SYNOPSIS

INN : FEXOFENADINE

Study number : M016455O/3101

Study title : Evaluation of the efficacy and safety of fexofenadine hydrochloride (MDL 16,455A) for the treatment of pediatric perennial allergic rhinitis (Double-blind, randomized, ketotifen fumarate controlled, parallel comparison)

CSR date : 13 November 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 M016455O/3101

Title

Evaluation of the efficacy and safety of fexofenadine hydrochloride (MDL 16,455A) for the treatment of pediatric perennial allergic rhinitis (Double-blind, randomized, ketotifen fumarate-controlled, parallel comparison)

Sponsor responsible medical officer, study site(s)

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Masaru Iwasaki, Head of PR Operations Center, Aventis Pharma Ltd.

Multi-center study (13 institutions)

Study duration and dates

Start: July 22, 2002
End: February 14, 2003

Phase Phase III

Objectives

• Primary objective
  – To evaluate the efficacy of fexofenadine hydrochloride 30 mg (7-11 years old) and 60 mg (12-15 years old) administered twice daily in the treatment of pediatric perennial allergic rhinitis, with ketotifen fumarate dry syrup as a control for the purpose of validating non-inferiority, using total score for 3 symptoms (sneezing, nasal discharge and nasal congestion) obtained from patient diaries.

• Secondary objectives
  – To evaluate the safety of fexofenadine hydrochloride when administered at doses of 30 mg (7-11 years old) or 60 mg (12-15 years old) twice daily to children with perennial allergic rhinitis, based on the incidence of adverse events during the administration period and using ketotifen fumarate dry syrup as a control.
  – To evaluate the efficacy of fexofenadine hydrochloride when administered at doses of 30 mg (7-11 years old) or 60 mg (12-15 years old) twice daily to children with perennial allergic rhinitis, based on evolution of the daily symptom score obtained from patient diary data and using ketotifen fumarate dry syrup as a control.
  – To evaluate the improvement of nasal findings obtained by administration of fexofenadine hydrochloride at a dose of 30 mg (7-11 years old) or 60 mg (12-15 years old) twice daily to children with perennial allergic rhinitis, based on the incidence of adverse events during the administration period and using ketotifen fumarate dry syrup as a control.
years old) twice daily to children with perennial allergic rhinitis, using ketotifen fumarate dry syrup as a control.

- To evaluate the impressions of the subjects from questionnaire (efficacy of the investigational drug while taking it, etc.), using ketotifen fumarate dry syrup as a control.
- To determine the plasma concentration of fexofenadine and compare with the data obtained in overseas children and the data for local adults.

**Study design**

Multicenter, double-blind, randomized, ketotifen fumarate-controlled, parallel comparison

**Administration period (4 weeks)**

- **30mg group**: (twice a day, after breakfast and before bedtime)
  One tablet of fexofenadine hydrochloride 30mg
  One sachet of dry syrup placebo 1g

- **Ketotifen group**: (twice a day, after breakfast and before bedtime)
  One placebo tablet 30mg
  One sachet of ketotifen fumarate dry syrup 1g

- **60mg group**: (twice a day, after breakfast and before bedtime)
  One tablet of fexofenadine hydrochloride 60mg
  One sachet of dry syrup placebo 1g

- **Ketotifen group**: (twice a day, after breakfast and before bedtime)
  One placebo tablet 60mg
  One sachet of ketotifen fumarate dry syrup 1g
Number of subjects planned

140 (fexofenadine hydrochloride: 70, ketotifen fumarate: 70)

Inclusion criteria

Seven to fifteen-years old children diagnosed with perennial allergic rhinitis who had nasal symptoms (sneezing and nasal discharge) excluding nasal congestion on the day prior to enrollment/allocation and who scored at least 3 points on 2 symptoms combined. However, the subjects who scored 4 points on nasal congestion on the day prior to enrollment/allocation were excluded.

