INN: FEXOFENADINE

Study number: PJPR0010

Study title: A placebo-controlled, double-blind, randomized parallel study comparing the safety and efficacy of four dosage strengths of MDL 16,455A in the treatment of spring allergies-II.

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**  PJPR0010

**Title**
A placebo-controlled, double-blind, randomized parallel study comparing the safety and efficacy of four dosage strengths of MDL 16,455A in the treatment of spring allergies-II.

**Investigator(s), study site(s)**
See Appendix C of the original Clinical Study Report K-94-0782-CDS.

**Study duration and dates**
The first subject was enrolled on 17 March 1994 and the last subject completed the study on 19 July 1994.

**Phase**  III

**Objectives**
To determine the safety and efficacy profile of MDL 16,455A (fexofenadine HCl) at 20 mg BID, 40 mg BID, 60 mg BID, and 80 mg BID as compared to placebo in the treatment of seasonal allergic rhinitis (SAR).

**Study design**
The study was a placebo-controlled, double-blind, randomized, parallel design in subjects with spring SAR. A 2-day single-blind placebo lead-in period was followed by a 2-week double-blind treatment period, with a total of 3 or 4 visits: Screen (which could be combined with Entry), Entry, Interim, and Final, or Early Discontinuation. Dosing was BID.

Efficacy was based on assessments of the severity of the following individual allergy symptoms: sneezing; rhinorrhea; itchy nose, palate and/or throat; and itchy, watery, red eyes. A 5-point subjective rating scale was used. The total symptom score (TSS) for any observation time was the sum of the individual symptom scores, excluding nasal congestion. Nasal congestion was also assessed, but its severity rating was not included in TSS, as relief of nasal congestion was not expected using an H1-antagonist.

Individual symptoms were rated by the investigator at the Entry Visit. The same individual symptoms were assessed and recorded by the subject in diaries at noon and bedtime daily, beginning with the placebo lead-in period. Assessments were reflective, based on the severity of the individual symptoms for the previous 12 hours. The subject also assessed individual allergy symptoms before dosing on the mornings of the Interim and Final Visits. Both subject and investigator rated individual symptoms at the Final Visit.

At the Final Visit the investigator rated the overall effectiveness of the study medication using a 5-point scale to indicate complete relief, marked relief, moderate relief, slight relief, or no relief, and the subject was asked if he/she would wish to take the study medication again.

The average change in Bedtime TSS between Baseline (average of 2-day placebo lead-in) and the double-blind treatment period (average of the 2-week treatment period) was the primary efficacy
parameter. Secondary efficacy parameters included the change between baseline and treatment period for: daily bedtime TSS, bedtime individual symptoms, noon TSS, and average AM predose TSS. In addition, secondary efficacy parameters included the physician's assessment of symptoms at Entry and Final Visits, the physician's overall effectiveness rating made at the Final Visit, and the subject's willingness to take study medication again, evaluated at the Final Visit.

Safety evaluations included clinical laboratory panels, physical examinations, and adverse event reporting.

**Study drug administration**

Subjects were randomized at the Entry Visit. During the 2-day single-blind placebo lead-in period, all subjects took placebo BID for a total of 4 doses. The first dose was taken at the Entry Visit, and subsequent doses were taken at 7 PM that day and 7 AM and 7 PM the following day. During the 2-week double-blind period which immediately followed, subjects took study medication according to their randomization to 1 of 5 treatment groups: MDL 16,455A (fexofenadine HCl) 20 mg, 40 mg, 60 mg, 80 mg, or placebo BID at 7 AM and 7 PM daily. The total double-blind treatment period was up to 16 days, maximum.

**Statistical methods**

An analysis of covariance (ANCOVA) model with baseline bedtime TSS as a covariate and investigative site, treatment, investigative site by treatment interaction, and baseline bedtime TSS by treatment interaction as predictor variables was used to analyze the primary efficacy variable change in bedtime TSS. The primary analysis was conducted using the Intent-to-Treat population. Secondary efficacy parameters and subgroups were analyzed with similar methods.

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

**Pharmacokinetic methods**

Two plasma samples were collected for measuring MDL 16,455 on the day of the Final Visit, 1 to 3 hours and 5 to 9 hours after the last dose of study medication. This was done at 5 investigative sites in 34 subjects.

**Results – Study subjects and conduct**

A total of 1021 subjects were randomized at 16 investigative sites. Of the 1021 randomized, 1012 subjects were exposed to double-blind medication (9 subjects discontinued before taking study medication). Of the 1012 exposed, 1004 subjects were identified as safety evaluable, having been exposed to double-blind medication and having had a postbaseline adverse event assessment; this group was used for all safety analyses. Of the 1012 exposed, 995 were identified as Intent-to-Treat, having both baseline and postbaseline Bedtime symptom assessments; this group was used for all Intent-to-Treat analyses. Of the 995 Intent-to-Treat subjects, 949 had no major protocol violations and were included in Protocol Correct analyses.
Results – Efficacy

Nine hundred ninety-five subjects received study medication and were evaluated for efficacy: 198 placebo, and 197, 201, 203, and 196 on 20 mg, 40 mg, 60 mg, and 80 mg of MDL 16, 455A (fexofenadine HCl), respectively. The primary efficacy parameter was change from baseline in average bedtime TSS. Results are summarized in Table 1 below.

The tests for treatment differences and linear dose response (linear trend) were significant (P=0.0034 and P=0.0022, respectively). All doses were statistically significantly superior to placebo.

Analysis of secondary efficacy parameters produced similar results.

Table 1 – Intent-to-Treat Analysis of Bedtime TSS (N=995)

<table>
<thead>
<tr>
<th>Treatment (BID)</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>198</td>
<td>5.52 ±0.20</td>
<td>4.73±0.18</td>
<td>-0.85±0.14</td>
</tr>
<tr>
<td>20 mg MDL 16,455A</td>
<td>197</td>
<td>5.90 ±0.20</td>
<td>4.56±0.21</td>
<td>-1.26±0.14</td>
</tr>
<tr>
<td>40 mg MDL 16,455A</td>
<td>201</td>
<td>5.56±0.21</td>
<td>4.20±0.18</td>
<td>-1.44±0.14</td>
</tr>
<tr>
<td>60 mg MDL 16,455A</td>
<td>203</td>
<td>5.71 ±0.19</td>
<td>4.10±0.18</td>
<td>-1.58±0.14</td>
</tr>
<tr>
<td>80 mg MDL 16,455A</td>
<td>196</td>
<td>5.73 ±0.21</td>
<td>4.38±0.19</td>
<td>-1.36±0.14</td>
</tr>
</tbody>
</table>

*P values, means and associated standard errors from an ANCOVA model containing investigative site, baseline, treatment, treatment by baseline interaction, and treatment by site interaction.
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>No. (%) of subjects in treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 200)</td>
</tr>
<tr>
<td>All</td>
<td>67 (33.5)</td>
</tr>
<tr>
<td>Serious</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>8 (4.0)</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 5.0% (40/804) of subjects receiving fexofenadine HCl and 5.5% (11/200) of subjects receiving placebo.

Following the current ICH guidelines for reporting of serious TEAEs, there were no serious TEAEs reported.

The frequencies for 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 be identified as a major reason for discontinuation.

There was no obvious relationship between dose of fexofenadine HCl and number of subjects reporting adverse events. No subject was discontinued because of laboratory findings. There were no differences among treatment groups in vital signs findings.

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 this study demonstrate that MDL 16,455A (fexofenadine HCl), at doses of 20 mg, 40 mg, 60 mg, and 80 mg BID, is safe and effective in the treatment of SAR.

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