Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

Efficacy and Safety Study of the Antihistamine V0114 CP 2.5mg in the Treatment of Seasonal Allergic Rhinitis.
Randomised, Double-Blind, 3-Arm Parallel-Group Study Including Placebo and Active Control (Desloratadine 5 mg) Arms

Investigational Product:	V0114CP / l-mequitazine / 2.5 mg tablet (encapsulated for blinding)
Protocol Number:	V00114 CP 3 04 2A
EudraCT Number:	2008-000133-22
Date of First Enrolment:	22 May 2008
Date of Last Completed:	27 August 2008
Coordinating Investigator:	Dr Joachim Mullol, MD, ENT Department, University Hospital of Barcelona *c/* Villarroel 170, 08036 Barcelona, Catalonia, Spain, Tel. +34 (0)932 279 872
Sponsor Representative for Study Report:	Head of Therapeutic Area: Alain Delarue, MD, IRPF Tel. +33 (0)5 34 50 61 88
Date of Report:	09 August 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:	**Efficacy and Safety Study of the Antihistamine V0114 CP 2.5mg in the Treatment of Seasonal Allergic Rhinitis.** ***Randomised, Double-Blind, 3-Arm Parallel-Group Study Including Placebo and Active Control (Desloratadine 5 mg) Arms***	
International Coordinating Investigator	**Dr Joachim Mullol**, MD, ENT Department, University Hospital of Barcelona, *c/* Villarroel 170, 08036 Barcelona, Catalonia, Spain	
Investigators	199 potentially recruiting investigators (mainly allergologists and ENT specialists) from 13 European countries: Belgium, Bulgaria, Czech Republic, Estonia, Germany, Hungary, Italy, Latvia, Lithuania, Poland, Romania, Slovakia, and Spain.	
Study Centres:	103 recruiting centres: 12 / Belgium, 6 / Bulgaria, 10 / Czech Republic, 5 / Estonia, 8 / Germany, 8 / Hungary, 8 / Italy, 4 / Latvia, 7 / Lithuania, 7 / Poland, 9 / Romania, 11 / Slovakia, and 8 / Spain.	
Publication (reference):	Not written to date	
Study Period: **Date of First Enrolment** **Date of Last Completed**	3 months: 22 May 2008 27 August 2008	**Phase of development:** III
Objectives:		
- **Primary**	To demonstrate the efficacy of a 2-week treatment by the antihistamine V0114 at 2.5 mg/day, *versus (vs.)* placebo, in reducing symptoms during seasonal allergic rhinitis,	
- **Secondary**	To evaluate the clinical safety of V0114CP 2.5 mg.	
Methods	Multicentre, randomised, double-blind, placebo-controlled, 3-parallel-group study. Desloratadine 5 mg/day was administered to the 3rd group as active control.	
Number of Patients	992 randomised patients (all treated): 326, 325, and 341in the Placebo, V0114, and Desloratadine groups, respectively.	
Diagnosis and Main Criteria for Inclusion	Male or female outpatients > 18 year-old, with seasonal allergic rhinitis to grass pollen grain defined by a: - Documented medical history (or diagnosis confirmed by the score for allergic rhinitis [SFAR]) of seasonal rhinitis during the grass pollen season (May to July) with symptoms (sneezing, palate itching, aqueous rhinorrhea, or nasal blockage) for at least 2 years, - Positive skin prick test to grass pollen grains, at Selection Visit or duly documented in the medical file within the last 6 months, - Patient-rated daytime reflective nasal symptom score (NSS_{0-12}) ≥ 6 at Randomisation visit.	
Test product,	**V0114 2.5 mg** tablet masked in a hard capsule,	
Dose,	**2.5 mg/day**,	
Mode of Administration	*Per os*, with water, in the morning (except on Day 1: at any time of the day during the Randomisation visit),	
Batch Number:	#SB0631, expiry date (exp.) February 2010.	
Duration of Treatment:	15 consecutive days.	
Reference Therapy 1:	**Placebo**, hard capsule similar to that masking the test product,	
Dose,	1 capsule/day,	
Mode of Administration,	See "Test Product" Section,	
Batch Number:	#SB0633, exp. February 2011.	

