SYNOPSIS

INN: FEXOFENADINE

Study number: PJPR0024

Study title: A double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of three dosage strengths of MDL 16,455A (40, 60, & 120 mg BID) in the treatment of fall allergies

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  PJPR0024

Title

A double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of three dosage strengths of MDL 16,455A (40, 60, & 120 mg BID) in the treatment of fall allergies

Investigator(s), study site(s)

See Appendix C of original Clinical Study Report K-95-0007-CDS.

Study duration and dates

The first subject was enrolled on 12 August 1994 and the last subject completed the study on 30 November 1994.

Phase  III

Objectives

The primary objective was to determine the efficacy and safety of MDL 16,455A (fexofenadine HCl) at 40 mg BID, 60 mg BID, and 120 mg BID compared to placebo in the treatment of fall seasonal allergic rhinitis (SAR).

A secondary objective was to determine the dose proportionality of MDL 16,455A (fexofenadine HCl) at the administered doses.

Study design

This was a double-blind, randomized, placebo-controlled, parallel study with a 3-day single-blind placebo lead-in followed by two weeks of double-blind randomized treatment, in subjects with fall SAR. Subjects were randomized to receive one of four treatments using a stratified randomization based on high vs. low baseline symptom scores.

The study consisted of four visits over a total of 17 days. There were 3 days between visit 1 and visit 2 (single-blind placebo lead-in period), and 7 days between visit 2 and visit 3 and visit 3 and visit 4 (weeks 1 and 2 of double-blind randomized treatment).

Subjects took study medication at 7 AM and 7 PM daily. They assessed their SAR symptoms prior to each dose; reflectively (for the previous 12-hour period) and instantaneously (for the previous 1-hour period). Additionally, they assessed their SAR symptoms instantaneously daily at 1-3 hours after taking the 7 PM dose (“Bedtime”).

Subjects rated the severity of the following five individual symptoms: nasal congestion; sneezing; rhinorrhea; itchy nose, palate, and/or throat; and 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.

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 primary analysis variable was the change in average daily 7 PM reflective TSS (average 7 PM reflective TSS during the 2-week double-blind dosing period) from average baseline 7 PM reflective TSS (average 7 PM reflective TSS during the 3-day placebo lead-in period).

Secondary analysis variables were:
- Changes in average daily 7 PM reflective TSS over time for: 1) week 1 vs baseline, 2) week 2 vs. baseline, and 3) all days of double-blind dosing period vs baseline
- Changes in average daily TSS in other scheduled assessments (average during the double-blind dosing period) from the average baseline TSS (average of the three corresponding assessments during the placebo lead-in period), including 7 AM reflective, 7 PM instantaneous, 7 AM instantaneous, and Bedtime assessments
- Changes in the subject's assessment of severity of individual symptoms for 7 AM reflective, 7 AM instantaneous, 7 PM reflective, 7 PM instantaneous, and Bedtime instantaneous assessments
- Physician's assessment of overall effectiveness of study drug at the final visit.

Safety parameters included physical examinations, vital signs, adverse events, laboratory panel, and 12-lead ECGs.

Study drug administration

Study medication was supplied in unit dose cards. The week 1 placebo lead-in unit dose card contained medication for 3 days (24 capsules for 6 doses). The week 2 and week 3 unit dose cards contained double-blind medication for 7 days (56 capsules for 14 doses). Subjects were instructed to take four capsules at 7 AM (± 1 hour) and 7 PM (± 1 hour). Four treatment groups were used: placebo BID, MDL 16,455A (fexofenadine HCl) 40 mg BID, 60 mg BID, and 120 mg BID.

Statistical methods

An analysis of covariance (ANCOVA) model with baseline 7 PM reflective TSS as a covariate and investigative site and treatment as predictor variables was used to analyze the primary efficacy variable change in 7 PM reflective TSS. The primary analysis was conducted using the Intent-to-Treat population.

Secondary symptom assessments were analyzed with similar methods.

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

Pharmacokinetic methods

A plasma sample for the measurement of MDL 16,455 (fexofenadine) was collected 1-3 hours after the morning dose of study drug on the day of the final visit (visit 4 or Early Discontinuation).
Protocol Amendment 3, implemented at three study sites, added the collection of a second sample 9-11 hours after the morning dose on the day of the final visit.

**Results – Study subjects and conduct**

A total of 589 subjects were randomized at 16 investigative sites. Of the 589 randomized, 588 were exposed to double-blind medication (one subject discontinued before taking study medication). All 588 subjects exposed to double-blind medication had a postbaseline adverse event assessment, qualifying them as safety evaluable; this group was included in safety analyses. The Intent-to-Treat group used for analysis of the efficacy variables included 545 subjects with baseline and postbaseline 7 PM reflective symptom assessments. In addition to excluding 4 subjects without baseline and postbaseline 7 PM reflective assessments, the analysis excluded all 39 subjects from investigative site 0155 because of questionable data integrity. (A separate analysis of the primary efficacy variable was done on 584 subjects with baseline and postbaseline 7 PM reflective symptom assessments, including data from investigative site 0155.) Of the 545 subjects in the Intent-to-Treat group, 511 had no major protocol violations and were included in the protocol correct analysis of the primary efficacy variable.

