1 SYNOPSIS

Name of sponsor : Pierre Fabre Médicament	
Product : Primalan® tablet containing 10 mg	
Active substance : Mequitazine	
Title of study: A randomised, double-blind, placebo controlled, parallel group study of the efficacy of mequitazine on symptoms and nasal obstruction in patients presenting with perennial allergic rhinitis.	
Coordinating investigator: Prof. Alain Didier, Service de Pneumologie, Hôpital Larrey, CHU[1] de Toulouse, 24, chemin de Pouvourville, 31059 Toulouse cedex 9	
Study Centre Investigators: ENT specialists/hospital or private practice allergologists	
Publications: No publications were submitted while this report was being written	
Research duration: - First visit of first patient included: 06 December 2007 - Last visit of last patient included: 24 February 2009	**Clinical phase** : Phase IV study

Objectives

Primary : to evaluate the efficacy of mequitazine on nasal symptoms (rhinorrhoea, nasal pruritus, nasal obstruction, sneezing).

Secondary :

- to demonstrate the efficacy of mequitazine on nasal obstruction measured with PNIF[2] test,
- evaluation of all symptoms taken separately
- evaluation of patient quality of life with the RQLQ self-administered questionnaire
- overall opinion of treatment by the patient
- overall opinion of treatment by the investigator
- safety end points

Methodology

A randomised, multi-centre, placebo-controlled, parallel group, double-blind clinical trial.
Clinical trial conducted on patients with perennial allergic rhinitis.

Number of research participants:

- Number of subjects expected: 156 patients were to be included, 78 of which treated with the investigational product, 78 treated with the placebo
- Number of subjects analysed: 157 patients were included, treated and analysed in the safety population, 154 were analysed in the ITT population and 125 in the PP population.

DIAGNOSIS AND PRINCIPAL INCLUSION CRITERIA

Inclusion criteria:

Patients eligible for inclusion in this study are patients who meet the following screening criteria:

[3] ARIA: Allergic rhinitis and its impact on asthma

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- male or female patient,
- 18 to 65 years of age,
- presenting with perennial allergic rhinitis (mites, cockroaches, moulds, animal dander, etc.),
- presenting with perennial allergic rhinitis according to ARIA[3] criteria (symptoms present for a duration > 4 days per week and for more than 4 weeks.
- a documented clinical history of symptomatic perennial rhinitis of at least 2 years duration (a suggestive clinical presentation consisting of the combination bursts of sneezing and/or nasal pruritus and/or clear rhinorrhoea and/or nasal obstruction), requiring symptomatic treatment during at least one of the last two years,
- a positive prick test and/or specific IgE class ≥ 3 duly documented in the patient's medical records and during the previous 2 years,
- nasal symptom score ≥ 6 at time of inclusion,
- a nasal obstruction score ≥ 2 at inclusion,
- followed-up and treated in ambulatory practice,
- able to understand the protocol and constraints of the study,
- able to understand the information leaflet and to provide written consent,
- patients who in the investigator's opinion can comply well with treatment,
- patients who are covered by the social security system or who are beneficiaries of this system.

<u>Exclusion criteria</u> :

Subjects who present with at least one of the following criteria will not be eligible for inclusion:

- severe cardiovascular, renal, hepatic, gastro-intestinal, endocrine, haematological or neuropsychiatric disorder considered by the investigator as incompatible with conduct of the trial.
- an acute or chronic disorder considered by the investigator as incompatible with conduct of the trial,
- angle-closure glaucoma,
- benign prostatic hyperplasia,
- asthma treated with corticosteroids, whatever the formulation,
- medicinal product-related rhinitis,
- nasal polyposis or severe deviation of the nasal septum which may hinder conduct or interpretation of the PNIF criteria,
- upper airway infection during the previous 3 weeks,
- known history of hypersensitivity to mequitazine or to the excipients,
- specific desensitisation started or increased during the previous month,
- treatment with a delayed action corticosteroid during the previous 6 months,
- treatment with a corticosteroid (nasal, ocular, inhaled or systemic) during the previous 4 weeks,
- treatment with cromone (nasal or ocular) or ketotifen during the previous 2 weeks,
- treatment with mequitazine during the previous week,
- treatment with loratadine, desloratadine, cetirizine, levocetirizine, ebastine, mysoline or fexofenadine during the previous week,
- treatment with a local anti-histamine (nasal or ocular) during the previous week,
- treatment with a first-generation anti-histamine or any other anti-histamine other than those in the aforementioned during the previous 2 weeks,
- treatment with an NSAID (other than an oxicam) during the previous 3 days,
- treatment with an oxicam NSAID during the previous week,
- treatment with a nasal decongestant (systemic or local) during the previous 24 hours,

