SYNOPSIS

INN: FEXOFENADINE

Study number: M016455A/4134

Study title: Multicenter Open-Label Non-Comparative Trial of Efficacy and Safety of TELFAST® (Fexofenadine) 30 mg B.I.D. for 2 Weeks: Effect on Symptoms of Seasonal Allergic Rhinitis in Children Aged 6 to 11 Years

CSR date: 10 February 2003

The study results and synopsis are supplied for informational purposes only.

Not all of the study results have necessarily been reviewed by the Regulatory Authorities.

The decision to prescribe and take a product should always be made on the basis of the most recent version of the product information and product package insert in the country of prescription.
CLINICAL TRIAL REPORT

MULTICENTER OPEN-LABEL NON-COMPARATIVE TRIAL OF EFFICACY AND SAFETY OF TELFAST® (FEXOFENADINE) 30 MG B.I.D. FOR 2 WEEKS: EFFECT ON SYMPTOMS OF SEASONAL ALLERGIC RHINITIS IN CHILDREN AGED 6 TO 11 YEARS

Open-label non-comparative trial

TRIAL NUMBER: MO 16455A/ 4134

Date of report - February 10, 2003

Synopsis

Summary: "Multicenter open-label non-comparative trial of efficacy and safety of Telfast® (fexofenadine) 30 mg b.i.d. for 2 weeks: effect on symptoms of seasonal allergic rhinitis in children aged 6 to 11 years" was conducted in 5 study sites, with 100 subjects enrolled in the trial.

Protocol number: MO 16455A/ 4134

Trial objectives:

The trial evaluated the effects of TELFAST 30 mg b.i.d. for 2 weeks on symptoms of seasonal allergic rhinitis in children aged 6 to 11 years.

Primary efficacy endpoint was evaluation of changes in the index of symptoms (sum of indices for nasal symptoms except congestion and for eye symptoms). Secondary efficacy endpoints included the following:

Average changes in indices for nasal symptoms versus baseline (sum of indices of nasal congestion, nasal discharge, sneezing and itching), average changes in each of the four rhinitis symptoms versus baseline; average changes of watering and conjunctival irritation versus baseline; average changes in each index versus baseline for each treatment week; global patient's and Investigator's assessment of treatment efficacy; incidence of
withdrawals for treatment failures, incidence of rescue treatment administration; study drug administration compliance.

In addition, objectives of this trial included assessment of Telfast safety in the dose of 30 mg b.i.d.

**Trial design and duration:**

 Trial type: Non-comparative open-label phase IV trial of efficacy and safety

 Number of patients: 100

 Trial duration: 2 weeks

 Date first patient in: February 13, 2002, date last patient in – August 2, 2002

 Number of patients - (expected and actual):

 100 patients were expected to be enrolled in 5 sites; 100 patients in 5 sites have been actually enrolled.

 **Dosing/ formulations and study drug dosing schedule.**

 Telfast®, Fexofenadine, (manufactured by Hoechst Marion Roussel) was provided by Aventis Pharma Distriservice in tablets of 30 mg.

 Patients were recommended to take one TELFAST tablet each morning and each evening.

 Maximal duration of treatment in an individual patient made 2 weeks, from Visit 1 (baseline visit) to Visit 2 (last visit).

 **Diagnosis and key inclusion criteria:**

 Out-patients aged 6 to 11 and above, with the diagnosis of seasonal allergic rhinitis (SAR) were enrolled into the trial. Only patients meeting all inclusion criteria and havening none of the exclusion criteria were enrolled into the trial.

 **Inclusion criteria.**

 Patients meeting the following inclusion criteria were enrolled into the trial:

 - Written Informed Consent provided by patient’s parent (or legally acceptable representative);
 - Boys or girls (before first menarche);
 - Aged 6 to 11 лет;
 - Patients with seasonal allergic rhinitis, allergic to pollen;
 - Duration of seasonal allergic rhinitis for more than one year;
 - Positive Prick test for pollen within 1 year;
- Composite index of rhinitis symptoms evaluated for the last 12 hours with parents’ help - score of no less than 6 (without nasal congestion), with two or more symptoms (without nasal congestion) with the score of no less than 2.
- Absence of other serious diseases;
- Ability to swallow the tablet.

