SYNOPSIS

INN : FEXOFENADINE

Study number : PJPR0039

Study title : A multicenter, double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of four dosage strengths of fexofenadine HCl (20, 60, 120, & 240 mg BID) in the treatment of chronic idiopathic urticaria

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 PJPR0039

Title
A multicenter, double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of four dosage strengths of fexofenadine HCl (20, 60, 120, & 240 mg BID) in the treatment of chronic idiopathic urticaria

Study duration and dates
The first subject was enrolled on 20 November 1996 and the last subject completed the study on 16 June 1997.

Objectives
The primary objective was to determine the efficacy and safety of fexofenadine HCl at oral doses of 20 mg BID, 60 mg BID, 120 mg BID, and 240 mg BID compared to placebo in the treatment of chronic idiopathic urticaria (CIU).
Secondary objectives were to:
− assess the pharmacokinetics of fexofenadine using population analyses
− assess the quality of life and work and classroom productivity in subjects with CIU treated with fexofenadine HCl 20 mg BID, 60 mg BID, 120 mg BID, and 240 mg BID as compared to placebo

Study design
This was a multicenter, double-blind, randomized, placebo-controlled, parallel study with a 24-hour single-blind placebo lead-in in subjects with CIU in the United States and Canada. Approximately 400 subjects 12 to 65 years of age, inclusive, were to be included in the study at a total of approximately 35 investigative sites. The study consisted of three or four visits. Subjects participated in the study for 4 to 6 weeks.
Subjects took study medication at 7:00 AM (±1 hour) and 7:00 PM (±1 hour) daily. Subjects assessed their urticaria symptoms reflectively (over the previous 12 hours) and recorded them in a daily diary prior to each dose of study medication. The following four symptoms were assessed by the subject:
− number of wheals (hives)
− pruritus
− interference with sleep (AM only)
− interference with activities of daily living (PM only)

Visit 1
At visit 1 subjects were screened for entry into the study. A medical history was obtained. Subjects were required to meet the following criteria:
a. history of CIU (diagnosis made or confirmed by the investigator and documented in the CRF)

b. history of wheals (hives) at least 3 days per week for the 6 consecutive weeks prior to visit 1

Subjects meeting a. and b. above were instructed to assess their urticaria symptoms by reflecting over the previous 12 hours. In order to qualify for randomization to double-blind study medication, the subjects' assessments must have reflected:

c. presence of at least one wheal (hive), confirmed by the investigator, with a score of 1 or greater

d. pruritus rated by the subject as moderate or greater (a score of 2 or greater)

Note: The sum of the scores from the subjects' assessments of number of wheals (hives) and severity of pruritus became the total symptom score (TSS), which must have been equal to 3 or greater. The investigator was instructed not to advise subjects of qualifications requirements at any time.

Subjects meeting entrance criteria were qualified for randomization. Subjects were given study medication and instructed to take their first dose of study medication at 7:00 PM (±1 hour) the evening of visit 1, and to continue dosing at 7:00 AM (±1 hour) and 7:00 PM (±1 hour) daily during the 2-week treatment period. Subjects were instructed to document all concomitant medications and any adverse events they experienced during the treatment period. Subjects were asked to complete the quality of life and work and classroom productivity questionnaires after randomization and prior to leaving the office.

Subjects who met all entrance criteria with the exception of c and/or d listed above, or those who used proscribed medications, may have been given another opportunity to qualify for entry into the study by returning for visit 1A for reassessment 24 hours to 14 days after visit 1 (see below).

Visit 1A (Second Opportunity to Qualify)

Subjects underwent physical examination and had medical and medication histories updated. Urine pregnancy tests were required of all females, and blood and urine samples for clinical laboratory and drugs of abuse tests were obtained. Subjects continuing to meet all entrance criteria based on these assessments, and also meeting the additional entrance criteria listed in visit 1 above were randomized, given study medication, and proceeded as indicated in visit 1 above. Subjects not meeting all entrance criteria were dismissed.

Visit 2

At this visit, following 15 (±2) days of treatment, subjects' unit dose cards were collected and compliance was assessed. Daily diaries were collected and reviewed for completeness (adverse events and concomitant medication were recorded on the appropriate pages of the CRF). Investigator assessments of urticarial wheals (hives) were performed. A blood sample was drawn for random measurement of plasma fexofenadine; the time of last dose of study medication and the time of the blood draw were recorded on the CRF. Subjects were issued the unit dose cards and daily diaries for the next treatment period. Subjects were asked to complete the quality of life and work and classroom productivity questionnaires.

