SYNOPSIS

INN : FEXOFENADINE

Study number : PJPR0017

Study title : A placebo-controlled double-blind, randomized, parallel study in an environmental exposure unit characterizing the onset of action, efficacy, and safety of a single dose of 60 mg or 120 mg MDL 16,455A in patients with fall allergies

CSR date : 23 July 2004

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

<table>
<thead>
<tr>
<th>Study number</th>
<th>PJPR0017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td>A placebo-controlled double-blind, randomized, parallel study in an environmental exposure unit characterizing the onset of action, efficacy, and safety of a single dose of 60 mg or 120 mg MDL 16,455A in patients with fall allergies</td>
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<tr>
<td><strong>Investigator(s), study site(s)</strong></td>
<td>James H. Day MD and Maureen P. Briscoe MD, Kingston General Hospital, Division of Allergy, 76 Stuart Street, Kingston, Ontario, K7L 2V7, Canada</td>
</tr>
<tr>
<td><strong>Study duration and dates</strong></td>
<td>The first subject was enrolled on 25 November 1994 and the last subject completed the study on 11 December 1994.</td>
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</table>

## Objectives

The primary objective was to characterize the time to onset of clinically important relief of symptoms of ragweed pollen-induced allergic rhinitis (RPAR) in patients taking a single dose of 60 mg MDL 16,455A (fexofenadine HCl), 120 mg MDL 16,455A (fexofenadine HCl), or placebo during exposure to ragweed pollen in an Environmental Exposure Unit (EEU).

Secondary objectives were to assess the efficacy and safety of a single dose of MDL 16,455A (fexofenadine HCl).

## Study design

This study was a placebo-controlled, double-blind, randomized, parallel study in patients with RPAR conducted at a single investigative site. The study consisted of six to eight visits: a Screening Visit, three to five Priming Visits, a Qualifying Visit and a Study Visit. At the Priming, Qualifying and Study Visits, patients were to be exposed to controlled levels of ragweed pollen at 4500-5500 gr/m³. Patients were instructed not to eat food within 1/2 hour prior to the Qualifying and Study Visits.

**Screening Visit.** Patients were screened approximately 3 to 4 weeks prior to the Qualifying Visit. Patients who had a history of seasonal allergic rhinitis during the previous two fall seasons, demonstrated a positive epicutaneous skin test response to ragweed allergen within the previous 15 months or at the Screening Visit, and who met other entrance criteria, had a history and physical performed and blood and urine samples collected for clinical lab. Patients continuing to meet entrance criteria were scheduled to return to the investigative site for the first Priming Visit in the EEU.

**Priming Visit(s).** Patients were primed with ragweed pollen in the EEU up to five separate visits, depending on the number of exposures required to produce adequate RPAR symptoms. Patients
assessed RPAR symptoms every 20 minutes during pollen exposure and remained in the EEU until symptoms were adequate (or at least 3 hours had elapsed). Patients having adequate symptoms (defined below) were eligible for entry into the Qualifying Visit after at least three of the five Priming Visits were completed.

The following five symptoms were assessed by the patient:

- nasal congestion
- sneezing
- rhinorrhea
- itchy nose, palate, and/or throat
- itchy, watery, red eyes

Each symptom was evaluated by the patient 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 would not interfere with 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 or intolerable as to warrant immediate evaluation and/or treatment by the investigator.

NOTE: Total Symptom Score (TSS) equaled the sum of individual symptom scores, excluding nasal congestion. The patient was not to be entered into the study if any symptom, including nasal congestion, was rated "very severe."

Adequate symptoms were defined as:

- TSS ≥ 5 (excluding nasal congestion), and
- Two symptoms rated "moderate" or "severe" (excluding nasal congestion) or one symptom rated "severe" (excluding nasal congestion), and
- No symptom (including nasal congestion) rated "very severe"

Qualifying Visit. Patients entered the EEU and assessed their RPAR symptoms at 20 minute intervals. Patients not having adequate baseline (1 hour after beginning pollen exposure) RPAR symptoms were discontinued. Patients having adequate baseline RPAR symptoms were dispensed a single dose of single-blind placebo medication. Patients receiving single-blind placebo assessed their RPAR symptoms and relief of RPAR symptoms every 20 minutes for up to 5 hours.

