SYNOPSIS

INN : FEXOFENADINE

Study number : M016455/3106

Study title : Evaluation of the efficacy and safety of MDL16,455A at doses of 60 and 120 mg b.i.d. in patients with seasonal allergic rhinitis (a double-blind, placebo-controlled, randomized study)

CSR date : 9 July 2010

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.

PDF name: Fexofenadine – Study 2

EMA request May 2011 – Publication of result-related information on paediatric studies submitted under Article 45 of Regulation (EC) No 1901/2006 (‘Paediatric Regulation’) August 2011
STUDY SYNOPSIS

Study number M016455/3106

Title
Evaluation of the efficacy and safety of MDL16,455A at doses of 60 and 120 mg b.i.d. in patients with seasonal allergic rhinitis (a double-blind, placebo-controlled, randomized study)

Investigator(s), study site(s)
Multicenter study; Coordinating investigator: Koji Ogawa (Ogawa Otorhinolaryngological Department)

Study duration and dates
The first subject was enrolled on 9 January 2000 and the last subject completed the study on 24 April 2000.

Objectives

Primary objective:

- The dose-response effect of MDL16,455A (fexofenadine HCl) (60 and 120 mg b.i.d., morning and evening) was investigated in subjects with seasonal allergic rhinitis (allergy to cedar pollen) using the total score for 3 symptoms (sneezing, rhinorrhea, and eye symptoms) obtained from data in a nasal allergy diary by a placebo-controlled, double-blind, inter-group comparison study. Then the dose-response curve obtained in this study was compared with curves drawn from data obtained in two foreign clinical studies (PJPR0023 and PJPR0023).

- The safety of MDL16,455A (fexofenadine HCl) was evaluated based on the incidence of adverse events occurring during the comparative observation period (TEAE).

Secondary objectives:

- The percent change of the score for each nasal symptom (sneezing, rhinorrhea, and nasal obstruction), each eye symptom, and the daily activity hindrance score was investigated.

- Changes of the scores for each symptom and the daily activity hindrance score were investigated on a daily basis.

- Changes of nasal findings were also investigated.

Study design
A multicenter, double-blind, parallel, inter-group comparison study.

Population
Three hundred subjects (100 per group)
Indication
Seasonal allergic rhinitis (allergy to cedar pollen)

Treatments
Investigational drug code : MDL16,455A (fexofenadine HCl)
Dosage and regimen : A placebo was administered for one week (or 2 weeks), and then either the placebo or MDL 16,455A (fexofenadine HCl) (60 mg or 120 mg) was administered orally twice a day (morning and evening) for 2 weeks.
Generic name (INN) : Fexofenadine hydrochloride
Formulation : Light orange, oval, film-coated tablets
Batch No. : FX99T13

Efficacy data
1. Primary endpoints:
   • Total score for 3 symptoms (the nasal symptom scores for sneezing and rhinorrhea, excluding nasal obstruction, and the eye symptom score) based on the daytime and nighttime scores recorded in a nasal allergy diary.

2. Secondary endpoints:
   • The score for each nasal symptom (sneezing, rhinorrhea, and nasal obstruction), each eye symptom, and daily activity hindrance.
   • Sneezing (number of sneezing attacks) and rhinorrhea (number of times that the nose was wiped).
   • Severity of each nasal finding.
   • Symptoms of each subgroup.
   • Subject’s impressions.

Safety data
1. Primary endpoints:
   • Incidence of TEAE (adverse events, subjective symptoms, objective findings, and abnormal laboratory data) in the MDL16.455A (fexofenadine HCl) 60 mg group, the MDL16.455A (fexofenadine HCl) 120 mg group, and the placebo group.

2. Secondary endpoints
   • Incidence of all adverse events.
   • Incidence of adverse events for which a causal relationship with the test drug could be not ruled out.
   • Time of first onset of adverse events.
   • Laboratory safety data: Changes of laboratory values at each time of measurement before and after drug administration and at the adjacent times.
• Incidence of abnormal laboratory findings.
• Changes of QTc in subjects undergoing electrocardiography at each specified time before and after drug administration and at the adjacent times.

Statistical procedures

Primary analyses:

• The change in the total of 3 symptom scores.
  Investigation of the dose-response relationship
  Between-group comparison is performed using analysis of covariance with the amount of change in the total of 3 symptom scores as the objective variable, the dosing group as the categorical explanatory variable, and the pre-treatment total of the 3 symptom scores as the continuous covariate. The placebo, 60 mg b.i.d., and 120 mg b.i.d. groups were assigned contract coefficients of -1, 0, and 1 or -1, 1, and 0, respectively, and the tests were performed sequentially.

• Investigation of bridging:
  The dose-response relationship was compared with that in 2 foreign clinical studies (PJPR0023 and PJPR0024) by nested analysis of variance using the amount of change in the total of 3 symptom scores to determine whether the interaction of clinical study and dose was significant.

Secondary analyses:

• The change in the score for each nasal symptom (sneezing, rhinorrhea, and nasal obstruction), the eye symptoms, and daily activity hindrance.

• The changes of sneezing (number of attacks) and rhinorrhea (number of nose wipings).

• Changes in the total score for 3 symptoms, the score for each symptom, and the daily activity hindrance score on a daily, daytime, and nighttime basis.

• Severity of each nasal finding.

• Subgroup analysis.

• Subject’s impressions.

Safety analysis

• Comparison of the incidence of TEAE.

• Incidence of all adverse events.

• Laboratory safety data: Changes of laboratory values at each specified time before and after drug administration and at the adjacent times.

• Incidence of abnormal laboratory findings

• Changes of QTc in subjects undergoing electrocardiography at each time of measurement before and after drug administration and at the adjacent times.