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Reference Therapy 2 (Active Control):	**Desloratadine 5 mg** tablet masked in a hard capsule similar to that masking the test product
Dose,	**5 mg/day**,
Mode of Administration,	See "Test Product" Section,
Batch Number	#SB0632, exp. March 2009.

Criteria for Evaluation

Efficacy:

Primary Efficacy Criterion:

Mean change from baseline across the 2-week treatment of the Patient-rated daytime (12 h) reflective NSS (sneezing, rhinorrhea, nose itching, nasal blockage) captured on the digital pen of a pen & paper device.

Secondary Efficacy Criteria:

- Mean change from baseline across the 2-week treatment in the Patient-rated daytime (12 h) reflective:
  - Non NSS (NNSS) (watery eyes, eye itching, eye redness, palate itching) captured on the digital pen,
  - Total symptom score (TSS=NSS+ NNSS),
  - Abridged NSS (without nasal blockage),
- Success rate (%patients with 50% reduction of the Patient-rated reflective NSS with no premature withdrawal [PW] for adverse event [AE] or treatment failure), at D8 and D15,
- Onset of action (when difference *vs.* PBO on the Patient-rated reflective NSS across the 1st week of treatment reaches 0.8),
- Time to maximum effect on the Patient-rated reflective NSS,
- Mean change from baseline, at D8 and D15, in the:
  - Investigator-rated instantaneous NSS, NNSS and TSS,
  - Patient-rated Sleep VAS score,
  - Patient-rated Smell Disorders VAS score,
- Patient-rated Weekly-recall Rhinitis Quality of Life Questionnaire (RQLQ) score, at D15: mean change from baseline, and success rate (%patients with 50% reduction),
- Patient's and Investigator's Clinical Global Improvement (CGI: stable/worse = 0 to complete relief = 3), at D15,
- Patients' and Investigators' global assessment of treatment(very unsatisfied=0 to very satisfied=3), at D15.

Safety:

Assessment or reporting at each visit from the Selection Visit, unless otherwise specified:

- AEs,
- Vital signs (systolic and diastolic blood pressure [SBP and DBP] and heart rate [HR]),
- Concomitant treatments,
- Nasal examination (speculum or endoscopy),
- ECG at the Selection Visit and D15/V4.

Statistical Methods (1/2):

Efficacy (1/2):

Unless otherwise specified,

– Analyses were performed on the full analysis set (FAS), *i.e.*, on the data from the randomised and treated patients with a baseline NSS assessment and at least 3 valid* post-baseline NSS assessments (**A valid assessment was attested by the dates and times given by the digital pen and upon the decision of the Validation Committee);*

– For each criterion, the main analysis compared the V0114 and the Placebo groups, and then (except for supportive and secondary analyses of the primary criterion*), secondary sensitivity analyses compared the Desloratadine and the Placebo groups.

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Statistical Methods (2/2):

Efficacy (2/2):

The following tests were performed:

– Likelihood-based mixed model for repeated measures (MMRM) test with the Pooled Centre, Day and Treatment effects as fixed effects and the baseline value as covariate:
  - Across the 2 weeks of treatment for changes from baseline of the Patient-rated NSS (= primary efficacy analysis and its supportive analyses°), NNSS, TSS and abridged NSS, and for the time to maximum effect on Patient-rated NSS;
  - Across the 1st week of treatment for the onset of action on the Patient-rated NSS;

– ANCOVA with the Pooled Centre and Treatment effects as main effects and the baseline value as covariate for changes from baseline of: the Investigator-rated NSS, NNSS and TSS, the sleep and smell disorders VAS scores, and the RQLQ score.

– Cochran-Mantel-Haenzel (CMH) test adjusting for the Pooled Centre for the success rates (on Patient-rated NSS and RQLQ score), and for CGI Patient and Investigator assessments.