Exclusion criteria:

Patients having any of the conditions mentioned below could not be enrolled into the trial:

- Upper respiratory infections, acute sinusitis, acute otitis media or other infectious diseases serous otitis not being an exclusion criterion) within 30 days prior to inclusion into the trial;
- Purulent conjunctivitis;
- Other rhinitis types other than SAR, including vasomotor, infectious, non-allergic with or without eosinophilia, idiopathic, medication-caused, as well as rhinitis due to systemic illnesses;
- Marked nasal congestion (with the individual assessment score of higher than 3);
- Nasal septum contortion with obstruction evidence or obstructive nasal polyps;
- Present or suspected chronic allergic rhinitis (according to skin tests);
- Cystic fibrosis;
- Hyposensibilization within 6 months prior to the first visit;
- Presence of any of the following:
  - hyponutrition;
  - renal or hepatic failure;
  - chronic infections;
  - drug or alcohol abuse;
  - malignancies;
  - malabsorption syndrome.
- Clinically significant cardiovascular, neurological, psychiatric, endocrine, liver diseases or other serious systemic diseases preventing the conduct of the trial Investigator jeopardizing patients' safety;
- Any diseases or surgeries affecting gastrointestinal absorptions of the drug;
- Patients on immune therapy;
- Immunosuppressive diseases;
- Hypersensitivity to Fexofenadine or any its excipient;
- Administration of any of the medications that are prohibited during the trial or within the specified time preceding the first visit (see Section 6.4);
- Need in frequent administration of antacides containing aluminium or magnesium hydroxide;
- Administration of other investigational products within 30 days preceding the first visit;
- Patient's of his/her parent's (legally acceptable representative’s) failure to comprehend the trial aim and objectives and/or sign the Informed Consent.

Withdrawal criteria

None of the patients was withdrawn from the trial.
Patients were to be withdrawn when -
- Found incompliant with the protocol;
- Any changes in eligibility criteria occurred;
- Inefficacy of TELFAST for 48 hours;
- Occurrence of an adverse event requiring treatment discontinuation;
  - Per patient’s or parent’s decision.

Prior therapy

Any medications taken by a patient within the last 3 months or during the trial, including over-the-counter medications, were captured in the Case Report Form. During the specified period preceding Visit 1 no administration of prohibited medications was recorded.

Efficacy and safety endpoints.

Primary endpoints (efficacy).

Average changes in the index of symptoms (sum of indices for nasal symptoms except congestion and for eye symptoms)

Secondary endpoints (efficacy, safety)

Efficacy

- Average changes in indices for nasal symptoms versus baseline (sum of indices of nasal congestion, nasal discharge, sneezing and itching);
- average changes in each of the four rhinitis symptoms versus baseline;
- average changes of watering and conjunctival irritation versus baseline;
- average changes in each index versus baseline for each treatment week;
- global patient’s and Investigator’s assessment of treatment efficacy;
- incidence of withdrawals for treatment failures;
- incidence of rescue treatment administration;
- study drug administration compliance

Safety

- adverse events;
- number of patients experiencing any adverse event;
- number of patients experiencing any adverse event possibly or probably related to study drug administration.

Statistical analysis plan and methods

Student’s pairwise criterion for co-variables and non-parametric Wilcoxon rank sum criterion to confirm results were applied to reveal statistically significant changes in the values of the index of rhinitis symptoms. Non-parametric Friedman and Mann-Whitney criteria were applied for analysis of diary records to evaluate changes in symptoms depending on the
days of week. Evaluation of changes in continuous values describing changes of each rhinitis symptoms between visits McNemar cross-tabulations were performed. Non-parametric Spearman correlation method was applied for evaluation of proximity between child’s, parent’s and Investigator’s assessment of treatment efficacy. Fisher exact test was applied for incidence evaluation. All statistical tests were two-sided with the level of significance of 0.05. Descriptive statistics was presented for variables such as age, sex, disease duration as point characteristics such as arithmetic mean, standard deviation, median, minimal and maximal values. For certain values 95% confidence interval was calculated.