Treatments

- **Investigational drug**
  
<table>
<thead>
<tr>
<th>Drug code</th>
<th>30mg tab</th>
<th>60mg tab</th>
</tr>
</thead>
<tbody>
<tr>
<td>INN</td>
<td>fexofenadine</td>
<td>fexofenadine</td>
</tr>
<tr>
<td>JAN</td>
<td>Fexofenadine hydrochloride</td>
<td>Fexofenadine hydrochloride</td>
</tr>
<tr>
<td>Dosage/duration</td>
<td>One tablet orally taken twice daily (after breakfast, before bedtime) for 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Dosage form</td>
<td>Film-coated tablet</td>
<td></td>
</tr>
<tr>
<td>Lot No.</td>
<td>KB2000005</td>
<td>KM2001014</td>
</tr>
</tbody>
</table>

- **Placebo for investigational drug**
  
  | Dosage form  | Film-coated tablets indistinguishable from the investigational drug and containing no active ingredient |
  | Lot No.  | KB2000012 | KB2001050 |

- **Control drug**
  
  | Drug code  |  |
  | INN        | ketotifen |
  | JAN        | Ketotifen fumarate |
  | Dosage/duration | One gram orally taken twice a day (after breakfast, before bedtime) for 4 weeks |
  | Dosage form  | Dry syrup |
  | Lot No.  | 02043 |

- **Placebo for control drug**
  
  | Dosage form  | Dry syrup indistinguishable from control drug and containing no active ingredient |
  | Lot No.  | 02044 |
Efficacy data

Primary endpoint: TSS (sneezing, nasal discharge, nasal congestion)

Secondary endpoints: score of each symptom, nasal findings and patients’ impressions

Safety data

Primary endpoint: adverse events

Secondary endpoints: laboratory findings, ECG QTc

Pharmacokinetic data

Observation item: plasma concentration levels of fexofenadine

Statistical procedures

• Efficacy

Primary efficacy analysis was mainly conducted in PPS (per protocol set).

Primary efficacy variable

− The primary efficacy variable is the change from pre-treatment in the mean of daily TSS. The covariance analysis model was adopted in which the change in the TSS was used as target variable and the total score for the 3 pre-treatment symptoms and age bracket (7-11, 12-15) were used as covariates. The upper limit of the one-sided 95% confidence interval for the point estimate of the difference in population means was obtained. When 0.9 was not included, non-inferiority was confirmed.

Secondary efficacy variables

− Change in score of each symptom
− Weekly change of the TSS and each symptom scores
− Daily change of the TSS and each symptom scores
− Nasal findings
− Patients’ impressions
− Change in the TSS, score of each symptom, nasal findings and patients’ impressions, by age group (7-11, 12-15 years old)

• Safety

Safety was analyzed in the safety analysis population.

Primary safety variable
− Incidence of adverse events was compared between treatment groups by Fisher’s exact test at two-sided 5% significance level.

Secondary safety variables
− Incidence of adverse events possibly related to study medication
− Sedation-related adverse events (important secondary variable)
− Laboratory finding values
− Changes in ECG QTc

Pharmacokinetics
− Described in Pharmacokinetic Statistical Analysis Plan

Interim analysis

Interim analysis was not planned or implemented.

Results - Study subjects and conduct

Although informed consent was obtained from 182 subjects, 3 did not reach the stage of provisional enrollment, and therefore, 179 subjects were registered as the whole study population. Of the whole study population, 32 subjects were not randomized, and therefore, 147 were included in the total randomized population. Of the total randomized population, safety was analyzed in 146 subjects [fexofenadine hydrochloride (Fexo): 75, ketotifen fumarate (Keto): 71]. The full analysis set (FAS) included 140 subjects (Fexo: 70, Keto: 70). PPS included 127 subjects (Fexo: 64, Keto: 63). Of the total randomized population, 7 were discontinued or dropped (Fexo: 5, Keto: 2), and two (Fexo: 1, Keto: 1) of them were discontinued due to adverse events.

No significant differences were observed between the two PPS treatment groups regarding patients’ background factors (gender, age, height, weight).

