Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

EFFICACY STUDY OF THE ANTIHISTAMINE V0114 CP 2.5 MG TABLET IN THE TREATMENT OF SEASONAL ALLERGIC RHINITIS. A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

Investigational product: **V0114 CP**

Protocol number: **V00114 CP 301 2A**
Phase of development: **PHASE III**

EudraCT number: **2006-006947-30**

Date of first enrolment: 24 April 2007

Date of last completed: 25 July 2007

Coordinator: Professor Jean-Michel KLOSSEK, MD
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Date of report: 22 August 2012

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: 1-mequitazine	**Vol.: .....Page: .....**	

Title of study:	Efficacy study of the antihistamine V0114 CP 2.5 mg tablet in the treatment of seasonal allergic rhinitis. A randomised, double-blind, placebo-controlled study. Protocol N° V00114 CP 301 2A with 1 amendment.	
Investigator coordinator:	Professor Jean-Michel KLOSSEK, MD, CHU La Milétrie, 2 rue de la Milétrie, BP 577, 86021 Poitiers Cedex, France	
Study centres:	ENT and/or allergology centres in Europe: 34 active centres in France (32 centres included at least 1 patient), 13 active centres in Czech Republic (13 centres included at least 1 patient), 8 active centres in Poland (7 centres included at least 1 patient), 6 active centres in Estonia (6 centres included at least 1 patient), 5 active centres in Lithuania (5 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)**	 24 April 2007 25 July 2007	**Phase of development:** **III**
Objectives:		
Primary:	The primary objective was to demonstrate the efficacy of a 2-week treatment by the antihistamine V0114 CP 2.5 mg in reducing symptoms during seasonal allergic rhinitis.	
Secondary:	- To evaluate the percentage of success to treatment - To evaluate the onset of action - To evaluate the clinical global improvement - To evaluate the systemic tolerance of V0114 CP 2.5 mg.	
Methodology:	Prospective, multicentre, international, randomised, double-blind trial in two parallel groups (V0114 2.5 mg group *versus* Placebo group). Four study visits were planned: selection 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: 460 patients (230 per group). 488 screened patients and 474 included patients (240 in the Placebo group and 234 in the V0114 2.5 mg group).	
Diagnosis and main criteria for inclusion:	Ambulatory male or female patients with written informed consent, older than 18, suffering from a seasonal allergic rhinitis to grass pollen grain (defined by a recorded symptomatic seasonal rhinitis for at least 2 years, or a positive Score For Allergic Rhinitis [≥7] for new patients), with a positive skin prick test to grass pollen grains and/or positive specific immunoglobin E (IgE) (class ≥ 3 or equivalent) duly documented in the medical file within the past 6 months, and with a Nasal Symptom Score (NSS) at least equal to 6 at inclusion.	
Test product:	V0114 CP 2.5 mg	
Dose:	One 2.5-mg tablet (V0114 CP 02A).	
Mode of administration:	One tablet on Day 1 during the visit whenever during the day, then 1 tablet every morning.	
Batch number:	SB0547	
Placebo:		
Dose:	One placebo tablet	
Mode of administration:	One tablet on Day 1 during the visit whenever during the day, then 1 tablet every morning.	
Batch number:	SB0548	
Duration of treatment:	2 weeks.	

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Criteria for evaluation:

Efficacy:

Each rhinitis symptom was graded using a 4-point scale (0 = no sign, 1 = mild [intermittent without trouble], 2 = moderate [frequent with trouble], 3 = severe [continuous with trouble at work and during sleep]) as follow:

- ***Self-rated by the patient everyday in his/her diary using optic pen*** *over the 2-week treatment period:*
  - REFLECTIVE of the past 12 hours, scored in the evening (at diner time or later, as far as possible at the same time during the whole treatment period);
  - **I**NSTANTANEOUS scores in the evening (at the same time as the reflective score) and in the morning (before drug intake).
- ***By the investigator*** after questioning the patient about symptoms at Selection, Inclusion, Day 7 and Day 14 visits.

The following global scores were computed:

- Nasal Symptom Score (NSS): sum of sneezing, rhinorrhea, nose itching, nasal blockade scores;
- "Abridged" NSS (ANSS): 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.

The main criterion was the patient-rated reflective nasal symptom score (rNSS).

