INN: FEXOFENADINE

Study number: M016455B/3081

Study title: A Double-Blind, Randomized, Placebo-Controlled, Parallel Study Comparing the Efficacy and Safety of Fexofenadine HCL 120 mg and 180 mg QD in the Treatment of Autumn 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.

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  M016455B/3081 (PJPR0081)

Title
A double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of fexofenadine HCl 120 mg and 180 mg QD in the treatment of autumn seasonal allergic rhinitis

Investigator(s), study site(s)
See Appendix C of original Clinical Study Report K-98-0040-C.

Study duration and dates
The first subject was enrolled on 7 August 1997 and the last subject completed the study on 21 November 1997.

Phase  III

Objectives
The primary objective was to determine the efficacy and safety of fexofenadine HCl 120 mg QD and 180 mg QD compared to placebo in the treatment of autumn seasonal allergic rhinitis (SAR).

A secondary objective was to characterize the population pharmacokinetics of fexofenadine HCl QD in SAR subjects.

Study design
This was a double-blind, randomized, placebo-controlled, parallel study with a 1-week placebo lead-in period followed by a 2-week double-blind treatment period. Subjects participated in the study a total of 16-26 days.

Subjects took study medication at 8 AM (± 1 hour) daily. Immediately before taking study medication, SAR symptoms were assessed and recorded in the daily symptom diary by the subject reflectively (for the previous 12 hours) and instantaneously (for the previous 1-hour).

Additionally, subjects assessed SAR symptoms reflectively (for the previous 12 hours) at 8 PM (± 1 hour) daily.

Subjects rated the severity of the following five symptoms:
- Nasal congestion (nasal stuffiness)
- Sneezing
- Rhinorrhea (runny nose)
- Itchy nose, mouth, throat and/or ears
- Itchy, watery, red eyes.

Each symptom was evaluated by the subject using the following scale:
0  Absent - Symptom not present
1  Mild - Symptom was present but was not annoying or troublesome
2  Moderate - Symptom was frequently troublesome but did not interfere with either normal daily activity or sleep
3 Severe - Symptom was sufficiently troublesome to interfere with normal daily activity or sleep.
4 Very Severe - Symptom was so severe as to warrant an immediate visit to the physician.

A total symptom score (TSS) was calculated by adding the individual symptom scores, excluding nasal congestion (nasal stuffiness). Nasal congestion was not included in the TSS because relief of nasal congestion was not expected with an H1-antagonist.

**Study drug administration**

Study medication was supplied in unit dose cards at Visits 1, 2 and 3. The week 1 placebo lead-in unit dose card contained medication for 7 days (plus one extra dose). The week 2 and week 3 unit dose cards contained double-blind medication for 9 (plus one extra dose) days. Subjects were instructed to take two tablets of study medication at 8 AM (± 1 hour) daily. Three treatment groups were used: placebo QD, fexofenadine HCl 120 mg QD, and fexofenadine HCl 180 mg QD.

**Efficacy measures**

The primary analysis variable was the change from baseline in average 8 AM instantaneous TSS over the 2-week double-blind treatment period.

To assess the treatment effect of fexofenadine HCl for the entire 24-hour period after each dosing, a 24-hour reflective assessment was calculated daily as the average of the 8 AM and 8 PM reflective assessments.

Secondary analysis variables were as follows:

- Change from baseline in average 24-hour reflective TSS over the 2-week double-blind treatment period.
- Change from baseline in average 8 AM 12-hour reflective TSS over the 2-week double-blind treatment period.
- Change from baseline in average 8 PM 12-hour reflective TSS over the 2-week double-blind treatment period.
- Change from baseline in average individual 24-hour reflective symptom scores over the 2-week double-blind treatment period.
- Change in baseline in average individual 8 AM instantaneous symptom scores over the 2-week double-blind treatment period.
- Change from baseline week 1 average 24-hour reflective TSS.
- Change from baseline week 2 average 24-hour reflective TSS.
- Change from baseline week 1 average 8 AM instantaneous TSS.
- Change from baseline week 2 average 8 AM instantaneous TSS.

For more details, refer to *Statistical Analysis Plan* in *Appendix E1 (Analysis Plan)* of original *Clinical Study Report K-98-0040-C*.

**Safety measures**

Safety parameters included physical examinations, vital signs, adverse events, and laboratory tests.
Pharmacokinetic measures
Population pharmacokinetic parameters were determined by plasma samples taken at Visit 3, at a variable time after dosing, and at Visit 4 at trough.

Statistical methods
An ANCOVA model with baseline 8 AM instantaneous TSS as a covariate and investigative site and treatment as predictor variables was used to analyze the primary efficacy parameter, change from baseline in the 8 AM instantaneous TSS. The primary analysis was performed using the Intent-to-treat population. Similar statistical models and the Intent-to-treat population were used for all secondary efficacy variables. The treatment effect on the primary efficacy parameter was also examined in population subgroups by investigative site, demographic characteristics (age, weight, race, and gender) and the level of subject's baseline symptoms.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 5.1.

Interim analysis
No interim analysis was planned or conducted for this study.