Final Visit (or Early Termination)

At the final visit (following 30 [±4] days of treatment) or early termination visit, subjects' unit dose cards were collected and compliance was assessed. Daily diaries were collected and
reviewed for completeness (adverse events and concomitant medications were recorded on the appropriate pages of the CRF). Subjects underwent a physical examination, including assessment of their urticarial wheals (hives) by the investigator, and had blood samples drawn for clinical laboratory tests (including a blood draw for fexofenadine levels). All females were to have a urine pregnancy test performed. Subjects were asked to complete the quality of life and work and classroom productivity questionnaires and were dismissed from the study.

Subjects who discontinued the study due to intolerable symptoms were encouraged to return to the study site for their early termination visit before proscribed medications were taken. Any subjects contacting the site to discontinue the study due to intolerable symptoms (including those subjects likely to take proscribed medications prior to the early termination visit) were asked to document their assessment of symptoms at that time on their diary at the next available entry, either AM or PM, prior to taking any proscribed medication. If the proscribed medication had already been taken, the subject was instructed to conduct their symptoms assessments only up to the time that proscribed medication was taken.

**Study drug administration**

At visits 1 (or 1A) and 2, study medication was supplied in unit dose cards. Unit dose cards (two cards for each 2-week treatment period) contained medication for a total of 15 days plus 2 additional days (136 tablets) for each treatment period. The first unit dose card (Card 1) contained single-blind placebo tablets for the first 24 hours (two doses). The remainder of study medication in this card and the study medication in Cards 2, 3, and 4 consisted of one of the five double-blind treatments: placebo BID, fexofenadine HCl 20 mg BID, fexofenadine HCl 60 mg BID, fexofenadine 120 mg BID, and fexofenadine HCl 240 mg BID. Subjects were instructed to take 4 tablets at 7:00 AM (±1 hour) and 7:00 PM (±1 hour) daily.

**Statistical methods**

In general, continuous variables were summarized by descriptive statistics (n, mean, standard deviation, and range); categorical variables were summarized in contingency tables (frequency and percentage in each category).

All statistical tests were two-sided, and differences resulting in P values less than 0.05 were considered statistically significant.

The analysis of the primary efficacy parameter used an ANCOVA model, adjusting for baseline, treatment, investigative site, and baseline by treatment interaction. All treatment comparisons were estimated at the average baseline score. All secondary analyses were performed using the model from the primary analysis.

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

**Results – Study subjects and conduct**

A total of 468 subjects were randomized to study medication at 37 investigative sites; of these, 449 were exposed to study medication. Of the 449 exposed subjects, 437 had at least one postbaseline adverse event assessment, qualifying them as safety evaluable. Four hundred eighteen subjects had both baseline and postbaseline pruritus scores and were included in the intent-to-treat population, while 261 subjects were included in the protocol-correct population.
Results – Efficacy

The primary assessment of efficacy was the change from baseline in mean pruritus score (MPS) over the 4-week treatment period for the intent-to-treat population. The intent-to-treat population consisted of randomized subjects with both baseline and postbaseline MPS data. Of the 468 randomized subjects, 418 (89%) were included in the intent-to-treat population.

There were statistically significant differences among the five treatment groups with respect to mean change from baseline MPS over the 4-week treatment period (P=0.0001), and the test for dose response (linear trend) was also statistically significant (P=0.0001). All four fexofenadine HCl dose groups were statistically superior to placebo (P ≤ 0.0098). There was a larger reduction from baseline in the 60 mg group (-1.00 units) compared to the 20 mg group (-0.68 units). However, similar reductions were seen in the 60 mg, 120 mg, and 240 mg groups (-1.00, -0.84, and -1.08 units, respectively). Table 1 summarizes the key findings of the intent-to-treat analyses of MPS along with two other most important secondary variables MNW and MTSS.

Table 1 – Change from Baseline in Subject’s Daily Symptom Assessment Over the 4-week Treatment Period - Intent-to-Treat Subjects