Secondary criteria:

- Patient self-rated reflective scores: NNSS, TSS, and abridged NSS;
- Patient self-rated instantaneous morning and evening scores: NSS, NNSS, TSS, and abridged NSS;
- Investigator-rated NSS, NNSS and TSS;
- Success rate (half reduction of rNSS, without premature withdrawal for adverse event linked to disease or treatment failure) on Day 7 and Day 14;
- Onset of action: time interval to reach the statistically and clinically significant difference between treatments for the change of patient-rated rNSS.
- Time to maximum effect: time interval to reach the best between-treatment difference for the change of patient-rated rNSS.
- Rate of patients without symptoms for a whole day (each individual symptom score < 2).
- Clinical Global Improvement (0 = Stable or worse; 1 = Mild improvement; 2 = Moderate improvement; 3 = Marked improvement; 4 = Complete relief) at Day 14 visit as rated separately by the patient and the investigator.

Safety:

Reported/observed adverse events, clinical physical examination, vital signs (supine heart rate and blood pressure), nasal examination (rhinorrhea, oedema, colour, and ulceration/necrosis), sleep quality (Visual Analogue Scale [VAS]), and sleep disorders (VAS).

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Statistical methods:

Analysis sets:

Randomised Set (N = 474): all randomised patients;

Full Analysis Set (FAS, N = 436): included patients having taken at least one dose of study medication and with at least 3 valid post-baseline assessments of the patient-rated rNSS;

Per Protocol (PP) set (N = 381): patients of the FAS without major protocol deviation;

Safety Set (N = 474): all included patients having taken at least one dose of study medication.

Analyses of the primary efficacy criterion:

- *Main analysis in the FAS*: treatment effect on the patient-rated rNSS change from baseline over the 2-week treatment period was tested using a likelihood-based Mixed-effects Model for Repeated Measurement (MMRM) approach with the baseline rNSS as covariate. The centre, day of assessment and the treatment effects were included in the MMRM.
- *Supportive analyses in the PP set and the Randomised Set:* same analysis as the main analysis.
- *Secondary analyses in the FAS*:

  Other MMRM analyses were used by putting the different interaction terms. The allergic profile (± allergic profile*treatment) and the pollen count profile (± pollen count profile*treatment) were to be explored separately through an MMRM model including these effects.

  Sensitivity analysis in the FAS: unadjusted estimates of the treatment effect on rNSS change over the 2-week treatment period were obtained through a likelihood-based MMRM with the centre, day of assessment and the treatment effects in the model.

Analysis of the secondary efficacy criteria in the FAS:

- Change from baseline of each global nasal/non nasal score: same analysis as the main analysis of patient-rated rNSS.
- For the other efficacy criteria: ANCOVA or Cochran-Mantel-Haenszel (CMH) test depending on the nature of the criterion (quantitative or categorical).

Analysis of the sleep quality and smell disorders in the Safety Set: covariance model with treatment and centre as main effects and baseline score as covariate.

Summary - Conclusions:

Subject's disposition:

In all, 488 of the 493 patients who signed an informed consent were screened, 474/488 (97.1%) were included and randomised. A total of 64 patients (13.5%) prematurely withdrew from the study: 55 (11.6%) due to treatment failure (12.9% of patients of the Placebo group and 10.3% in the V0114 2.5 mg group). In all, 38 patients without at least 3 valid post-baseline assessments of the rNSS were excluded from the FAS (N = 436).

Baseline characteristics:

In the Safety Set, patients (54.2% of males) were aged from 18 to 80 years (mean: 32.0 ± 10.5 years), without between-group differences for baseline characteristics as well as for baseline rNSS (mean: 7.6 ± 2.5 in the V0114 2.5 mg group and 7.8 ± 2.5 in the Placebo group).