° The primary efficacy analysis was repeated on the Perprotocol (PP) data set (*i.e.*, data from the FAS patients with no major protocol deviations) and the intent-to-treat (ITT) data set (*i.e.*, data from all randomised and treated patients) for supportive purpose. Paper data were used for this ITT analysis only.

Secondary analyses of the primary criterion were performed on the FAS, and consisted of the primary efficacy analysis:

– Including the [Pooled Centre*Treatment] interaction in the model,

– With adjustment for the allergic profile (included as fixed effect),

– Without adjustment for the baseline value.

– With adjustment for the pollen count (included as fixed effect). *<u>Note</u>: *A post-hoc comparison of the Desloratadine and Placebo groups was also performed for this analysis in the view of the main comparison results.*

Safety:

All safety analyses were performed on the ITT data set.

AEs:

- N (%) of patients: with at least one: AE, treatment-emergent AE (TEAE), serious AE (SAE), AE leading to a study treatment definitive discontinuation, TEAE by most severe intensity (mild/moderate/severe), TEAE by closest relationship to study drug (excluded/not assessable/not excluded), drug-related (relationship other than 'excluded') TEAE,
- N (%) of patients with at least one TEAE by System Organ Class and Preferred Term (PT) of MedDRA,
- Individual listings for SAEs and AEs leading to definitive study treatment discontinuation or change in dose;

Vital Signs:

- Descriptive statistics for values and changes over time,
- N (%) of patients with: i/ predefined potentially clinically significant changes (PCs), ii/ PCs leading to predefined potentially clinically significant values (CSCs);

ECG: n (%) of patients by CHMP categories of QTc-Bazett (QT_CB) and -Fridericia (QT_CF) values and changes from baseline. On-site and centralised reading sources were both taken into account for ECG data analyses as no complete reconciliation could be made;

Concomitant Treatments: Frequencies of use by WHO-DRUG ATC classes.

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Summary - Conclusions:

Patients

Disposition

1083 patients were screened of whom 992 were randomised; all randomised patients were treated (ITT).

The patient disposition from randomisation to study completion is tabulated below (several reasons may have led to the premature withdrawal).

	Placebo	**V0114 2.5 mg**	**Desloratadine 5 mg**	**Total**
Randomised	**326**	**325**	**341**	**992**
Prematurely Withdrawn	***27 (8.3%)***	***15 (4.6%)***	***14 (4.1%)***	***56 (5.6%)***
Safety Concern	*8 (2.5%)*	*2 (0.6%)*	*7 (2.1%)*	*17 (1.7%)*
Therapeutic Failure	*10 (3.1%)*	*4 (1.2%)*	*6 (1.8%)*	*20 (2.0%)*
Loss to follow-up	*1 (0.3%)*	*3 (0.9%)*	*-*	*4 (0.4%)*
*Other Reason**	*12 (7.1%)*	*7 (4.4%)*	*3 (3.5%)*	*22 (2.2%)*
Completers	**299 (91.7%)**	**310 (95.4%)**	**327 (95.9%)**	**936 (94.4%)**

**exclusive of the other classes of reasons*

The patient disposition across the different data sets analysed was the following:

	Placebo	**V0114 2.5 mg**	**Desloratadine 5 mg**	**Total**
ITT (safety analysis set and supportive efficacy analysis set)	**326**	**325**	**341**	**992**
FAS (main efficacy analysis set)	308 (94.5%)	310 (95.4%)	325 (95.3%)	943 (95.1%)
PP data set (supportive efficacy analysis set)	272 (83.4%)	273 (84.0%)	289 (84.8%)	834 (84.1%)

Baseline Characteristics (ITT)

Treatment groups did not relevantly differ with respect to demographic and other baseline characteristics.