<table>
<thead>
<tr>
<th></th>
<th>Placebo BID</th>
<th>Fexofenadine HCl BID</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mg</td>
<td>60 mg</td>
<td>120 mg</td>
</tr>
<tr>
<td>MPS (N=418)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>79</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Mean*</td>
<td>-0.40</td>
<td>-0.68</td>
<td>-1.00</td>
</tr>
<tr>
<td>SE*</td>
<td>0.082</td>
<td>0.076</td>
<td>0.075</td>
</tr>
<tr>
<td>P value**</td>
<td>--</td>
<td>0.0098</td>
<td>0.0001</td>
</tr>
<tr>
<td>MNW (N=414)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>79</td>
<td>89</td>
<td>87</td>
</tr>
<tr>
<td>Mean*</td>
<td>-0.47</td>
<td>-0.86</td>
<td>-1.20</td>
</tr>
<tr>
<td>SE*</td>
<td>0.114</td>
<td>0.105</td>
<td>0.107</td>
</tr>
<tr>
<td>P value**</td>
<td>--</td>
<td>0.0115</td>
<td>0.0001</td>
</tr>
<tr>
<td>MTSS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>79</td>
<td>89</td>
<td>87</td>
</tr>
<tr>
<td>Mean*</td>
<td>-0.89</td>
<td>-1.53</td>
<td>-2.19</td>
</tr>
<tr>
<td>SE*</td>
<td>0.189</td>
<td>0.174</td>
<td>0.176</td>
</tr>
<tr>
<td>P value**</td>
<td>--</td>
<td>0.0109</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* P values, adjusted means (LSMEANS), and adjusted standard errors are from an ANCOVA model with baseline, treatment, site, and treatment-by-baseline interaction for the overall changes from baseline.

** P values are from the above ANCOVA and for comparing fexofenadine HCl dose and placebo. Treatment comparisons are performed at the average baseline score.

Results – Safety

A total of 449 subjects were randomized and exposed to study medication: 89 received placebo BID, 92 received fexofenadine HCl 20 mg BID, 100 received fexofenadine HCl 60 mg BID, 81 received fexofenadine HCl 120 mg BID, and 87 received fexofenadine HCl 240 mg BID.
Overall frequencies of treatment-emergent adverse events (TEAEs) are summarized in Table 2 below.

<table>
<thead>
<tr>
<th>Type of TEAE</th>
<th>Placebo (N = 85)</th>
<th>20 mg (N = 92)</th>
<th>60 mg (N = 97)</th>
<th>120 mg (N = 79)</th>
<th>240 mg (N = 84)</th>
<th>Total (N = 352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>44 (51.8)</td>
<td>57 (62.0)</td>
<td>57 (58.8)</td>
<td>48 (60.8)</td>
<td>52 (61.9)</td>
<td>214 (60.8)</td>
</tr>
<tr>
<td>Serious</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>2 (2.4)</td>
<td>4 (4.3)</td>
<td>5 (5.2)</td>
<td>4 (5.1)</td>
<td>1 (1.2)</td>
<td>14 (4.0)</td>
</tr>
</tbody>
</table>

Tables Table T1, Table T2, and Table T3

Adverse events were reported with similar incidence in the treatment groups. The system organ class with the highest incidence of TEAEs was nervous system disorders. The most common TEAE was headache, and was reported in 25.0% (88/352) of subjects receiving fexofenadine HCl and 20.0% (17/85) of subjects receiving placebo.

Following the current ICH guidelines for reporting of serious TEAEs, 2 (0.6%) subjects in the fexofenadine HCl group and 0 (0.0%) subjects in the placebo group had serious TEAEs. Breast cancer was reported for one subject in the fexofenadine 60 mg BID group; the investigator assessed the event as not related to study medication. One subject in the fexofenadine HCl 20 mg BID group was hospitalized for severe headaches; the investigator assessed the event as unlikely related to study medication. There was one pregnancy reported during the study. (Duration of subject’s exposure to study drug is unknown.)

TEAEs leading to discontinuation were reported in 14 (4.0%) subjects receiving fexofenadine HCl and 2 (2.4%) subjects receiving placebo. The most common TEAE leading to discontinuation was headache, which was reported in 3 (0.9%) subjects in the pooled fexofenadine HCl group and 0 (0.0%) subjects in the placebo group. All other TEAEs leading to discontinuation of study medication were reported in only 1 or 2 subjects in each treatment group.

Changes in laboratory values and vital signs were similar between the treatment groups, and no pattern indicating a safety concern was observed.

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

The results of the analysis of mean pruritus score (MPS) and mean number of wheals (MNW) demonstrated that fexofenadine HCl, administered orally in doses of 20 mg BID, 60 mg BID, 120 mg BID, and 240 mg BID for 4 weeks, was statistically superior to placebo in reducing signs and symptoms of chronic idiopathic urticaria. In addition, there was a statistically significant dose response for the four fexofenadine HCl doses. For both MPS and MNW, the 60 mg dose group showed a larger treatment effect than the 20 mg group and was similar to the 120 and 240 mg dose groups. Statistical analyses also revealed that subjects with more severe disease respond better to higher doses of fexofenadine HCl.
Fexofenadine HCl was safe and well tolerated in all four doses.
The recoding of adverse event data did not change the safety profile of fexofenadine HCl.