- Nasal Symptom Score (NSS): sum of sneezing, rhinorrhea, nose itching, nasal blockade scores;
- "Reduced" NSS (RNSS): sum of sneezing, rhinorrhea, nose itching scores;
- Non Nasal Symptom Score (NNSS): sum of watery eyes, eye itching, eye redness, palate itching scores;
- Total Symptom Score (TSS): sum of NSS and NNSS.

Primary criterion: evolution of the NSS from baseline to Day 7 visit (replaced by the Last Observation Carried Forward [LOCF] under treatment in case of missing value due to premature withdrawal from the study within the first week of treatment).

Secondary criteria:

- NSS change from baseline to Day 14 visit (missing value replaced by value at Day 7 visit);
- RNSS ("Reduced NSS"), NNSS and TSS change from baseline to Day 7 and to Day 14 visits;
- Success rate (defined as half reduction of NSS, without premature withdrawal for adverse event linked to disease or treatment failure) at Day 7 and Day 14 visits;
- Sneezing, rhinorrhea, nose itching and nasal blockade scores (baseline, Day 7 and Day 14 visits);
- Patient's assessment of nasal and non-nasal symptoms everyday from Day 1 to Day 14 (and/or on Day 15) permitting the NSS and TSS calculation (score missing if 1 missing symptom);
- Investigator's and patient's global assessment (0 = Stable or worse, 1 = Mild improvement, 2 = Moderate improvement, 3 = Severe improvement, 4 = Complete relief) at Day 14 visit (or end of study visit).

Safety:

Spontaneously reported adverse events, clinical physical examination, and biological tolerance.

Statistical methods:

Analysis sets:

APT set (N = 421): included patients having taken at least one dose of study medication and with at least one post-baseline efficacy assessment;

PP set (N = 395): patients of the APT set without major protocol deviation;

Safety analyses were to be performed in all included patients having taken at least one dose of study medication; this set (N = 421) was identical to the APT set in this study.

Analyses of the primary criterion:

- *Main analysis in the APT set*: comparison of the 4 doses of V0114 to placebo by an analysis of covariance (ANCOVA) of the changes from baseline (at inclusion visit on D1) to Day 7 visit with the baseline NSS value as a covariate, followed by pairwise comparisons of each dose with placebo using Dunnett's test. The country and the treatment effects were included in the covariance model (interaction terms were explored). Unadjusted estimates of the treatment effect were obtained through an analysis of variance (ANOVA) model with the country and the treatment effects.
- *Secondary analysis in the APT set*: linearity and deviation from linearity of the dose-effect relationship (using appropriate contrasts with/without the placebo group).
- *Sensitivity analysis in the APT set*: comparison of Mequitazine and Placebo groups.

Same analyses were performed in the PP set.

Analysis of the secondary criteria:

- NSS at Day 14 visit (APT set and PP set): same analysis as at Day 7 visit.

For the other efficacy criteria (APT set): ANCOVA or Cochran-Mantel-Haenszel test depending on the nature of the criterion (quantitative or categorical).

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Summary - Conclusions:

Subject's disposition: 443 patients were screened (inform consent), 431 selected, 423/431 (98.1%) included and randomised. A total of 49 patients (11.6%) prematurely withdrew from the study: 36/49 (73.5%) due to treatment failure (3-fold more patients in the Placebo [19.4%] than in the active [close to 6%] groups).

Baseline characteristics: In the APT set, patients (49.6% of males) were aged from 18 to 65 years (mean: 31.4 ± 9.6 years) without relevant between-group differences for baseline characteristics.

Efficacy results:

1 – Primary criteria : evolution of the NSS from baseline to Day 7 visit.

No relevant between-group differences were observed at baseline with a mean NSS close to 8 on average. The changes of NSS from baseline to Day 7 visit were as following:

NSS at D 7 (V3)	**Placebo**	**V0114**				**Mequitazine**
	n = 72	**2.5 mg n = 74**	**5 mg n = 71**	**7.5 mg n = 69**	**10 mg n = 71**	**10 mg n = 64**
Baseline						
Mean (SD)	7.8 (1.7)	8.1 (1.7)	8.0 (1.8)	7.9 (1.7)	8.1 (1.7)	8.2 (1.9)
Min/Median/Max	6 / 7.0 / 12	6 / 8.0 / 12	6 / 8.0 / 12	4 / 8.0 / 12	6 / 8.0 / 12	4 / 8.0 / 12
D 7						
Mean (SD)	4.9 (2.8)	3.8 (3.0)	4.2 (2.8)	4.2 (3.2)	3.3 (2.6)	4.1 (3.0)
Min/Median/Max	0 / 4.0 / 12	0 / 3.0 / 12	0 / 4.0 / 12	0 / 4.0 / 12	0 / 3.0 / 10	0 / 3.5 / 12
Change from baseline						
Mean (SD)	-2.9 (2.5)	-4.3 (2.8)	-3.7 (2.6)	-3.7 (3.2)	-4.8 (2.7)	-4.1 (3.4)
Min/Median/Max	-9 / -3.0 / 3	-10 / -5.0 / 4	-11 / -4.0 / 2	-11 / -4.0 / 2	-11 / -5.0 / 1	-12 / -4.5 / 3