50.7% of patients were men, the mean (SD) age and BMI were 34.2 (12.1) years and 24.9 (4.3) kg/m^2. The skin prick and IgE tests confirmed in all patients with data (986) the sensitization to grass pollens and its participation in most cases ($\geq$ 86%) to a polysensitization. Allergic conjunctivitis and asthma were associated with the SAR in around 56% and 10% of patients, respectively. The overall baseline mean (SD) Patient-rated NSS (~7.8 [2.0]) attested of the patients' moderate-to-severe intensity of nasal SAR symptoms.

Efficacy Results

Over 2-weeks of the spring-summer allergy season, V0114 2.5 mg/day therapy reduced the (daytime reflective) Patient-rated NSS by 3.84 (a ~49% reduction) on average. This reduction was significant compared with placebo, where the Patient-rated NSS was reduced by 3.17 (a ~40% reduction) on average, the corresponding adjusted between-treatment difference being of -0.68 (FAS; p<0.0001). The robustness of these results and the sensitivity of the study were respectively confirmed by similar results in other efficacy subsets (ITT and PP) and in the FAS comparing over the same period the active reference treatment (desloratadine 5 mg/day) to the placebo. The allergic profile had no significant effect on the main results; neither had the pollen count; however, the adjustment on the pollen count relevantly increased the magnitude of the difference in favour of each *verum* treatment as compared to the placebo (-0.81 and -0.86 for V0114 and desloratadine, respectively).

A significant reduction in the Patient-rated NSS on V0114 as compared to the placebo was observed as early as on D1 and this persisted throughout the 2-week treatment period. Mean adjusted between-treatment differences ranged between -0.45 (D2; p=0.031) and -1.12 (D15; p=0.001).

All other evaluated SAR symptom scores (abridged Patient-rated NSS, Investigator-rated NSS, Patient- and Investigator-rated NNSS, and TSS) exhibited results consistent with the main results for each verum treatment as compared to the placebo.

All other efficacy parameters also exhibited improvements in all groups at all assessment time-points (D15 ± D8) andsignificantly higher in each verum group as compared to the Placebo group (except for sleep quality on desloratadine at both D8 and D15).

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Main efficacy outcomes over or after 2 weeks of treatment are summarized in the following table. *Note: for each score, the adjustment obtained in each comparative analysis (V0114 vs. PBO and desloratadine vs. PBO), led to non strictly similar adjusted values and changes in the PBO group.*

Variable [worst-best Scoring range]	*Criterion*	*PBO N=308*	*V0114 N=310*	*Δ V0114-PBO; p value*		*PBO N=308*	*Desloratadine N=325*	*Δ Desloratadine - -PBO; p value*
ALLERGIC SYMPTOM SCORES								
Patient-rated rNSS [12-0]	**Adjusted Change over 2 weeks**	**-3.17**	**-3.84**	**-0.68; <0.0001†**		**-3.10**	**-3.79**	**-0.69; <0.0001†**
Patient-rated reflective Abridged NSS [9-0]		**-2.39**	**-2.97**	**-0.58; <0.0001**		**-2.33**	**-2.95**	**-0.62; <0.0001**
Patient-rated rNNSS [12-0]		**-2.38**	**-2.86**	**-0.48; <0.0001**		**-2.36**	**-2.96**	**-0.60; <0.0001**
Patient-rated rTSS [24-0]		**-5.55**	**-6.69**	**-1.14; <0.0001**		**-5.46**	**-6.75**	**-1.29; <0.0001**
Investigator-rated iNSS [12-0]	**Adjusted Change at D15**	**-4.07**	**-4.96**	**-0.89; <0.0001‡**		**-3.89**	**-4.54**	**-0.65; =0.001‡**
Investigator-rated iNNSS [12-0]		**-2.88**	**-3.61**	**-0.73; <0.0001‡**		**-2.86**	**-3.44**	**-0.58; =0.001‡**
Investigator-rated iTSS [24-0]		**-6.95**	**-8.57**	**-1.62; <0.0001‡**		**-6.74**	**-7.98**	**-1.24; <0.001‡**
GLOBAL ASSESSMENTS and QUALITY of LIFE								
Patient-rated CGI [0-4]	**% improvements rated 3 (important improvement) or 4 (complete relief) at D15**	**28.4%**	**41.2%**	**+12.8%, <0.0001§**		**28.4%**	**42.0%**	**+13.6%, <0.0001§**
Investigator-rated CGI [0-4]		**28.8%**	**41.9%**	**+13.1%, <0.0001§**		**28.8%**	**42.6%**	**+13.8%, <0.0001§**
Patient-rated GA* [0-3]	**% assessments rated 3 (very satisfied) at D15**	**19.2%**	**29.6%**	**+10.4%; <0.0001§**		**19.2%**	**31.9%**	**+12.7%; <0.0001§**
Investigator-rated GA* [0-3]		**16.3%**	**28%**	**+11.7%; <0.0001§**		**16.3%**	**27.1%**	**+10.8%; <0.0001§**
Sleep Quality [0-10]	**Adjusted Change at D15**	**1.17**	**1.58**	**+0.41; =0.011‡**		**1.11**	**1.34**	**+0.23; 0.15‡**
Smell Disorders [0-10]		**1.10**	**1.56**	**+0.46; =0.006‡**		**1.13**	**1.62**	**+0.49; =0.002‡**
Overall RQLQ* [6 - 0]		**-1.18**	**-1.48**	**-0.29; <0.001‡**		**-1.10**	**-1.44**	**-0.33; <0.0001‡**
	% of 50%-responders at D15	**66.6%**	**76.5%**	**+9.9%; =0.011‖**		**66.6%**	**78.1%**	**+11.5%; =0.002‖**

