SYNOPSIS

INN : FEXOFENADINE

Study number : M016455C/3212

Study title : A double-blind, randomized, placebo-controlled, parallel group study assessing the efficacy and safety of oral fexofenadine HCl tablets 30 mg twice a day in pediatric subjects (6 to 11 years) in the treatment of seasonal allergic rhinitis.

CSR date : 15 December 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.

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STUDY SYNOPSIS

Study number  M016455C/3212

Title
A double-blind, randomized, placebo-controlled, parallel group study assessing the efficacy and safety of oral fexofenadine HCl tablets 30 mg twice a day in pediatric subjects (6 to 11 years) in the treatment of seasonal allergic rhinitis

Investigator(s), study site(s)
Co-ordinating investigators: Dr Carlos Baena Cagnani (South America), Dr Ian Charlton (Australia), Dr Jesus Garde (Spain), Pr Marek Kowalski (Poland), Pr Mario La Rosa (Italy), Pr Eli O Meltzer (USA), Pr Paul Potter (South Africa), Dr Patrick Rufin (France), Dr Erkka Valovirta (Finland), Pr Ulrich Wahn (Germany).

Multinational, multicenter study, 148 centers in 15 countries: Argentina (16), Australia (9), Austria (1), Chile (3), Finland (3), France (12), Germany (5), Israel (3), Italy (7), Poland (10), Portugal (2), South Africa (18), Spain (6), Uruguay (2) and United States (51).

Study duration and dates
The first subject was enrolled on 17 May 2000 and the last subject completed the study on 31 July 2001.

Phase  III

Objectives
Primary Objective:
The primary objective was to demonstrate efficacy and safety of oral fexofenadine HCl 30 mg b.i.d. compared to placebo in the treatment of SAR in pediatric subjects aged 6 to 11 years.

Secondary Objectives:
The secondary objectives were to provide supportive efficacy data from individual symptom scores, and other efficacy variables.

Study design
This was a multinational, multicenter, double-blind, randomized, parallel group, placebo-controlled study conducted at 148 centers. The study included five visits: screening (Visit 1, Day -8 to Day -4), randomization (Visit 2, Day 1), on double-blind treatment (Visit 3, Day 6 to Day 10), end of double-blind treatment (Visit 4, Day 15 to Day 17) and follow-up (Visit 5, Day 22 to Day 24). Subjects were planned to participate in the study for a total of 19 to 32 days.

Population
Pediatric subjects from Europe, United States and Southern hemisphere, aged 6 to 11 years, with symptoms of moderate to severe SAR, who had a history of approximately 1 year or more of SAR during at least one previous relevant spring or fall season. Subjects must have had a positive prick test to at least one allergen for the current season and showed concordance of at least one allergen
in allergen specific immunoglobulin E testing. The allergen must be indigenous to the subject’s residence area and correspond to season. It was also required that the expected duration of the local pollen season was sufficient for the study. Subjects must have been able to swallow a study tablet.

For inclusion at Visit 1, the previous 12-hour reflective total symptom score (TSS) (excluding nasal congestion), assessed by the subject or caregiver, was to be ≥ 6 (see Clinical Study Report R2001CLN0283, Section 3.5.2 – Description of study days). In addition, a minimum score of “2” (“moderate”) was required for two or more symptoms (excluding nasal congestion).

For randomization to double-blind medication at Visit 2, all symptom assessments must have been completed, and with the average (excluding nasal congestion) of the last two 19:00 hours 12-hour reflective TSS assessments by the subject or caregiver ≥ 5.

**Treatments**

A single-blind placebo period of 5 to 9 days (one placebo tablet twice daily) started on the evening of Visit 1. Subjects fulfilling the entry criteria at Visit 2 were randomized to one of two treatment groups as listed below. Randomized double-blind treatment lasted for 14 full treatment days, and subjects were provided with enough double-blind treatment for 17 full treatment days. The double-blind treatment groups were:

- Fexofenadine HCl 30 mg, one tablet twice daily p.o.
- Placebo, one matching tablet twice daily p.o.