Results – Study subjects and conduct
A total of 1758 subjects were screened at 40 investigative sites. (One subject was screened twice in error.) Of those screened, 864 were exposed to double-blind medication (511 subjects discontinued before taking double-blind study medication and 383 were screening failures). Eight hundred sixty-three 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 864 exposed, 861 subjects had both baseline and postbaseline 8 AM instantaneous symptom assessments; this group was used for Intent-to-treat analysis of the primary efficacy variable. Of the 861 subjects in the Intent-to-treat group, 775 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
The primary efficacy parameter was change from baseline in average 8 AM instantaneous TSS. Results of the Intent-to-treat analysis are summarized in Table T1.

There was a statistically significant overall difference among the three treatment groups (P=0.0060). Fexofenadine HCl 180 mg showed statistically significant improvement over placebo (P=0.0016). The comparison of the 120 mg dose vs. placebo was marginally statistically significant (P=0.0505).

Similar results were observed in the supportive protocol-correct analysis of the primary efficacy parameter. The size of the treatment effect of the active doses was comparable to the Intent-to-treat analysis although fexofenadine 120 mg lost statistical significance compared to placebo. The results of the individual 8 AM instantaneous symptoms were consistent with those observed for TSS.
Table 1 – Intent-to-treat Analysis of 8 AM Instantaneous TSS (N=861)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline Mean±SE</th>
<th>Double Blind Period Mean±SE</th>
<th>Change from Baseline Mean±SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>292</td>
<td>7.61 ± 0.10</td>
<td>6.78 ± 0.13</td>
<td>-0.87 ± 0.11</td>
</tr>
<tr>
<td>Fex HCl 120 mg</td>
<td>287</td>
<td>7.72 ± 0.10</td>
<td>6.54 ± 0.14</td>
<td>-1.17 ± 0.11</td>
</tr>
<tr>
<td>Fex HCl 180 mg</td>
<td>282</td>
<td>7.69 ± 0.11</td>
<td>6.34 ± 0.14</td>
<td>-1.36 ± 0.11</td>
</tr>
</tbody>
</table>

Treatment Comparison

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Mean Difference Mean±SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fex HCl 120 mg vs Placebo</td>
<td>-0.30 ± 0.15</td>
<td>0.0505</td>
</tr>
<tr>
<td>Fex HCl 180 mg vs Placebo</td>
<td>-0.49 ± 0.16</td>
<td>0.0016</td>
</tr>
<tr>
<td>Fex HCl 120 mg vs 180 mg</td>
<td>0.19 ± 0.16</td>
<td>0.2227</td>
</tr>
</tbody>
</table>

Model Effects:
- Baseline: P value=0.0001
- Treatment: P value=0.0060
- Site: P value=0.0001

Results – Safety

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

Table 2 – Number (%) subjects with TEAEs (safety-evaluable population)

<table>
<thead>
<tr>
<th>Type of TEAE</th>
<th>No. (%) of subjects in treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 293)</td>
</tr>
<tr>
<td></td>
<td>120 mg (N = 287)</td>
</tr>
<tr>
<td>All</td>
<td>88 (30.0)</td>
</tr>
<tr>
<td>Serious</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>4 (1.4)</td>
</tr>
</tbody>
</table>

The system organ class with the highest incidence of TEAEs was nervous system disorders. The most common TEAE was headache, and was reported in 50 (8.8%) fexofenadine HCl subjects [21(7.3%) fexofenadine HCl 120 mg and 29 (10.2%) fexofenadine HCl 180 mg] and 21 (7.2%) placebo subjects.

Following the current ICH guidelines for reporting of serious TEAEs, 1 (0.2%) subject in the fexofenadine HCl (0.3% in fexofenadine HCl 120 mg group) and 1 (0.3%) subject in the placebo group had serious TEAEs. One subject receiving placebo was hospitalized with kidney stones and one subject who had completed the study on fexofenadine HCl 120 mg went to the emergency room with shortness of breath 36 hours after the last dose of study medication. There were no deaths.
TEAEs leading to discontinuation were reported in 1.2% (7/570) of subjects receiving fexofenadine HCl (all subjects fexofenadine HCl 180 mg) and 1.4% (4/293) of subjects receiving placebo. The most common TEAE leading to discontinuation was sinusitis NOS, which was reported in 0.5% (3/570) of subjects receiving fexofenadine HCl and 0.0% (0/293) subjects receiving placebo. The frequencies for other specific TEAEs leading to discontinuation of study medication were only 1 or 2 subjects in each treatment group. No specific TEAE or system organ class could clearly be identified as a major reason for discontinuation.

Vital sign results were similar in active and placebo groups; no subject was discontinued from the study as a result of clinical laboratory or vital sign safety evaluations.

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.

Results – Pharmacokinetics/pharmacodynamics

The pharmacokinetic and pharmacodynamic data for this study are presented in a separate report (K-98-0093-D).

Conclusions

The results of this study demonstrate that fexofenadine HCl is well tolerated and effective at doses of 120 mg and 180 mg QD in the treatment of (autumnal) SAR.

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