In the FAS (N = 436), the mean global nasal/non nasal symptom scores rated by the patient at baseline were as follow:

FAS		**Placebo group**			**V0114 2.5 mg group**		
Baseline		**Reflective**	**Instantaneous**		**Reflective**	**Instantaneous**	
Assessment		**Evening**	**Morning**	**Evening**	**Evening**	**Morning**	**Evening**
NSS	Mean (SD)	7.8 (2.4)	7.4 (2.5)	7.4 (2.5)	7.7 (2.4)	7.3 (2.2)	7.3 (2.2)
NNSS	Mean (SD)	5.6 (2.9)	5.1 (2.9)	5.1 (2.9)	5.4 (3.0)	5.1 (2.9)	5.1 (2.9)
TSS	Mean (SD)	13.4 (4.6)	12.5 (4.6)	12.5 (4.6)	13.0 (4.8)	12.5 (4.4)	12.5 (4.4)
ANSS*	Mean (SD)	5.9 (2.0)	5.5 (2.1)	5.5 (2.1)	5.8 (1.9)	5.4 (1.8)	5.4 (1.8)

**Abridged NSS*

No relevant between-group differences were observed at baseline for global scores. As foreseeable, the reflective global scores were higher than those assessed instantaneously.

Similar results were observed for symptom scores assessed by investigators.

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Efficacy results:

- **MAIN CRITERION: change from baseline in the patient-rated rNSS over the 2-week treatment period**

As summarized in table below, the estimated difference of the adjusted rNSS was statistically significantly in favour of the V0114 2.5 mg treatment.

Main analysis: FAS population	**Placebo**	**V0114 2.5 mg**
Adjusted change		
E (SE) *	-3.2 (0.1)	-3.6 (0.1)
95% CI*	[-3.5 ; -2.9]	[-3.9 ; -3.3]
Placebo – V0114		
E (SE)**	0.4 (0.2)	
95% CI**	[0.0 ; 0.8]	
Treatment effect**	**0.029**	

**E (SE): Adjusted estimated mean change (Standard Error) (covariance model); Least Square Mean (LSM) 95% confidence interval (CI).*
*** Mixed-effects Model for Repeated Measures*

These results were confirmed by the sensitivity analyses on the PP set and the Randomised Set:

- PP set: **E (SE) = 0.5 (0.2), 95% CI = [0.1 ; 0.8], p = 0.020**;
- Randomised Set: **E (SE) = 0.5 (0.2), 95% CI = [0.1 ; 0.9], p = 0.006**.

- **SECONDARY CRITERIA**

Patient-rated nasal and non nasal symptom scores:

Differences for the rTSS and the reflective abridged NSS respectively were also statistically significant (p = 0.030 and p = 0.024 respectively) and thus confirmed the results of the main criterion. V0114 2.5 mg also improved the reflective NNSS and the difference was close to the statistical significance (p=0.076).

All instantaneous scores were improved by V0114 2.5 mg statistically significantly in the evening after the whole day of exposure to pollen, but not statistically significantly in the morning before pollen exposure.

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Efficacy results (Continued)**:**

Secondary analysis: change from baseline in the patient-rated global scores over 2 weeks

FAS	**Reflective**		**Instantaneous in the morning**		**Instantaneous in the evening**	
Assessment	**Placebo**	**V0114**	**Placebo**	**V0114**	**Placebo**	**V0114**
NSS						
Placebo – V0114						
E (SE)*	-		0.2 (0.2)		0.4 (0.2)	
95% CI*	-		[-0.2 ; 0.6]		[0.0 ; 0.8]	
Treatment effect**	-		0.32		**0.042**	
NNSS						
Placebo – V0114						
E (SE)*	0.3 (0.2)		0.4 (0.2)		0.4 (0.2)	
95% CI*	[-0.0 ; 0.7]		[-0.0 ; 0.7]		[0.0 ; 0.7]	
Treatment effect**	0.076		0.056		**0.049**	
TSS						
Placebo – V0114						
E (SE)*	0.7 (0.3)		0.6 (0.4)		0.7 (0.3)	
95% CI*	[0.1 ; 1.4]		[-0.2 ; 1.3]		[0.1 ; 1.4]	
Treatment effect**	**0,030**		0.12		**0.033**	
Abridged NSS						
Placebo – V0114						
E (SE)*	0.3 (0.1)		0.2 (0.2)		0.3 (0.2)	
95% CI*	[0.0 ; 0.6]		[-0.1 ; 0.5]		[0.0 ; 0.6]	
Treatment effect**	**0.024**		0.28		**0.033**	

**E (SE): Adjusted estimated mean change (Standard Error) (covariance model); Least Square Mean (LSM) 95% confidence interval (CI).*
*** Mixed-effects Model for Repeated Measures.*