**Efficacy data**

The primary efficacy data for the calculation of the primary efficacy variable were the 12-hour reflective TSS at 19:00 hours calculated from the corresponding individual SAR symptom scores. TSS was composed of symptoms of sneezing; rhinorrhea; itchy nose, mouth, throat and/or ears; and itchy, watery, red eyes.

Secondary efficacy data were the daily individual 12-hour reflective symptom score assessments at 7:00 and 19:00 hour and the daily 12-hour reflective TSS at 7:00 hours. Nasal congestion was also assessed but not included in the TSS.

**Safety data**

Safety data were evaluated using adverse events reported during the study, clinical laboratory data at baseline (Visit 1 or 2) and end of double-blind treatment (Visit 4 or 5), and vital signs at Visit 1, Visit 2 and Visit 4.

**Statistical procedures**

Demographic and baseline characteristics were compared between the treatment groups using Wilcoxon rank sum tests for continuous variables and Fisher’s exact test for categorical variables. The average randomization baseline 19:00 hour 12-hour reflective TSS was calculated as the mean of the evaluable 19:00 hour assessments during the single-blind period on Day –2, Day –1 and Day 1 before the double-blind period drug was taken.

Double-blind TSS was the average of the daily TSS over the double-blind period.

The primary efficacy variable, change from baseline in average 12-hour reflective TSS at 19:00 hours, was analyzed using an analysis of covariance model with the baseline 19:00 hours 12-hour
reflective TSS as covariate, and treatment and pool center as fixed effects. The modified intent-
to-treat (mITT) (all randomized subjects who received at least one dose of double-blind treatment
and had a randomized baseline and at least one double-blind period 19:00 hour 12-hour reflective
assessment) data set was used for the primary analysis of the primary efficacy variable. The per
protocol (PP) population was the number of subjects in the mITT population with no major
protocol violations. The average TSS was computed using non-missing data only. A one-sided
and two sided 95% confidence interval of the treatment difference was derived using adjusted
(least squares) mean from the analysis of covariance model.
Secondary efficacy variables were the change from baseline in individual symptom score at
19:00 hours and 7:00 hours, the change in TSS at 7:00 hours, the daily individual symptom score and
the average daily symptom score during Week 1 and Week 2 of double-blind treatment. These
were analyzed using the same model as the primary efficacy variable on the mITT population.
In addition, the number of days with all individual 19:00 hours 12-hour reflective symptom score
absent or mild i.e. <2 (excluding nasal congestion scores) were analyzed using a Student test if
adequate transformation (for example square root) was applicable, or if not using Wilcoxon rank-
sum test.
The daily change from baseline in average 19:00 hours 12-hour reflective TSS was described.
The numbers of subjects with at least one treatment emergent adverse event were compared
between the treatment groups using Fisher’s exact test.
Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA)
Version 5.1.

Interim analysis
No interim analysis was performed for this study.

Results – Study subjects and conduct
A total of 1961 subjects were enrolled.

Table 1 – Numbers of subjects in analyses

<table>
<thead>
<tr>
<th>Population</th>
<th>Placebo</th>
<th>Fexofenadine HCl</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>471</td>
<td>466</td>
<td>937</td>
</tr>
<tr>
<td>Safety double-blind</td>
<td>471</td>
<td>464</td>
<td>935</td>
</tr>
<tr>
<td>mITT</td>
<td>469</td>
<td>463</td>
<td>932</td>
</tr>
<tr>
<td>PP</td>
<td>393</td>
<td>388</td>
<td>781</td>
</tr>
</tbody>
</table>

mITT = Modified intent-to-treat PP = Per protocol

Subjects in the mITT population had a median age of 9 years (mean 8.8 years; range 5–12 years).
Most subjects were white (80.5%), other races included multiracial (10.9%), black (7.2%) and
Asian/oriental (1.4%). There were no statistically significant differences between treatment
groups in pre-entry/entry characteristics apart from gender (p=0.0417). Median treatment duration
(15 days for each treatment group) and mean number of doses (fexofenadine HCl: 28.6;
placebo: 28.4) were also comparable between treatment groups in the mITT population.
Thirty-three subjects were withdrawn/discontinued from treatment during the double-blind period
(fexofenadine HCl: 18; placebo: 15) and 4 were withdrawn during the follow-up period
(fexofenadine HCl: 3; placebo: 1). Reasons included not randomized (2), without baseline TSS
(3), lack of efficacy (fexofenadine HCl: 3; placebo: 4), new or worsening of an existing adverse
event (fexofenadine HCl: 3), poor compliance (fexofenadine HCl: 1; placebo: 1), subject did not wish to continue (fexofenadine HCl: 1; placebo: 1), protocol violation (placebo: 1) and other reasons (fexofenadine HCl: 7; placebo: 6).