[3] ARIA: Allergic rhinitis and its impact on asthma

- treatment with a tricyclic antidepressant or with an MAO inhibitor during the previous month,
- treatment with a product with atropine-like effects during the previous month,
- treatment which can produce induction or inhibition of hepatic microsomal enzymes during the previous month,
- participation in another ongoing clinical trial or during the previous month,
- surgery during the previous month,
- risk of urinary retention related to urethro-prostatic disorders. Due to the existence of lactose, this medicinal product is contraindicated in case of congenital galactosaemia, glucose and galactose malabsorption syndrome or lactase deficiency,
- a history of agranulocytosis related to use of other phenothiazines,
- a patient who, in the investigator's opinion, is not likely to cooperate during the study,
- patient with a physical or psychological inability to complete the self-assessment diary,
- linguistic or psychological inability to understand the information, patient who has lost his/her administrative or legal rights or who is under guardianship or a tutorship,
- patient who works at night.

For women :

- pregnancy or breastfeeding,
- absence of an effective method of contraception (oral contraceptives, intrauterine device, tubal ligation): a pregnancy urine test will be performed systematically in all women of child-bearing potential.

Investigational medicinal product [name, dose, route of administration and batch number(s)]:
Mequitazine 10 mg tablet for oral administration in the evening, batch no. G00156 (expiry date: 10/2008) and batch no. G00167 (expiry date: 06/2010)

Duration of treatment : 21 days.

Reference investigational medicinal product [name, dose, route of administration and batch number(s)]:

Placebo tablet identical to the mequitazine tablet, for oral administration in the evening, batch no. SB0342 (expiry date 11/2008) and batch no. SB0342 (expiry date 11/2010)

ENDPOINTS:

Primary endpoint: The primary endpoint was the outcome in the nasal symptoms score (NSS) including nasal obstruction between D0 and D21 ± 3.

The nasal symptom score (NSS) consists of the following items:

- sneezing
- nasal pruritus
- rhinorrhoea
- nasal obstruction

Each end point will be scored according to a 4 point categorical rating scale:

0 = absence of symptoms

1 = mild and hardly bothersome symptom

2 = moderate, but bothersome symptom

3 = severe symptom resulting in continuous impairment.

The nasal symptom clinical score is the total of the 4 criteria.

Other criteria of interest:

- Outcome of measurements performed with PNIF between D0 and D21 ± 3.
- Outcome of all symptoms taken separately between D0 and D21 ± 3.

- Outcome of patient quality of life with the RQLQ questionnaire between D0 and D21 ± 3.
- Severity of allergic rhinitis
    - Normal or impaired sleep
    - Daily activities, normal or impaired athletic activity and leisure
    - Normal or impaired school or occupational activities

- Overall opinion of treatment by the patient at D21 ± 3.

  Overall opinion of treatment by the patient will be evaluated according to the following scale:

  0 = stability or worsening

  1 = slight improvement

  2 = moderate improvement

  3 = marked improvement

  4 = complete improvement

- Overall opinion of treatment by the investigator at D21 ± 3.

  Overall opinion of treatment by the investigator will be evaluated according to the following scale:

  0 = stability or worsening

  1 = slight improvement

  2 = moderate improvement

  3 = marked improvement

  4 = complete improvement
- Adverse effects recorded throughout the duration of the study
- General clinical examination at D0 and D21 ± 3 including measurement of vital signs.

Statistical analyses:

The significance threshold was set at 0.05.
For the sample analysed, quantitative variables were described as mean, standard deviation, n, min, max and median, and qualitative variables as frequency and percentage.

For the primary endpoint, the score raw values were described on D0 and D21±3; as was change.

Inter-group analysis: Comparisons covered the differences compared to the baseline value (after - before treatment). Comparisons could also cover the percentage variation compared to the baseline value (after - before treatment).

The tests used were the same as those used to compare the groups at inclusion (Student t-test or Wilcoxon test, according to normality of value distribution).

Inspiratory flow values and total RQLQ quality of life questionnaire scores were noted on D0 and D21±3, as were the changes since D0
Intra-group and inter-group analyses were performed in the same way as for the primary endpoint.

An inter-group analysis was performed for overall assessment of the improvement brought by the treatment, in the investigator's opinion and in the patient's opinion.

Disease severity and symptom intensity were noted at D0 and D21±3 as were the changes compared to D0.
The safety analysis was performed on all patients having received at least one or the other investigational product, at least once. A descriptive analysis was performed for the adverse effects recorded.
A descriptive analysis was performed for the vital sign reading results at D0 and D21±3.