As summarized in table below, the differences (estimated differences of the adjusted means) for NSS change from baseline to Day 7 showed a statistically higher improvement of symptoms for both V0114 2.5 mg and V0114 10 mg than placebo, and no clear dose effect was demonstrated.

Main analysis: change from baseline to Day 7 visit of the NSS - APT set					
		V0114 2.5 mg	**V0114 5 mg**	**V0114 7.5 mg**	**V0114 10 mg**
V0114 – placebo					
E (SE)*	-	-1.3 (0.4)	-0.8 (0.5)	-0.8 (0.5)	-1.8 (0.5)
95% CI*	-	[-2.2 ; -0.4]	[-1.7 ; 0.1]	[-1.7 ; 0.1]	[-2.7 ; -0.9]
p-value*	-	**0.013**	0.23	0.24	**≤0.001**

E(SE): Estimated difference of the adjusted means (Standard Error); 95% CI: Confidence interval of the estimated difference[V0114-placebo] ;p-value :Dunnett s test

Sensitivity analysis (ANCOVA) of the NSS at Day 7 visit confirmed the ability to detect a difference of Mequitazine *versus* placebo E [95% CI] = -4.0 [-4.8; -3.3] *versus* E [95% CI] = -3.0 [-3.8; -2.3], p = **0.043**.

Similar results to the APT set were also observed in the PP set or other analyzed subsets.

2 – Secondary criteria

- Reduced NSS improved on average in all study groups at Day 7 visit by comparison to baseline. Improvement was statistically significant in the V0114 2.5 mg and the V0114 10mg groups versus placebo.
- For NNSS, the clinical effect observed with V0114 2.5 mg and V0114 10 mg was not statistically significant.
- For TSS, a statistically significant superiority over placebo was observed for V0114 2.5 mg and V0114 10 mg at Day 7 visit.

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Efficacy results (Ctd):

Secondary analyses in the APT set:

Estimated differences [V0114 - placebo] of the adjusted mean changes from baseline for the global symptom scores - APT set

APT set		**V0114 2.5 mg**	**V0114 5 mg**	**V0114 7.5 mg**	**V0114 10 mg**
Day 7 visit					
RNSS	E [95% CI]	-1.0 [-1.7 ; -0.4]	-0.6 [-1.3 ; 0.1]	-0.6 [-1.3 ; 0.1]	-1.6 [-2.3 ; -0.9]
	p-value	**0.012**	0.26	0.21	≤**0.001**
NNSS*	E [95% CI]	-0.9 [-1.8 ; -0.1]	-0.5 [-1.4 ; 0.4]	-0.8 [-1.7 ; 0.1]	-1.1 [-2.0 ; -0.2]
	p-value	0.11	0.64	0.22	0.058
TSS	E [95% CI]	-2.3 [-3.9 ; -0.7]	-1.3 [-3.0 ; 0.3]	-1.7 [-3.3 ; -0.1]	-2.9 [-4.5 ; -1.3]
	p-value	**0.021**	0.31	0.13	**0.002**

*ANCOVA analysis (treatment effect) *p = 0.12;*
E: Estimated difference of the adjusted means; [95%CI]: 95% Confidence interval of the estimated difference [V0114 - placebo]; p-value: Dunnett's test.

In summary, a statistically significantly treatment effect was observed for the main efficacy end point : Nasal Symptom Score at Day 7 (p=0.001). A statistically higher improvement of symptoms was showed for both 2.5 and 10 mg doses but no clear dose effect was demonstrated.
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Thus, the efficacy of the lowest dose (2.5 mg) has been particularly studied. For the primary efficacy criterion, a statistically significant benefit over placebo was demonstrated: E (SE) = -1.3 (0.4), 95 % CI = [-2.2, -0.4], p=0.013. The clinical effect observed on nasal symptoms with the lowest dose (2.5mg) was confirmed for other efficacy criteria: RNSS (p=0.012), TSS (p=0.021) and success rate at Day 14 (p=0.03).