Patients assessed relief of RPAR symptoms using the following scale:

0  Complete Relief - Symptoms not present.
1  Marked Relief - Symptoms are vastly improved and, although still present, are scarcely troublesome.
2 **Moderate Relief** - Symptoms are noticeably improved but are still present and may be troublesome.

3 **Slight Relief** - Symptoms are present and only minimal improvement has been obtained.

4 **No Relief** - Symptoms are unchanged or worse.

Placebo responders, defined as patients having three consecutive relief of RPAR symptom assessments rated as "marked" to "complete" relief, were to be discontinued from the study. Placebo nonresponders were to be scheduled for the Study Visit, 1 or 2 days later, if they continued to meet entrance criteria.

**Study Visit.** Patients entered the EEU and assessed their RPAR symptoms at 20 minute intervals. Patients not having adequate baseline (1 hour after beginning pollen exposure) RPAR symptoms were discontinued. Patients having adequate baseline RPAR symptoms were randomized to one of three double-blind treatment groups (placebo, 60 mg or 120 mg MDL 16,455A (fexofenadine HCl)) and were dispensed a single dose of study medication. Patients receiving double-blind study medication assessed their RPAR symptoms and Relief of RPAR symptoms every 20 minutes for 5 hours. At the end of the Study Visit, patients were assessed for treatment-emergent adverse events and dismissed from the study.

Safety data collected in this study were: adverse event reporting, a laboratory panel including serum chemistry, electrolytes, CBC with differential, and a urinalysis. At the Screening Visit and the Qualifying Visit, all females had a serum pregnancy test performed.

### Number of patients/subjects

The Sponsor required approximately 100 total randomized patients to receive study drug: placebo, 60 mg MDL 16,455A (fexofenadine HCl), or 120 mg MDL 16,455A (fexofenadine HCl).

### Study drug administration

Study drug was supplied in individual bottles, each containing two capsules (one dose). Three treatment groups were used: placebo, 60 mg MDL 16,455A (fexofenadine HCl), and 120 mg MDL 16,455A (fexofenadine HCl).

### Statistical methods

The primary efficacy endpoint was the time to onset of clinically important relief of RPAR symptoms as assessed by the patient. "Clinically important relief of symptoms" was predefined as the first of three time points at which relief symptoms were characterized as "Marked" or "Complete." Additional definitions of clinically important relief were added and included "Moderate" to "Complete" relief and "Slight" to "Complete" relief.

Changes from baseline in average postdose TSS were examined as were the TSSs at each time point postdose based on both actual (not imputed) and imputed symptom scores. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 5.1 and are reported using MedDRA Version 6.1.

### Interim analysis

No interim analysis was performed for this study.
Results – Efficacy

Ninety-nine patients received study medication and were evaluated for efficacy: 33 each on placebo, 60 mg, and 120 mg MDL 16,455A (fexofenadine HCl). The primary efficacy parameter was the time to onset of clinically important relief defined as the first of three consecutive time points with Marked or Complete relief. The onset of action could not be assessed using the primary efficacy parameter because of the small number of patients meeting this criteria.

Secondary analyses examined relaxed criteria (Slight to Complete) for clinically important relief. Using these criteria the median time to onset of clinically important relief was found to be 60 minutes for both the 60 mg and 120 mg MDL 16,455A (fexofenadine HCl) treatment groups and 100 minutes for the placebo group. Additional secondary analyses were done using the change from baseline in TSS which demonstrated statistical significant reduction in TSS for 60 mg MDL 16,455A (fexofenadine HCl) as early as 60 minutes postdose, and 80 minutes postdose for 120 mg MDL 16,455A (fexofenadine HCl). Results of the primary analysis and secondary analyses are summarized in Table 1 and Figure 1.