Results – Efficacy

Fexofenadine HCl was found to be significantly superior to placebo in the primary efficacy analysis (p=0.0001). The mean treatment difference was 0.73 in favor of fexofenadine for the change from baseline in average 19:00 hours 12-hour reflective TSS. The mean improvement from baseline was 1.94 for the fexofenadine HCl group and 1.21 for the placebo group.

Table 2 – Double-blind period assessment of TSS at 19:00 hours – modified intent-to-treat population

<table>
<thead>
<tr>
<th>Total Symptom Score (TSS) a (mean ± SE)</th>
<th>Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo N=469</td>
<td>Fexofenadine HCl N=463</td>
</tr>
<tr>
<td>Randomization baseline 7.07 ± 0.103</td>
<td>6.80 ± 0.097</td>
</tr>
<tr>
<td>Double-blind period 5.76 ± 0.134</td>
<td>4.85 ± 0.121</td>
</tr>
<tr>
<td>Change from baseline b -1.21 ± 0.100</td>
<td>-1.94 ± 0.101</td>
</tr>
</tbody>
</table>

F-P 95% CI Two sided p-value Two sided
-0.73 (-0.99, -0.46) 0.0001

a Only the average of complete sets of symptoms were computed
F-P = fexofenadine HCl minus placebo
b Least squares means (LS means) SE and p-value using the primary ANCOVA model

The mean percentage change from baseline for TSS at 19:00 hours during the double-blind period for the mITT population was –29.1% for fexofenadine HCl group and –19.5% for placebo group (p=0.0001), supporting the main analysis. The results for the PP population were similar to the results of the primary efficacy analysis and confirmed the robustness of this analysis.

Complementary and subgroup analyses did not identify any factors likely to significantly affect the efficacy of fexofenadine HCl, and in particular there was no effect of gender.

Fexofenadine HCl was superior to placebo for improvement in all component symptoms of the TSS, and nasal congestion, at 19:00 hours.
Table 3 – Double-blind period assessment of average 19:00 hours 12-hour individual reflective symptoms to show the change from baseline for each symptom – modified intent-to-treat population

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Change from Baseline (LS means ± SE) a</th>
<th>Treatment Difference</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=469</td>
<td>Fexofenadine HCl N=463</td>
<td>F-P Two sided</td>
<td>p-value</td>
</tr>
<tr>
<td>Sneezing</td>
<td>-0.27 ± 0.031</td>
<td>-0.49 ± 0.031</td>
<td>-0.23 (-0.31; -0.15)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>-0.34 ± 0.032</td>
<td>-0.49 ± 0.032</td>
<td>-0.15 (-0.24; -0.07)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Itchy nose, mouth, throat and/or ears*</td>
<td>-0.33 ± 0.031</td>
<td>-0.51 ± 0.031</td>
<td>-0.18 (-0.26; -0.10)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Itchy, watery, red eyes</td>
<td>-0.24 ± 0.031</td>
<td>-0.45 ± 0.031</td>
<td>-0.21 (-0.29; -0.13)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>-0.08 ± 0.029</td>
<td>-0.18 ± 0.030</td>
<td>-0.11 (-0.18; -0.03)</td>
<td>0.0079</td>
</tr>
</tbody>
</table>

a Least squares means (LS means) SE and p-value using the primary ANCOVA model
F-P = fexofenadine HCl minus placebo
* Corrected, error in original study report

All secondary efficacy analyses supported the results of the primary analysis, and consistently showed superiority of fexofenadine HCl over placebo. All individual symptoms contributing to the TSS, and the TSS itself, were statistically significant in favor of fexofenadine HCl for the 7:00 hours assessment. There was a statistically significant difference for Week 1 and Week 2 in favor of fexofenadine HCl in TSS at 19:00 and 7:00 hours and for each individual TSS symptom for the 19:00 hour assessments.