**SUMMARY:**

100 patients with history of SAR of 8 to 54 months were enrolled into the open-label non-comparative multicenter (5 sites) trial evaluating efficacy of Telfast in the treatment of seasonal rhinitis in children aged 6 to 11, with mean disease duration for the whole group being $18.87 \pm 1.75$ года. Mean age was $8.5 \pm 1.69$ years. The disease was confirmed by skin test which was performed in 100% patients. The population consisted of 63/100 (63%) boys and 37/100 (37%) girls, respectively.

During the trial all patients were administered Telfast in the dose of 30 mg b.i.d., in the morning and in the evening. Trial duration was 2 weeks. Patient accrual was underway for the period of February 13, 2002 – August 02, 2002. Each study site enrolled 20 patients into the trial. All 100 patients enrolled into the trial completed the trial of Telfast safety and efficacy. None of the patients discontinued Telfast administration for an adverse event or treatment failure.

By the time of treatment onset all patients had marked SAR symptoms. During the treatment clear positive changes in the extent of symptoms was observed.

Primary efficacy endpoint for the treatment of seasonal rhinitis – total index of symptoms (sum of index for nasal symptoms except congestion and eye symptoms) reduced by 88.5%, or by 5.81 points from 6.56 (Visit 1) to 0.75 points (Visit 2). Secondary efficacy endpoint (sum of all nasal symptoms) reduced by the end of treatment by 6.93 points, or 85%. Positive changes both for primary and secondary efficacy endpoints for Telfast administration in the treatment of seasonal rhinitis was statistically significant ($p<0.001$).

Analysis of each separate seasonal rhinitis symptoms confirmed statistically significant reductions in the intensity of symptoms. For instance, the number of patients with severe nasal congestion by the time of trial onset reduced from 5 subjects to 0, with moderate congestion – from 48 to complete absence of such symptom. Diary analysis revealed that by treatment Day 3 the extent of that symptom statistically significantly reduced versus baseline.

By the end of the trial the number of patients with severe nasal discharge reduced from 43 subjects to 1 subject, with moderate – from 58 subjects to 3 subjects. Diary analysis revealed that as early as by treatment Day 2 statistically significant differences in the extent of symptoms were found.
Following 2-weeks treatment the number of patients with severe nasal itching reduced from 22 subjects to 0. According to the diary records early as by treatment Day 2 statistically significant reductions in itching were achieved.

On Visit 1 moderate watering was observed in 17 subjects, still present in 2 subjects by the end of the trial. Diary analysis revealed that as early as by treatment Day 3 statistically significant differences in the extent of this symptom were found.

Moderate conjunctival irritation was noticed in 35 subjects by the beginning of the trial, and in just 2 subjects by the end of the trial. Marked reductions in this value were observed since treatment Day 3.

Therefore, 2-weeks treatment period was accompanied by statistically significant reductions in all rhinitis symptoms. Extent of nasal congestion reduced by 60%, nasal discharge by 86.16%. Nasal itching reduced by 89.8%.

Global assessment of treatment results was performed by the physician, the child and the child's parents using the score consisting of 5 points- during the treatment of seasonal allergic rhinitis, according to the patients' assessment (73%), parents' assessment (73%) and physicians (77%), significant improvement was observed. High correlation between patients' and Investigators' assessments of Telfast efficacy had a coefficient of r= 0.75 and was statistically significant ( p <0.001).

During the trial in no patients serious adverse events were recorded. Overall, during the trial Telfast was well tolerated. In 3% (3/100) adverse events occurred during Telfast administration; those were considered minor. In the Investigators' opinion, in 2 (2 %) patients the developing adverse events (somnolence) were possibly related to Telfast administration. In none of the cases he Investigator decided to discontinue Telfast administration due to the occurrence of an adverse event.