SYNOPSIS

INN: FEXOFENADINE

Study number: PJPR0032

Study title: A double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of two dosage strengths of fexofenadine hydrochloride (120, and 180 mg once a day) versus cetirizine (10 mg once a day) in the treatment of seasonal allergic rhinitis (SAR)

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

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Title
A double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of two dosage strengths of fexofenadine hydrochloride (120, and 180 mg once a day) versus cetirizine (10 mg once a day) in the treatment of seasonal allergic rhinitis (SAR)

Investigator(s), study site(s)
See Appendix C of original Clinical Study Report K-96-0284-C.

Study duration and dates
The first subject was enrolled in May 1995 and the last subject completed the study in January 1996.

Objectives
The primary objective of the study was:
1. To examine the efficacy of once-a-day dosing of fexofenadine hydrochloride (120 mg vs 180 mg vs placebo) in seasonal allergic rhinitis (SAR).

The secondary objectives were:
1. To determine its duration of action over 24 hours,
2. To determine its onset of action,
3. To verify its non-sedative profile,
4. To compare efficacy/safety with cetirizine 10 mg once daily.

Study design
This was a double-blind, randomized, placebo-controlled, parallel study with a single-blind placebo lead-in, in subjects with pollen SAR. The study consisted of four visits. Subjects participated in the study for a total of 19 days.

Subjects took study medication at 8:00 AM (1 ± hour). They assessed their SAR daily symptoms at 8.00 AM ± 1 hour, immediately before taking study medication, reflectively for the previous 12-hour period, and instantaneously for the previous 30 minute period. Additionally, they assessed their symptoms in the evening, prior to bedtime reflectively for the previous 12-hour period.

The following five symptoms were assessed by the subject:
- nasal congestion
- sneezing
- rhinorrhea
- itchy nose, palate, and/or throat
- itchy, watery or red eyes.
Each symptom was evaluated by the subject on the following scale:

0  Absent - Symptom not present.
1  Mild - Symptom is present but is not annoying or troublesome.
2  Moderate - Symptom is frequently troublesome, but does not interfere with either normal daily activity or sleep.
3  Severe - Symptom is sufficiently troublesome to interfere with normal daily activity or sleep.
4  Very Severe - Symptom is so severe as to warrant an immediate visit to the physician.

The total symptom score (TSS) was calculated by adding the individual symptom scores, excluding nasal congestion. Nasal congestion was not included in the TSS because relief of nasal congestion was not expected with an H1-antagonist. The 24 hour reflective TSS was calculated by averaging the reflective TSS of the previous night and the reflective TSS for the previous day.

Additionally subjects recorded the time at which they first noticed an improvement of the condition on the first day of dosing during the double-blind study period.

The primary analysis variable was:

1. The change in the average 24 hour reflective TSS (average of daily 24 hour reflective TSS during the double-blind treatment period) from average baseline 24 hour reflective TSS (average of daily 24 hour reflective TSS during the placebo lead-in period) for the duration of the study.

Secondary analysis variables were:

2. Daily 24 hour reflective TSS. Change in the daily and average weekly 24 hour reflective TSS from the average baseline 24 hour reflective TSS.

3. The change in the average trough instantaneous TSS (average of daily trough instantaneous TSS during the double-blind treatment period) from average baseline trough instantaneous TSS (average of daily trough instantaneous TSS during the placebo lead-in period) for the duration of the study.

4. The change in the daily trough instantaneous TSS from the average baseline trough instantaneous TSS (weeks 2 and 3, daily).

5. The onset of action: time on the first day of medication that subject feels improvement of condition (as recorded on the diary card at week 2, day 2 (pm).)

6. The subject's assessment of overall study drug effectiveness using a visual analogue scale.

7. The physician's overall assessment of effectiveness using a 5-point rating scale (0-4).

8. The change in average somnolence (average of daily visual analogue scale scores for somnolence during the double-blind treatment period) from average baseline somnolence (average visual analogue scale score during the placebo lead-in period).

Safety parameters included physical examinations, vital signs, subject's assessment of somnolence, adverse events and haematology, serum chemistry and urinalysis.

**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 card contained medication for 5 days (15 capsules for 5 doses). The Week 2 and Week 3 unit dose cards each contained double-blind medication for 9 days (27 capsules for
9 doses). Subjects were instructed to take 3 capsules at 8:00 AM (± 1 hour) half an hour before breakfast. Four treatment groups were used:

- Placebo once a day,
- Fexofenadine hydrochloride 120 mg once a day,
- Fexofenadine hydrochloride 180 mg once a day,
- Cetirizine 10 mg once a day.

**Statistical methods**

The primary efficacy measure, change in the average 24 hour reflective TSS from average baseline, was analysed using an ANCOVA model. Investigative site, treatment, and average baseline TSS were included as independent variables. The same statistical model used in the primary analysis was used to analyse all secondary measures, except for:

- Improvement in 24 hour reflective TSS (AM and PM TSS)
- Physician overall assessment of effectiveness

both of which were analysed using the Mantel-Haenszel method, stratifying on investigative site.

Change in average somnolence was assessed using a rank ANCOVA model (ANCOVA after ranking baseline and change from baseline). Investigative site, treatment, and (rank) average baseline somnolence were included as independent variables. Subject assessment of overall study drug effectiveness visual analogue scale (VAS) was assessed using a rank ANOVA model (ANOVA after ranking dependent variable). Investigative site and treatment were included as independent variables.

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

**Interim analysis**

No interim analysis was planned or performed for this study.