Efficacy was also consistently better with fexofenadine HCl on a day by day basis.

Results – Safety

Overall frequencies of treatment-emergent adverse events (TEAEs) are summarized below.

Table 4 – Number (%) subjects with TEAEs (safety-evaluable population)

<table>
<thead>
<tr>
<th>Type of TEAE</th>
<th>Placebo (N = 471)</th>
<th>Fexofenadine HCl 30 mg BID (N = 464)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>88 (18.7)</td>
<td>85 (18.3)</td>
</tr>
<tr>
<td>Serious</td>
<td>0 (0.0)</td>
<td>1* (0.2)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>0 (0.0)</td>
<td>3 (0.6)</td>
</tr>
</tbody>
</table>

* SAE possibly related to study medication, error in table in synopsis of original clinical study report

The numbers of subjects who reported at least one treatment-emergent adverse event were comparable in the fexofenadine HCl group and in the placebo group. The system organ class with the highest incidence of TEAEs was nervous system disorders. The most common TEAE was headache, and was reported in 23 (5.0%) of fexofenadine HCl subjects and 12 (2.5%) placebo subjects.
One (0.2%) subject in the fexofenadine HCl group and 0 (0.0%) subjects in the placebo group had serious TEAEs. Subject 1307/001 (fexofenadine HCl) reported a TEAE of leukopenia (verbatim term neutropenia: coded as leukopenia in HARTS, neutropenia in MedDRA), considered to be medically important and possibly related to study medication. However the subject was asymptomatic and alternative explanations could account for the event.

TEAEs leading to discontinuation were reported in 0.6% (3/464) of subjects receiving fexofenadine HCl and 0.0% (0/471) of subjects receiving placebo. The 3 discontinuations of study medication were due to TEAEs of asthma NOS (1), vomiting NOS (1) and upper respiratory infection viral NOS (1). These events were not reported as serious adverse events and none were considered by the investigator to be causally related to the study medication.

Predefined change abnormal for laboratory values was observed in 73/446 (16.4%) fexofenadine HCl compared with 70/460 (15.2%) placebo subjects. The most frequently observed abnormal change for both treatment groups was an increase in eosinophils.

Clinically noteworthy abnormal laboratory values for the double-blind safety population were observed in 108/935 (11.6%) subjects; fexofenadine HCl: 60 abnormal values in 59/464 (12.7%) subjects; placebo: 50 abnormal values in 49/471 (10.4%) subjects. The majority of these were for an increase in eosinophils in both treatment groups. Abnormal laboratory values in nine subjects were reported as treatment emergent adverse events by the investigators (fexofenadine HCl: 5; placebo: 4).

Predefined change abnormal for vital signs during the double-blind period were reported for 42/452 (9.3%) fexofenadine HCl subjects and 36/459 (7.8%) placebo subjects. The most commonly reported were changes in diastolic blood pressure, and the frequencies across treatment groups were similar. A decrease was reported in 11/451 (2.4%) fexofenadine HCl and 9/458 (2.0%) placebo subjects and an increase in 14/451 (3.1%) fexofenadine HCl and 10/458 (2.2%) placebo subjects.

The recoding of adverse events data in MedDRA did not change the safety profile of fexofenadine HCl, and the nature of adverse events reported remain consistent with those reported in the original study report.

**Conclusions**

- Fexofenadine HCl was found to be significantly superior to placebo in the treatment of SAR in children.
- In the primary efficacy analysis (mITT population) the mean treatment difference was 0.73 (p=0.0001) in favor of fexofenadine HCl for the primary efficacy variable i.e. change from baseline in average 12-hour reflective TSS at 19:00 hours.
- Efficacy of fexofenadine HCl was supported by secondary analyses and subgroup analyses.
- The efficacy demonstrated in this worldwide study, with varying climates, cultures and pollens, supports the robustness of the findings.
- Fexofenadine HCl was safe and well tolerated. The incidence of adverse events was similar for fexofenadine HCl and placebo and raised no safety concerns.
- The recoding of adverse event data did not change the safety profile of fexofenadine HCl.