rNSS, rNNSS,and rTSS: reflective NSS, NNSS, and TSS;iNSS, iNNSS, and iTSS: instantaneous NSS, NNSS, and TSS
** on ITT data set (on FAS for all other parameters);† MMRM;‡ ANCOVA;§ CMH on all classes;‖ CMH on this specific class*

Safety Results (1/2)

Two SAEs were reported in 2 patients, both on desloratadine, and none was considered study-drug-related: a death on D12 due to a traffic accident in a 35-year old man and an acute renal colic (1st episode of nephrolithiasis) in a 30-year old woman, not leading to study drug discontinuation.

The overall incidence of TEAEs was low and similar between groups: 11.7%, 10.8%, and 10.3% in the PBO, V0114 and Desloratadine groups, respectively. Almost all TEAEs (93.3%) were mild or moderate in severity (40/44, 48/50, and 38/41 in the PBO, V0114, and Desloratadine groups, respectively).

The most common TEAEs (PT or HLT; incidence > 1% in either group) were (into brackets: incidences in the PBO, V0114 and Desloratadine groups, respectively): headache (PT; 4%, 3.7%, and 1.2%), somnolence (PT; 0%, 1.8%, and 1.2%), asthenic conditions (HLT; 0.6%, 2.8%, and 1.8%), and dry mouth (0, 1.2%, and 0.6%). Somnolence, asthenic conditions and dry mouth, which were specific of the *verum* groups, predominantly occurred around D2-D4, and (except for somnolence in the V0114 group) generally lasted at least 1 week or did not resolve during the study course. As no sedation was reported as AE in either group, the comparison of the predefined sedative TEAEs' incidence was limited to that of somnolence; the Fisher's test *vs.* PBO provided a statistically significant result for V0114 (p=0.01) and a borderline significant result for desloratadine (p=0.051). Respiratory tract disorders (infectious or not), gathered with viral infections such as flu, were more frequent in the PBO group than in the *verum* groups (3.7%, 0.9%, and 1.2%) although no specific relating HLT or PT clearly distinguished the PBO group from the *verum* groups. The overall incidence of study drug-related TEAEs was similar between groups (7.4%, 7.7% and 7.9%). All the most common TEAEs accounted for the most common study-drug-related TEAEs.