**Results – Study subjects and conduct**

A total of 842 subjects were randomized at 49 investigative sites. Of the 842 randomized, 839 subjects were exposed to double-blind medication (3 subjects discontinued before taking study medication). All 839 subjects were included in the safety analyses. Of these safety subjects 722 completed the study. A further 18 subjects were excluded from the intent to treat (ITT) population as they had no 24 hour reflective baseline or post-baseline TSS, leaving 821 in the ITT population. Of the 821 ITT subjects, 765 had no major protocol violations and were classified as protocol correct.

**Results – Efficacy**

**Primary Efficacy Analysis.** The primary efficacy parameter was an ITT analysis of subject's change in 24 hour reflective TSS. This analysis included all subjects who had both a baseline and post-baseline evaluation of 24 hour reflective TSS. Results of the ITT analysis are summarized in Table 1. Statistically significant differences were observed among the four treatment groups (p=0.0001). The active treatments were statistically significantly superior to placebo in the reduction of TSS (p=0.0001 for all active treatments).

A secondary analysis using 765 subjects with no major protocol violations (Protocol Correct Subjects) was performed. All active comparisons produced greater reduction in TSS than placebo, which was consistent with the results of the ITT analysis.
Table 1 – 24 hour Reflective TSS (Intent-to-Treat) N=821

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline</th>
<th>Double-blind Period</th>
<th>Change from baseline**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>201</td>
<td>7.3 ± 0.1</td>
<td>5.8 ± 0.2</td>
<td>-1.9 ± 0.2</td>
</tr>
<tr>
<td>120mg Fex</td>
<td>211</td>
<td>7.2 ± 0.1</td>
<td>4.7 ± 0.2</td>
<td>-3.0 ± 0.2</td>
</tr>
<tr>
<td>180mg Fex</td>
<td>202</td>
<td>7.4 ± 0.1</td>
<td>4.5 ± 0.2</td>
<td>-3.3 ± 0.2</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>207</td>
<td>7.3 ± 0.1</td>
<td>4.4 ± 0.2</td>
<td>-3.3 ± 0.2</td>
</tr>
</tbody>
</table>

Treatment Comparison
(Change from Baseline)

<table>
<thead>
<tr>
<th>Mean ± SE**</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Difference</td>
<td>.0001</td>
</tr>
<tr>
<td>Combined Fex vs Placebo</td>
<td>-1.2 ± 0.2</td>
</tr>
</tbody>
</table>

Pairwise Comparison

<table>
<thead>
<tr>
<th>Mean ± SE**</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>120mg Fex vs Placebo</td>
<td>-1.1 ± 0.2</td>
</tr>
<tr>
<td>180mg Fex vs Placebo</td>
<td>-1.4 ± 0.2</td>
</tr>
<tr>
<td>Cetirizine vs Placebo</td>
<td>-1.4 ± 0.2</td>
</tr>
<tr>
<td>180mg Fex vs 120mg Fex</td>
<td>-0.3 ± 0.2</td>
</tr>
<tr>
<td>Cetirizine vs 120mg Fex</td>
<td>-0.3 ± 0.2</td>
</tr>
<tr>
<td>Cetirizine vs 180mg Fex</td>
<td>-0.0 ± 0.2</td>
</tr>
</tbody>
</table>

* P-Value from an ANCOVA model containing investigative site, treatment and baseline.
** Means (least square means) and SEs from an ANCOVA model containing investigative site, treatment and baseline.

Secondary Efficacy Analyses. All secondary efficacy parameters relating to the symptoms of SAR showed statistically significant improvements for active treatments compared to placebo. Subgroup analysis confirmed that there were no interactions either by baseline characteristics, investigative site or country. Comparison with cetirizine showed no statistically significant difference between cetirizine and either dose of fexofenadine in 24 hour reflective TSS.

The change in average somnolence as measured by a visual analogue scale showed no overall statistically significant difference.
Results – Safety

Overall frequencies of treatment-emergent adverse events (TEAEs) are summarized in Table 2 below.

<table>
<thead>
<tr>
<th>Type of TEAE</th>
<th>Number (%) of subjects in treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 209)</td>
</tr>
<tr>
<td>All</td>
<td>82 (39.2)</td>
</tr>
<tr>
<td>Serious</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>4 (1.9)</td>
</tr>
</tbody>
</table>

The system organ class with the highest incidence of TEAEs was nervous system disorders. The most common TEAEs in all 4 treatment groups were headache and somnolence. Headache was reported in 12.4% (52/421) of subjects receiving fexofenadine HCl, 11.5% (24/209) of subjects receiving placebo, and 14.4% (30/209) of subjects receiving cetirizine. Somnolence was reported in 4.5% (19/421) of subjects receiving fexofenadine HCl, 4.3% (9/209) of subjects receiving placebo, and 7.2% (15/209) of subjects receiving cetirizine.

Serious TEAEs were reported in 2 (0.5%) subjects receiving fexofenadine HCl, in 0 (0.0%) subjects receiving placebo, and 0 (0.0%) of subjects receiving cetirizine.

TEAEs leading to discontinuation were reported in 2.1% (9/421) of subjects receiving fexofenadine HCl, 1.9% (4/209) of subjects receiving placebo, and 1.0% (2/209) of subjects receiving cetirizine.

There were no deaths. There was no apparent relationship between incidence of adverse events and dose of fexofenadine.

Clinical laboratory and vital sign results were similar in active and placebo groups.

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

Seven hundred and sixty five subjects with seasonal allergic rhinitis were classified as protocol correct in this double-blind, randomized, placebo controlled parallel study comparing the efficacy and safety of two dosage strengths of fexofenadine hydrochloride and cetirizine given once a day. The results of this study demonstrate that fexofenadine at doses of 120 mg and 180 mg once daily is superior to placebo in the treatment of seasonal allergic rhinitis. There were no differences in efficacy between the two doses of fexofenadine or between either dose of fexofenadine and cetirizine.

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