SYNOPSIS

INN : FEXOFENADINE

Study number : PJPR0066 and PJPR0077

Study title : A Double-blind Randomized, Placebo-controlled Parallel Study Comparing the Efficacy and Safety of Three Dosage Strengths of Fexofenadine HCl (15, 30 and 60 mg BID) in Pediatric Patients (Ages 6 to 11 Years) in the Treatment of Seasonal Allergic Rhinitis

CSR date : 13 April 2004

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.
STUDY SYNOPSIS

Study number PJPR0066 and PJPR0077

Title
A double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of three dosage strengths of fexofenadine HCl (15, 30 and 60 mg BID) in pediatric patients (ages 6 to 11 years) in the treatment of seasonal allergic rhinitis

Study duration and dates
The first subject was enrolled on 8 August 1997 and the last subject completed the study on 29 November 1997.

Phase III

Objectives
The primary objective was to determine the efficacy and safety of fexofenadine HCl at 15 mg BID, 30 mg BID, and 60 mg BID compared to placebo in pediatric subjects 6 to 11 years of age in the treatment of seasonal allergic rhinitis (SAR).

Secondary objectives were to:
- characterize population pharmacokinetics of fexofenadine in pediatric SAR subjects
- assess the quality of life in pediatric subjects with SAR treated with fexofenadine HCl 15 mg BID, 30 mg BID, and 60 mg BID as compared to placebo BID.

Study design
This was a double-blind randomized, placebo-controlled, parallel study with a single-blind placebo lead-in, in pediatric subjects (ages 6 to 11 years) with fall SAR. Two identical studies (PJPR0066 and PJPR0077) were conducted separately. The results of these studies have been pooled for purposes of this report. The study included four visits. A 1-week placebo lead-in period preceded a 2-week double-blind treatment period. Subjects participated in the study a total of 18 to 25 days.

NOTE: The subject’s daily study participation was to be supervised by an adult throughout the entire study duration. This supervision could be provided by either the subject’s parent or another adult primary caregiver and was referred to hereafter as "caregiver." The caregiver was required to be present for all study visits. (Written informed consent to participate in the study was required from the subject’s parent or legal guardian.)

Subjects took study medication at 7 AM (± 1 hour) and 7 PM (± 1 hour) daily. Twice daily, immediately before taking study medication, SAR symptoms were assessed jointly by the subject and caregiver reflectively (for the previous 12-hour period) and instantaneously (for the previous 1-hour period).
SAR symptom scores were recorded for the following five symptoms:

- nasal congestion (stuffy nose)
- sneezing
- rhinorrhea (runny nose)
- itchy nose, mouth, throat and/or ears
- itchy, watery, red eyes.

Each symptom was evaluated using the following scale:

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent Symptom not present</td>
</tr>
<tr>
<td>1</td>
<td>Mild Symptom was present but was not annoying or bothersome</td>
</tr>
<tr>
<td>2</td>
<td>Moderate Symptom was annoying or bothersome but did not interfere with normal daily activity or sleep</td>
</tr>
<tr>
<td>3</td>
<td>Severe Symptom was annoying or bothersome and interfered somewhat with normal daily activity or sleep</td>
</tr>
<tr>
<td>4</td>
<td>Very Severe Symptom prevented normal daily activity or sleep</td>
</tr>
</tbody>
</table>

Note: Total Symptom Score (TSS) equaled the sum of individual symptom scores, excluding nasal congestion.

The primary analysis variable was the change in average daily 7 PM reflective TSS (average of 7 PM reflective TSS during the double-blind dosing period) from average baseline 7 PM reflective TSS (average of the 7 PM reflective TSS during the placebo lead-in period).

Secondary analysis variables were:

- Change from baseline in average 7 PM Reflective individual symptom scores
- Change from baseline in daily 7 PM Reflective TSS
- Change from baseline in average week one 7 PM Reflective TSS
- Change from baseline in average week two 7 PM Reflective TSS
- Change from baseline in average 7 PM Instantaneous TSS
- Change from baseline in average 7 AM Reflective TSS
- Change from baseline in average 7 AM Instantaneous TSS

Safety parameters were:

- adverse events
- pretreatment and posttreatment laboratory panels including serum chemistry and CBC with differential
- pretreatment and posttreatment 12-lead ECGs
- pretreatment and posttreatment physical exams.

Pregnant or lactating females were excluded from study entry.

Quality of life measures were assessed using the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ).

**Study drug administration**

At Visits 1, 2, and 3, study medication was supplied in unit dose cards. The week 1 placebo lead-in unit dose cards contained placebo for 7 days (14 doses). The week 2 and week 3 unit dose cards contained double-blind medication for 7 (plus 2 extra) days (18 doses). The caregiver was instructed to dispense to the subject 2 tablets at 7 AM (± 1 hour) and 2 tablets at 7 PM (± 1 hour).
daily. There were four treatment groups: placebo BID, fexofenadine HCl 15 mg BID, 30 mg BID, and 60 mg BID.