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Safety Results (2/2)

Drug-related TEAEs having led to definitive study drug discontinuation were less frequent in the V0114 group (2 AEs in 2 [0.6%] patients) than in the PBO group (6 AEs in 4 [1.3%] patients) and the Desloratadine group (5 AEs in 5 [1.5%] patients). We note among these AEs, a severe case of nasal congestion and respiratory disorder in the PBO group, 3 (mild) cases of skin disorder in the *verum* groups (1 on V0114 and 2 on desloratadine), and 2 cases (1 mild, 1 moderate) of somnolence in the Desloratadine group.

There were no trends towards either increase or decrease over time in supine SBP, DBP or HR in the *verum* groups compared to either within-group baseline or contemporary changes in the PBO group: whatever the treatment group or time point, the median changes were 0 mmHg for SBP and DBP and +2 bpm for HR. Consistently, incidences of PCs, non relevantly different between groups, were small for either vital sign except for PCs of HR increase which incidences ranged between 13.8% on V0114 and 16.0% on desloratadine. For either vital sign parameter, between 0 and 3 (0.9%) patients of either group at each time point had CSCs. None of these CSCs were reported as AEs. Besides, no cardio-vascular AEs were reported except 2 potentially study drug-related TEAEs of tachycardia: 1 on PBO patient (D9) and 1 on desloratadine (D1); both cases had resolved at study end without corrective treatment.

QTcF and QTcB changes from baseline to D15 showed high inter-individual variability. QTcF changes from baseline showed no overall relevant trends. For QTcB, small trends towards increase were seen in both *verum* groups: the largest median changes were +5 ms and +3 ms in the V0114 and Desloratadine groups, respectively, as compared to 0 ms in the PBO group (on-site reading). At D15, QT_C values > 450 ms remained rare (< 1%) for QTcF in all groups; for QTcB, they had more pronouncedly increased in the Desloratadine group than in the other groups: largest increase by +6.4% as compared to +2.7% and +3.2% in the PBO and V0114 groups, respectively (on-site reading). In 2 cases (1 on V0114 and 1 on desloratadine) the QTc > 450 ms (according to both reading sources) was reported as an AE(drug-related); in both cases, the QTc increase was < 60 ms and the AE resolved a few weeks later. QT_C values > 500 ms were found in one patient (#181304, Desloratadine group) at D8 on an unscheduled ECG only read at the centralised reading structure: QT_CB and QT_CF of 623 ms and 556 ms, resulting from changes of +177 ms and +152 ms, respectively. As this unscheduled ECG was not read at the Investigating site, the Investigator did not ask for a confirmatory ECG reading by a Cardiologist and did not report the abnormality as an AE. However, as this patient was the patient who died during the study course as a consequence of a motorcycle accident 4 days after the ECG had been performed, a manual reading by a Cardiologist was asked by the Sponsor after the database lock and invalidated the abnormality (QT_CB and QT_CF of 378 ms and 424 ms, respectively, in this patient who had sinus tachycardia [118 bpm] from baseline [108 bpm]). Three other patients (2 on V0114 and 1 on desloratadine) had QT_C increases > 60 ms; in all cases, the resulting values were < 450 ms; one case (on desloratadine) was reported as an AE (drug-related). Further controls (up to 2 months later) did not show improvements, but QT_C values were still < 450 ms, and, as she felt well, the patient did not want to continue ECG controls.

Conclusion

The trial results show that V0114 administered at 2.5 mg once daily for 15 days is an effective treatment for SAR. V0114 2.5 mg/day significantly improved not only SAR nasal and non-nasal reflective and instantaneous symptoms but also the disease impact on quality of life, quality of sleep, and smell disorders. V0114 2.5 mg/day significant effect on nasal symptoms was observed as early as on D1 and persisted throughout the 2-week treatment period. The (similar) significant size effect of the active control as compared to placebo confirmed the good trial sensitivity. V0114 2.5 mg/day presented a good safety profile in accordance with the safety knowledge of the product.

Date of Report: 09 August 2012

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