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 – Study subjects and conduct

• Number of subjects giving consent: 708 subjects.

• Number of subjects allocated: 310 subjects (placebo group: 107 subjects, 60 mg group: 101 subjects, 120 mg group: 102 subjects).

• Primary subject group analyzed: 307 subjects (placebo group: 105 subjects, 60 mg group: 100 subjects, 120 mg group: 102 subjects).

• Subjects analyzed for safety: 310 subjects (placebo group: 107 subjects, 60 mg group: 101 subjects, 120 mg group: 102 subjects).

Results – Pharmacodynamics

Primary endpoints:

When the dose-response relationship was investigated based on the change in the total of 3 symptom scores (the difference between the mean score for 3 days before the start of treatment during the observation period and the mean score during treatment), assessment of the interaction between the pretreatment score and the treatment group revealed the presence of an interaction (p=0.0788). The scores of the 120 mg and 60 mg groups decreased to a similar extent as that of the placebo group. Comparison between the placebo group and the 120 mg group yielded p=0.0561. Subsequent exploratory comparison between the placebo group and the 60 mg group yielded p=0.024, while that between the 60 mg group and the 120 mg group yielded p=0.7255.

The above results showed a dose-response relationship, with maximum efficacy being seen in the 60 mg group.

Therefore, the recommended dose was considered to be 60 mg b.i.d.

Table 1 – Change in the total of the 3 symptom scores

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>Placebo group</th>
<th>60 mg group</th>
<th>120 mg group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment (mean ± SE)</td>
<td>105</td>
<td>100</td>
<td>102</td>
</tr>
<tr>
<td>6.74 ± 0.14</td>
<td>6.64 ± 0.14</td>
<td>6.68 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>After treatment (mean ± SE)</td>
<td>6.81 ± 0.15</td>
<td>6.28 ± 0.16</td>
<td>6.37 ± 0.18</td>
</tr>
<tr>
<td>Amount of change (mean ± SE)</td>
<td>0.07 ± 0.18</td>
<td>-0.36 ± 0.18</td>
<td>-0.31 ± 0.17</td>
</tr>
</tbody>
</table>

Paired comparison

<table>
<thead>
<tr>
<th>P group vs.</th>
<th>120 mg group</th>
<th>p=0.0561</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg group</td>
<td>P group vs.</td>
<td>p=0.0244*</td>
</tr>
<tr>
<td>60 mg group vs. 120 mg group</td>
<td>p=0.7255</td>
<td></td>
</tr>
</tbody>
</table>

Interaction

<table>
<thead>
<tr>
<th>Before treatment x Dosage group</th>
<th>p=0.0788!</th>
</tr>
</thead>
</table>

*: p<0.05; !: p<0.15
Secondary endpoints:
Investigation of the change (the difference between the mean score for 3 days before the start of the treatment during the observation period and the mean score during treatment) of nasal and eye symptoms showed that the number of sneezing attacks was significantly decreased in the 120 mg and 60 mg groups compared with the control group (p<0.05). The severity of eye symptoms and itchiness were also significantly decreased in the 120 mg group when compared with the control group (p<0.05).

No significant changes of nasal findings were noted.

There was no significant influence on daily activities or on the impressions of the subjects.

Results – Safety

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

<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 = 107)</td>
</tr>
<tr>
<td></td>
<td>Fexofenadine HCl (N = 203)</td>
</tr>
<tr>
<td></td>
<td>60 mg (N = 101)</td>
</tr>
<tr>
<td></td>
<td>120 mg (N = 102)</td>
</tr>
<tr>
<td>All</td>
<td>23 (21.5)</td>
</tr>
<tr>
<td></td>
<td>18 (17.8)</td>
</tr>
<tr>
<td></td>
<td>19 (18.6)</td>
</tr>
<tr>
<td></td>
<td>37 (18.2)</td>
</tr>
<tr>
<td>Serious</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>0 (0.0)</td>
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<tr>
<td></td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

The system organ classes with the highest incidence of TEAEs were nervous system disorders and investigations. The most common TEAEs were somnolence, which was reported in 6 (3.0%) fexofenadine HCl subjects and 2 (1.9%) placebo subjects, and headache, which was reported in 6 (3.0%) fexofenadine HCl subjects and 1 (0.9%) placebo subject.

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

As for changes of QTc on the electrocardiogram, there were no significant differences between the 3 groups with respect to the incidence of QTc prolongation or the extent of change in QTc.

From the above results, the safety profile was approximately similar in the placebo, 60 mg, and 120 mg groups, and it was considered that it was not necessary to exclude a particular dose based on safety considerations when selecting the recommended dose of the investigational drug.

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 dose-response effect of MDL16,455A (60 and 120 mg b.i.d.) was investigated in subjects with seasonal allergic rhinitis (allergy to cedar pollen) using the total score for 3 symptoms (sneezing, rhinorrhea, and eye symptoms) obtained from data in a nasal allergy diary by a placebo-controlled, double-blind, inter-group comparison study.
The difference in the change of total for 3 symptom scores compared with the placebo group was 0.43 (p=0.0244) and 0.38 (p=0.0561) in the 60 mg and 120 mg groups, respectively, and thus the score was decreased to a similar degree in both groups.

There were no significant differences in the incidence of adverse reactions between the placebo, 60 mg, and 120 mg groups.

Based on the above results, the recommended dose of the investigational drug was considered to be 60 mg b.i.d.

When compared with foreign clinical studies, the interaction between clinical study and dose group in this study (J3106) versus the foreign clinical study PJPR0023 or the foreign study PJPR0024 was not significant in terms of the amount of change in the total score for 3 symptoms, and the dose-response curves were parallel. Therefore, bridging using data from foreign clinical studies was considered to be possible.

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