**Statistical methods**
Analysis of covariance (ANCOVA) was used to compare the effects of 15, 30, and 60 mg BID fexofenadine HCl and placebo. The primary efficacy parameter, change from baseline in average 7 PM reflective TSS over the 2-week double-blind treatment period, was included as the dependent variable. The ANCOVA model contained terms for investigative sites, treatment groups, and average baseline 7 PM reflective TSS as predictor variables. The baseline TSS was included as a continuous covariate.
The same statistical model used in the primary analysis (intent-to-treat analysis of the 7 PM reflective TSS) was used to analyze all secondary efficacy assessments. The intent-to-treat population was used for all secondary analyses. Some subjects may have been included in the intent-to-treat population but had missing secondary efficacy parameters. These missing data were not imputed (ie, subject was excluded from the intent-to-treat analysis of the secondary parameter for which data were missing).
Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 5.1.

**Pharmacokinetic methods**
Immediately after obtaining the ECG, at Visit 4 (Final Visit) or Early Discontinuation Visit, a blood sample was collected, processed and shipped to Hoechst Marion Roussel for measuring plasma fexofenadine concentration. The blood samples were collected 1 to 3 hours after the subject had taken the 7 AM dose of study medication.
At designated study sites, a blood sample was also collected for measuring plasma fexofenadine concentration at Visit 3 (Interim Visit) 6 to 11 hours after the subject had taken the 7 AM dose of study medication.

**Results – Study subjects and conduct**
A total of 877 subjects were randomized at 58 investigative sites. Of the 877 randomized, 875 were exposed to double-blind medication (two subjects discontinued before taking double-blind study medication). All 875 subjects exposed to double-blind medication had a postbaseline adverse event assessment, qualifying them as safety evaluable; this group was included in safety analyses. Of the 875 exposed, 872 subjects had both baseline and postbaseline 7 PM reflective symptom assessments; this group was used for Intent-to-Treat analysis of the primary efficacy variable. Of the 872 subjects in the Intent-to-Treat group, 711 had no major protocol violations and were included in the Protocol Correct group used for protocol correct analysis of the primary efficacy variable.

**Results – Efficacy**
Data from the individual protocols (PJPR0066 and PJPR0077) were pooled to form a combined dataset. Prior to pooling, analyses of the primary efficacy variable, 7 PM reflective TSS, were conducted on the individual protocols to assess the similarity of the results. These analyses revealed very different results; in PJPR0066, there were no differences found between any active dose and placebo, while in PJPR0077, each active dose was highly statistically superior to placebo.
After pooling the data, the primary (intent-to-treat) analysis of the 872 subjects indicated that there were overall no statistically significant differences between the four treatment groups (P=0.4043) and the test for dose response (linear trend) was not significant (P=0.1894). The change from baseline in the average 7 PM reflective TSS indicated a reduction in TSS for all treatment groups, including placebo. The greatest reduction was experienced by the 60 mg fexofenadine HCl group (-1.55), and the smallest by the placebo group (-1.21). All the fexofenadine HCl groups had a larger treatment effect than placebo; however, none of the dose groups were statistically superior to placebo when considering the overall 2 week double-blind treatment period, see Table 1. When considering weekly changes from baseline, all active treatment groups had a larger effect than the placebo group for both weeks. For week 1, all three active dose groups were statistically or marginally statistically significantly superior to the placebo group (P=0.0642, 0.0569 and 0.0286 for 15 mg, 30 mg and 60 mg, respectively). For week 2, however, this superiority was not statistically sustained for any of the three active dose groups.
### Table 1 – Summary of Efficacy Results - Analysis of Change from Baseline in 7 PM Reflective Total Symptom Score (TSS) Over the 2-Week Double-blind Treatment Period - Intent-to-Treat Subjects

<table>
<thead>
<tr>
<th>Treatment (BID)</th>
<th>N</th>
<th>Baseline</th>
<th>Double-blind Treatment Period</th>
<th>Change From Baseline*</th>
<th>P Value Comparison to Placebo*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>124</td>
<td>8.19 ± 0.221</td>
<td>6.68 ± 0.285</td>
<td>-1.59 ± 0.236</td>
<td>0.3559</td>
</tr>
<tr>
<td>Fexofenadine HCl 15 mg</td>
<td>118</td>
<td>7.90 ± 0.236</td>
<td>6.73 ± 0.285</td>
<td>-1.30 ± 0.248</td>
<td>0.0470</td>
</tr>
<tr>
<td>Fexofenadine HCl 30 mg</td>
<td>108</td>
<td>7.96 ± 0.226</td>
<td>6.53 ± 0.290</td>
<td>-1.53 ± 0.258</td>
<td>0.0464</td>
</tr>
<tr>
<td>Fexofenadine HCl 60 mg</td>
<td>111</td>
<td>7.75 ± 0.224</td>
<td>6.49 ± 0.293</td>
<td>-1.44 ± 0.256</td>
<td>0.0464</td>
</tr>
<tr>
<td>Overall Treatment Difference*</td>
<td>P value=0.8138</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear Trend Test*</td>
<td>P value=0.8467</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Placebo        | 105 | 7.87 ± 0.241 | 7.03 ± 0.241 | -0.84 ± 0.241 | 0.0023 |
| Fexofenadine HCl 15 mg | 105 | 7.50 ± 0.241 | 5.88 ± 0.277 | -1.83 ± 0.246 | 0.0138 |
| Fexofenadine HCl 30 mg | 100 | 7.58 ± 0.232 | 6.17 ± 0.298 | -1.65 ± 0.253 | 0.0064 |
| Fexofenadine HCl 60 mg | 101 | 7.66 ± 0.225 | 6.07 ± 0.277 | -1.73 ± 0.252 | 0.0064 |
| Overall Treatment Difference* | P value=0.0087 |
| Linear Trend Test* | P value=0.0318 |