Safety results:

Treatment duration ranged from 1 to 19 days (mean duration: 14.0 ± 2.6 days; median: 15 days) and mean compliance to study treatments was higher than 99% in each study group.

Adverse events

No major or serious adverse event occurred during this study.

In all, 60 patients (14.3%) of the APT set experienced 77 treatment-emergent adverse events (TE AE) in about 1.5-fold less patients in the Placebo, V0114 2.5 mg and the V0114 5 mg groups than in the V0114 7.5 mg, V0114 10 mg and the Mequitazine, groups with a dose-effect for the number of TE AEs.

The most commonly reported TE AEs were somnolence/sedation (20 patients, 4.8%), headache (6 patients, 1.4%), dry mouth (6 patients, 1.4%) and pharyngitis (4 patients, 1.0%).

Sedative effects were statistically significantly more frequent in the Mequitazine group than in the Placebo group (p = **0.047**), and in the V0114 groups at the highest doses of 7.5 mg and 10 mg (p = **0.006** and p = **0.028**, respectively). No significant differences were shown between the V0114 2.5 mg and the V0114 5 mg groups by comparison to Placebo.

TE AE intensity was mild (39 TE AEs) or moderate (31 TE AEs) in most cases.

TE AE outcome was complete recovery without action taken in most cases.

Four patients (1.0%) developed 7 severe TE Aes and these TE AEs completely recovered (except 1 somnolence ongoing at the end of study) without treatment.

Definitive treatment discontinuation occurred in 8 patients (1.9%) due to 13 TE AEs: 1 patient (hypersensitivity) of the Placebo group, 1 patient (somnolence) of the V0114 2.5 mg group, 2 patients of the V0114 5 mg group (one for abdominal pain, then urticaria, and the other for cough/dyspnea), 1 patient (dry mouth/sedation/anxiety) of the V0114 10 mg group, 3 patients of the Mequitazine group (1 for dry mouth and abnormal movements, 1 for epistaxis and another for deafness / hearing loss).

Six patients (1.4%) withdrew from the study for tolerance reason.

In summary, side effects (and more precisely sedation effects) appeared since the 7.5 mg dose of V0114. At the highest doses (7.5 and 10 mg), the sedative effect was statistically more frequent than in the placebo group.

The doses of 2.5 and 5 mg showed very low sedative effect (<3%), thus confirming that the global safety profile of these two doses was very satisfactory.

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Discussion and Conclusion

Due to the natural evolution of the seasonal allergic rhinitis, a parallel-group design was the only one adapted to evaluate the efficacy of the different tested doses of V0114. The evolution of NSS (Nasal Symptom Score) from baseline was used as the primary criterion. Treatment duration was set at 14 days. However as allergic rhinitis typically may spontaneously recover earlier, and since the obvious aim of treatment is to bring on fast symptoms relief as needed in common clinical practice, it was considered as relevant to place the main efficacy end point after 7 days of treatment in this dose-effect study. In order to detect small differences between groups in terms of frequency of adverse events, the number of patients was arbitrarily chosen to 100 per group.

As regards to its well known anti-allergic activity, mequitazine was chosen as active control arm to assess the sensitivity of the study. Mequitazine is an H1 receptor antagonist which has demonstrated his clinical efficacy in allergic diseases and it has marketing authorization for the symptomatic treatment of seasonal and perennial allergic rhinitis in Europe and in many others countries worldwide. The sensitivity analysis of the NSS at Day 7 confirmed the ability of the study to detect the difference of efficacy of Mequitazine versus placebo.

In the APT set (patients with at least one post – baseline efficacy assessment) 421 patients were included (about 70 patients in each group). In spite of this smaller than planned number of patients, this double-blind, parallel group study showed that V0114 is effective and safe. The NSS (i.e. the primary efficacy criterion) was improved at Day 7 visit by comparison to baseline whatever the study group taken into consideration, i.e. since the lowest dose of 2.5 mg, but without any clear dose effect . The clinical effect observed on NSS (p=0.013) with the lowest dose (2.5mg) was confirmed for other efficacy criteria: RNSS, TSS and success rate.

No serious adverse event occurred during the study. Adverse events occurred increasingly with the doses. The doses of 2.5 and 5 mg showed very low rate (<3%) of sedative effect, thus confirming that the global safety profile of these two doses was very satisfactory.

In this study, no clear dose effect could be demonstrated. As V0114 2.5 mg was statistically different from placebo on Nasal Symptom Score and had a good safety profile, this dose was selected for confirmatory efficacy clinical trials. This dose could be an alternative for diurnal management of invalidating allergic rhinitis as regards to the improvement of symptoms and its low rate of sedative effects.

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Date of report	**08 March 2010**

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