Investigator-rated symptom scores:
The improvement of symptom scores judged by the investigator was significantly better with V0114 2.5 mg than placebo for the adjusted change from baseline of the TSS (**E (SE) = 1.0 (0.4), 95% CI = [0.1 ; 0.8], p = 0.023**), the NNSS (**E (SE) = 0.6 (0.2), 95% CI = [0.1 ; 1.0], p = 0.014**) at Day 7 visit, but no statistically significant differences were shown at Day 14 visit.
Success rate (defined as half reduction of NSS without premature withdrawal for adverse event linked to disease or insufficient effiacacy) was slightly higher in the V0114 2.5 mg group than in the Placebo group, and **global efficacy** was better, statistically significantly when assessed by the Investigator.
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Safety results:

Mean treatment duration was 13.8 ± 3.1 days, and mean compliance to study treatments was higher than 98% on average in each study group.

Adverse events

No major or serious adverse event occurred during this study.

In all, 33 patients (7.0%) of the Safety Set experienced a total of 41 treatment-emergent adverse events (TE AE). Thse treatment-emergent adverse events were experienced by few patients in both groups:

- Placebo group: 20 TEAEs experienced by 17 patients (7.1%);
- V0114 2.5 mg group: 21 TEAEs experienced by 16 patients (6.8%).

The most frequently affected System Organ Classes (SOC) were represented by nervous system disorders (12 patients, 2.5%), gastrointestinal disorders (6 patients, 1.3%), and infections/infestations (6 patients, 1.3%) without relevant differences between groups.

The most commonly reported TEAEs were as follow without relevant differences between the V0114 2.5 mg group and the Placebo group:

- Somnolence/disturbance in attention: 4 patients, (1.7%) *versus* 4 patients, (1.7%);
- Headache: 4 patients, (1.7%) *versus* 2 patients, (0.8%).

For *Treatment-emergent sedative effects*, relationship to treatment could not be excluded in investigator's opinion. Most of these sedative effects were graded as mild in the Placebo group (3 patients) and as moderate in the V0114 2.5 mg group (3 patients). No sedative effect was considered as severe.

TEAE outcome was complete recovery without action taken in about half of cases.

Definitive treatment discontinuation occurred in 5 patients (1.1%) due to 6 TEAEs: 3 patients of the Placebo group (one for headache, one for acute tonsillitis and one for somnolence) and 2 patients of the V0114 2.5 mg group (one for headache and one for somnolence and disturbance in attention). All these TEAEs but 1 acute tonsillitis were considered as possibly in relationship to the study drug; all but tonsillitis were resolved at the end of the study.

No relevant signs at physical and nasal examination and no relevant changes in vital signs were observed whatever the study group taken into consideration.

The dose of 2.5 mg showed very low sedative effect (<2%) and was similar to placebo, thus confirming that the global safety profile of this dose was very satisfactory.

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Conclusions

The primary objective of this study was to demonstrate *versus* placebo the efficacy of a 2-week treatment by the antihistamine V0114 2.5 mg in reducing symptoms during seasonal allergic rhinitis.

V0114 2.5 mg induced a statistically significantly (p = 0.029) higher improvement of the reflective Nasal Symptom Score during 14 days of treatment. This improvement was also observed for the other symptom scores (NNSS, TSS, abridged NSS) assessed in the evening. These results were confirmed in the other populations (PP set and Randomised Set).

In patients of the FAS population, V0114 2.5 mg induced a decrease of symptom intensity from baseline over the 2- week treatment period of 46.8% for the Nasal Symptom Score and 48.5% for the Total Symptom Score. The estimated difference between V0114 2.5 mg and placebo was lower than expected and that might be explained by a symptom decrease in the placebo group more important that usually reported.

No serious adverse event occurred during the study.

Global safety profile of V0114 2.5 mg administered in the morning was very satisfactory, in particular sedative effects were observed in only 1.7% of patients as it was seen in placebo group.

Efficacy of the V0114 at the 2.5 mg dose was confirmed by this trial. It can be a diurnal treatment of invalidating allergic rhinitis as regards to its low rate of sedative effects and improved NSS during daytime.

Date of report	**22 August 2012**

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