**Results – Efficacy**

The primary efficacy parameter was change from baseline in average 7 PM reflective TSS. Results of the Intent-to-Treat analysis are summarized in Table 1.

The tests for treatment differences and linear dose response (linear trend) were significant (P=0.0020 and P=0.0005, respectively). All doses of MDL 16,455A (fexofenadine HCl) were statistically significantly superior to placebo (40 mg, P=0.0087; 60 mg, P=0.0075, and 120 mg, P=0.0002).

Similar results were obtained with the protocol correct analysis of the primary efficacy parameter and all secondary efficacy symptom assessments. Quantitative improvements seen for MDL 16,455A (fexofenadine HCl) vs placebo in the physician's evaluation of overall effectiveness were not statistically significant.

Statistically significant differences in symptom reduction between placebo and 60 mg and 120 mg BID MDL 16,455A (fexofenadine HCl) were seen beginning with the first dose (Bedtime instantaneous, day 1, 1-3 hours after the first dose). This effect was maintained through the dosing interval, and was seen in assessments made the following morning prior to dosing (7 AM reflective and 7 AM instantaneous, day 2).
Table 1 – Intent-to-Treat Analysis of 7 PM Reflective TSS (N=545)

<table>
<thead>
<tr>
<th>Treatment (BID)</th>
<th>N</th>
<th>Mean± Standard Error</th>
<th>Mean± Standard Error</th>
<th>Change from Baseline*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Double -Blind Period</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>137</td>
<td>8.66±0.13</td>
<td>7.54±0.19</td>
<td>-1.21±0.18</td>
</tr>
<tr>
<td>40mg MDL 16,455A</td>
<td>135</td>
<td>8.69±0.16</td>
<td>6.93±0.21</td>
<td>-1.86±0.18</td>
</tr>
<tr>
<td>60mg MDL 16,455A</td>
<td>138</td>
<td>8.72±0.14</td>
<td>6.93±0.19</td>
<td>-1.86±0.18</td>
</tr>
<tr>
<td>120 mg MDL 16,455A</td>
<td>135</td>
<td>8.61±0.15</td>
<td>6.59±0.21</td>
<td>-2.11±0.18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>Mean± Standard Error * (Active-Placebo)</th>
<th>P value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Treatment Differences</td>
<td></td>
<td>.0020</td>
</tr>
<tr>
<td>Dose Response (Linear Trend)</td>
<td></td>
<td>.0005</td>
</tr>
<tr>
<td>40 mg MDL 16,455A vs. Placebo</td>
<td>-0.65±0.25</td>
<td>.0087</td>
</tr>
<tr>
<td>60 mg MDL 16,455A vs. Placebo</td>
<td>-0.66±0.24</td>
<td>.0075</td>
</tr>
<tr>
<td>120 mg MDL 16,455A vs. Placebo</td>
<td>-0.91±0.25</td>
<td>.0002</td>
</tr>
</tbody>
</table>

* P values, means and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.

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 = 148)</td>
</tr>
<tr>
<td>All</td>
<td>50 (33.8)</td>
</tr>
<tr>
<td>Serious</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>3 (2.0)</td>
</tr>
</tbody>
</table>

The system organ class with the highest incidence of TEAEs was investigations (changes in laboratory parameters and vital signs). The most common TEAE was headache, and was reported in 19 (4.3%) fexofenadine HCl subjects and 9 (6.1%) placebo subjects.

There was no obvious relationship between incidence of treatment-related adverse events and dose, with the possible exception of headache, which occurred more frequently in the 120 mg BID MDL 16,455A (fexofenadine HCl) dose group than in all other groups.

Following the current ICH guidelines for reporting of serious TEAEs, there were no serious TEAEs reported. There were no deaths.
TEAEs leading to discontinuation were reported in 1.4% (6/440) of subjects receiving fexofenadine HCl and 2.0% (3/148) of subjects receiving placebo. 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.

Clinical laboratory, vital signs, and ECG findings were similar in active and placebo groups. There was no statistically significant overall treatment effect or dose response in any ECG parameter after treatment with MDL 16,455A (fexofenadine HCl) BID. In addition, there was no statistically significant mean change from baseline in any ECG parameter, including QTc, after treatment with MDL 16,455A (fexofenadine HCl) BID, and the incidence of potentially clinically significant ECG values based on Sponsor-defined outlier criteria was similar for subjects receiving MDL 16,455A (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.

Results – Pharmacokinetics/Pharmacodynamics

Because of identical study design and overlapping doses used in the fall studies, pharmacokinetic and pharmacodynamic data for PJPR0023 and PJPR0024 were combined and the results presented in a separate report (K-95-0154-DS). Plasma concentrations of MDL 16,455 increased proportionally with increasing doses of MDL 16,455A (fexofenadine HCl) over the 40 mg to 240 mg BID dose range in the two studies.

Conclusions

The results of this study demonstrate that MDL 16,455A (fexofenadine HCl) is safe and effective at doses of 40 mg, 60 mg, and 120 mg BID in the treatment of seasonal (fall) allergic rhinitis. The recoding of adverse event data did not change the safety profile of fexofenadine HCl.