| Placebo        | 229 | 8.04 ± 0.163 | 6.84 ± 0.190 | -1.21 ± 0.161 | 0.2197 |
| Fexofenadine HCl 15 mg | 223 | 7.72 ± 0.169 | 6.33 ± 0.201 | -1.49 ± 0.163 | 0.1585 |
| Fexofenadine HCl 30 mg | 208 | 7.78 ± 0.162 | 6.36 ± 0.208 | -1.54 ± 0.169 | 0.1416 |
| Fexofenadine HCl 60 mg | 212 | 7.71 ± 0.158 | 6.29 ± 0.203 | -1.55 ± 0.167 | 0.1416 |
| Overall Treatment Difference* | P value=0.4043 |
| Linear Trend Test* | P value=0.1894 |

* Adjusted means (least squares means), adjusted standard errors, and P values from an ANCOVA model containing site, treatment and baseline.

### Results – Safety

Of the 877 randomized subjects, 875 were exposed to study medication: 229 subjects received placebo, 224 subjects received fexofenadine HCl 15 mg BID, 209 received fexofenadine HCl 30 mg BID, and 213 received fexofenadine HCl 60 mg BID. Adverse events were reported with similar incidence in the treatment groups.

Overall frequencies of treatment-emergent adverse events (TEAEs) are summarized in Table 2 below.
Table 2 – Number (%) subjects with TEAEs (safety-evaluable population)

<table>
<thead>
<tr>
<th>Type of TEAE</th>
<th>Placebo</th>
<th>Fexofenadine HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 229)</td>
<td>15 mg (N = 224)</td>
</tr>
<tr>
<td>All</td>
<td>83 (36.2)</td>
<td>79 (35.3)</td>
</tr>
<tr>
<td>Serious</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>5 (2.2)</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

The system organ class with the highest incidence of TEAEs was nervous systems disorders. The most common TEAE was headache, and was reported in 56 (8.7%) fexofenadine HCl subjects and 17 (7.4%) placebo subjects.

There was one serious adverse event reported during the study. One subject in the 30 mg fexofenadine HCl group with a history of mild asthma/"reactive airways" was hospitalized for wheezing, shortness of breath, and chest tightness. Diagnosis was status asthmaticus with exposure to outdoor allergens as a contributing factor. The investigator assessed the event as severe and unlikely related to study drug.

TEAEs leading to discontinuation were reported in 0.8% (5/646) of subjects receiving fexofenadine HCl and 2.2% (5/229) of subjects receiving placebo. No specific TEAE or system organ class could clearly be identified as a major reason for discontinuation. None of the adverse events that resulted in discontinuation were attributed to study medication by the investigators.

Clinical laboratory, vital signs, and ECG results were similar in active and placebo groups. There was no statistically significant mean change from baseline in any ECG parameter after treatment with fexofenadine HCl, and the incidence of potentially clinically significant changes in ECG values based on Sponsor defined outlier criteria was similar in subjects receiving fexofenadine HCl and placebo.

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.

**Pharmacokinetics/pharmacodynamics**

Pharmacokinetics/pharmacodynamics are presented in a separate report (*Report K-98-0119-D*).

**Conclusions**

The results of the pooled studies suggested a difference between placebo and fexofenadine HCl (15 mg, 30 mg, and 60 mg) administered to pediatric subjects ages 6 to 11 years with seasonal allergic rhinitis, however this difference was not statistically significant over the two-week treatment period. Results from the weekly analysis of the pooled studies showed that the difference was statistically significant during the first week of treatment. Results from the analysis of the individual studies revealed that one of the studies, PJPR0077, demonstrated a statistically significant difference between each active dose vs placebo over the entire 2 week treatment period, with 15 mg showing the largest treatment effect. The other study, PJPR0066, showed no
statistically significant differences between treatments. All doses of fexofenadine HCl were safe and well tolerated.

The recoding of adverse event data did not change the safety profile of fexofenadine HCl.