Figure 1 – Average TSSs over time - imputed values from intent-to-treat data set

Asterisk (*) denotes a significant difference from placebo (p<.05).
Table 1 – Analysis for time to onset and proportion of patients receiving clinically important relief

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Comparison</th>
<th>Placebo</th>
<th>MDL 16,455A</th>
<th>P value* for treatment comparisons</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td></td>
<td></td>
<td>60 mg</td>
<td>120 mg</td>
<td></td>
</tr>
<tr>
<td>Active doses vs Placebo</td>
<td>MDL 16,455A</td>
<td>0.1765</td>
<td>0.1317</td>
<td>0.3315</td>
</tr>
<tr>
<td>Protocol Correct</td>
<td>MDL 16,455A</td>
<td>0.1051</td>
<td>0.0604</td>
<td>0.2968</td>
</tr>
<tr>
<td>Relief Scores of Complete and Marked</td>
<td>Median time to onset of clinically important relief (minutes postdose)</td>
<td>&gt;300 minutes</td>
<td>&gt;300 minutes</td>
<td>&gt;300 minutes</td>
</tr>
<tr>
<td>Proportion of patients receiving clinically important relief</td>
<td>15% (5/33)</td>
<td>33% (11/33)</td>
<td>27% (9/33)</td>
<td>0.141</td>
</tr>
<tr>
<td>Protocol Correct</td>
<td>Median time to onset of clinically important relief (minutes postdose)</td>
<td>&gt;300 minutes</td>
<td>&gt;300 minutes</td>
<td>&gt;300 minutes</td>
</tr>
<tr>
<td>Proportion of patients receiving clinically important relief</td>
<td>13% (4/32)</td>
<td>35% (11/31)</td>
<td>25% (7/28)</td>
<td>0.073</td>
</tr>
<tr>
<td>Relief Scores of Complete, Marked and Moderate</td>
<td>Median time to onset of clinically important relief (minutes postdose)</td>
<td>260 minutes</td>
<td>120 minutes</td>
<td>120 minutes</td>
</tr>
<tr>
<td>Proportion of Intent-to-Treat patients receiving clinically important relief</td>
<td>45% (15/33)</td>
<td>58% (19/33)</td>
<td>67% (22/33)</td>
<td>0.135</td>
</tr>
<tr>
<td>Relief Scores of Complete, Marked, Moderate and Slight</td>
<td>Median time to onset of clinically important relief (minutes postdose)</td>
<td>100 minutes</td>
<td>60 minutes</td>
<td>60 minutes</td>
</tr>
<tr>
<td>Proportion of patients receiving clinically important relief</td>
<td>64% (21/33)</td>
<td>82% (27/33)</td>
<td>85% (28/33)</td>
<td>.043</td>
</tr>
</tbody>
</table>

* P values based on comparison of survival curves using log-rank test for time to onset and on Fisher's Exact test for proportions receiving relief.

Results – Safety

Overall frequencies of treatment-emergent adverse events (TEAEs) are summarized in Table 2.
Table 2 – Number (%) subjects with TEAEs (safety-evaluable population)

<table>
<thead>
<tr>
<th>Type of TEAE</th>
<th>Placebo (N = 33)</th>
<th>Fexofenadine HCl (N = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 33) 60 mg QD</td>
<td>(N = 33) 120 mg QD</td>
</tr>
<tr>
<td>All</td>
<td>6 (18.2)</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>Serious</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>0 (0.0)</td>
<td>0 (0.0)</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 6 (9.1%) fexofenadine HCl subjects and 4 (12.1%) placebo subjects.

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

There was no obvious relationship between doses of MDL 16,455A (fexofenadine HCl) and the number of patients reporting adverse events.

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 MDL 16,455A (fexofenadine HCl) is safe and well tolerated at single doses of 60 mg and 120 mg. Results from the analysis of time to Slight-Complete relief and change from baseline TSS showed a time to onset of effect by 60-80 minutes after dosing, for single doses of 60 mg and 120 mg MDL 16,455A (fexofenadine HCl).

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