Research summary – conclusion:

The primary objective was to evaluate the efficacy of mequitazine (Primalan®) on nasal symptoms (rhinorrhoea, nasal pruritus, nasal obstruction and sneezing).

One hundred and fifty-seven (157) patients (73 women and 84 men), age 18 to 58 years (average age = 30.9 years) were included and randomised in the study (80 patients in the placebo group and 77 patients in the Primalan® group). One hundred and fifty-four (154) patients were included in the ITT population and 125 patients in the PP population.

Tests to compare the subjects in the 2 treatment groups were carried out before treatment administration. The patients from the 2 groups had similar demographic and clinical characteristics. They presented with perennial allergic rhinitis, meeting the criteria set out by the ARIA.

- Efficacy evaluation results:

The primary efficacy outcome measure was the change in nasal symptom score (NSS) including nasal obstruction between D0 and D21±3.

A reduction in the NSS score was noted in the 2 treatment groups: - 3.05 (3.13) points in the placebo group compared to -3.61 (3.16) points in the Primalan® group. However, the reduction in the score observed in the Primalan® group was not significantly greater than that observed in the placebo group (p=0.2448). Reductions in the scores for the various symptoms, taken separately, were also observed in the 2 treatment groups, but without there being a significant difference between the groups.

Reductions in the mean RQLQ quality of life questionnaire scores were observed in the 2 treatment groups, but without there being a significant difference between the treatments. Primalan® did not therefore provide better quality of life than the placebo in the population studied, perhaps as the trial was only short. In effect, 3 weeks may seem short with regard to the objective which is to improve patient quality of life

Most of the patients from the 2 treatment groups did not feel an improvement in their allergic rhinitis after taking the treatment: less than 10% of patients saw their sleep stabilise (6 patients (7.7%) taking the placebo and 7 patients (9.2%) taking Primalan®), less than 15% of patients felt an improvement in their daily activities (10 patients (12.8%) taking the placebo and 11 patients (14.5%) taking Primalan®) or felt an improvement in their school and work activities (6 (7.7%) and 8 (10.5%) patients in the placebo and Primalan® groups respectively).

More patients experienced disturbed sleep or impaired daily or school and work activities again than patients experienced improvement.

Most patients felt an improvement in their rhinitis. The number was higher in the Primalan® group than in the placebo group: 63.2% versus 46.8%. Few patients were fully relieved in both treatment groups: 3 patients taking the placebo (3.9%) and 2 patients (2.6%) taking Primalan®.

These results saw a significantly greater improvement in patients taking Primalan® than in patients taking the placebo (1.34 versus 0.91, p=0.0262).

The results observed according to the investigator's judgement were similar:

- 54.5% of patients taking the placebo and 71.1% of patients taking Primalan® improved
- An average score of 1.03 versus 1.45 (p=0.0233) in favour of Primalan®

Increases in nasal inspiratory flow were observed in the two treatment groups; (23.57 (39.49) L/min in the placebo group and 17.78 (48.80) L/min in the Primalan® group) but without there being a significant difference between the treatment groups (p=0.6884).

The results observed in the PP population confirmed the results of the various analyses conducted in the ITT population.

- Safety assessment results:

Median exposure to the placebo and to Primalan® was 21 days in the 2 treatment groups, as initially planned.

No deaths or SAEs were reported during the study.

Overall, 31 AEs were described in 26 patients (16.6%) of which 29 emerging AEs observed in 25 patients (15.9%).

The emerging AEs were mainly nervous system disorders (4 patients taking the placebo (5.0%) and 7 patients taking Primalan® (9.1%)) and drowsiness (2 episodes with the placebo and 6 episodes with Primalan®).

The frequency of the emerging AEs was similar between the treatment groups, with 12 (15.0%) and 13 patients (16.9%) taking the placebo and Primalan® respectively. The number of emerging AEs having led to treatment discontinuation was higher among patients taking Primalan® than among those taking the placebo (5 AEs with Primalan, 4 of which were considered to be in all likelihood related to the treatment, compared to 2 considered to be possibly related to the placebo).

Vital sign values were similar between the treatment groups, and varied little during the study. Vital sign values outside the reference limits were noted but were not considered to be clinically significant.

Overall, administration of the investigational products was well tolerated during this study.

- Conclusion:

The various assessments conducted during this study, as much objective such as nasal flow, as subjective such as NSS, disease severity and quality of life, did not demonstrate superior efficacy from Primalan® over the placebo after 21 days' treatment in patients with perennial allergic rhinitis as defined by the ARIA criteria. However, the patients and investigators considered that the improvement in the rhinitis was significantly greater with Primalan® than with the placebo.

Report date: 20/01/2010