<table>
<thead>
<tr>
<th>Breakdown of subjects</th>
<th>Fexo group (fexofenadine hydrochloride)</th>
<th>Keto group (ketotifen fumarate)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>7-11 years old</td>
</tr>
<tr>
<td>Whole randomized population</td>
<td>147</td>
<td>56</td>
</tr>
<tr>
<td>Safety analysis population</td>
<td>146</td>
<td>55</td>
</tr>
<tr>
<td>FAS (full analysis set)</td>
<td>140</td>
<td>53</td>
</tr>
<tr>
<td>PPS (per protocol set)</td>
<td>127</td>
<td>47</td>
</tr>
</tbody>
</table>
Results - Efficacy

Primary efficacy variable

Non-inferiority of the Fexofenadine (Fexo) to the Ketotifen (Keto) treatment group was demonstrated using the ANCOVA model with the changes from the pre-treatment TSS (sneezing, nasal discharge, nasal congestion) as the response variable and pre-treatment score as covariable. The point estimate of the mean treatment difference was -0.227. The mean and the upper limit of the one-sided 95% confidence interval of 0.172 did not include the non-inferiority limit (0.9). The means changes in the TSS were -2.06 in the Fexo group and -1.83 in the Keto group.

Secondary efficacy variables

The changes in the each symptom scores, sneezing and nasal discharge were improved to the same extent in the Fexo group as in the Keto group. Nasal congestion was significantly improved in the Fexo group compared to the Keto group. The point estimate of the mean treatment difference for the changes in nasal congestion scores and the two-sided 95% confidence interval were -0.335 [-0.564, -0.106], and 0 was not included.

No significant differences were observed between the treatment groups in the weekly changes of the TSS. However, the point estimates of the Fexo group were lower than those of the Keto group in each week. Except for 2 days, the daily point estimates were lower in the Fexo group than in the Keto group. In both groups, efficacy was achieved quickly, and steady state was reached in 3 days.

In all weeks, the weekly point estimates of the nasal congestion scores were better in the Fexo group in comparison to the Keto group. Similarly, the daily point estimates were also lower in the Fexo group than those in the Keto group. The effects of fexofenadine hydrochloride quickly appeared, attaining the steady state in 3 days.

The time course of the changes of the sneezing and nasal discharge scores was similar between the Fexo and Keto groups. The effects of the drugs quickly appeared, attaining the steady state by the 3rd day in both groups.

As for nasal findings, the post-treatment scores on all variables were better than pre-treatment levels in both groups, except for the nature of nasal discharge at 4 weeks in the Keto group. No significant differences were observed between the treatment groups except for swelling of inferior turbinate mucosa at 2 weeks and the nature of nasal discharge at 4 weeks.

No significant difference was observed between the treatment groups in patients’ impressions, as both groups were improved in symptoms.

The analysis by age group supported the results of primary analyses.
Results – Safety

Primary safety variable

The incidence of adverse events was 52.0% (39/75) in the Fexo group and 63.4% (45/71) in the Keto group. Fisher’s exact test did not indicate any significant difference (p=0.3155).

Secondary safety variables

The incidence of adverse events possibly related to study medication was 5.3% (4/75) in the Fexo group, which was significantly lower than 23.9% (17/71) of the Keto group (p=0.0115).

The incidence of sedation-related adverse events was 4.0% (3/75) in the Fexo group, which was significantly lower than 14.1% (10/71) of the Keto group (p=0.0421). Likewise, the incidence of sedation-related adverse events possibly related to study medication was 2.7% (2/75) in the Fexo group, which was significantly lower than 14.1% (10/71) of the Keto group (p=0.0151).

There were no serious adverse events in the Fexo group, whereas 2 serious adverse events (enterogastritis and acute appendicitis) were noted in the Keto group. The causal relationship between enterogastritis and the study drug was not ruled out, but the causality of acute appendicitis was denied.

No significant differences were observed between the treatment groups regarding the incidence of abnormalities in any laboratory finding items.

The mean QTc change was +4.4msec in the Fexo group and +5.3msec in the Keto group. Since the increases in both groups were less than 10msec, they are not considered clinically relevant.

Results – Pharmacokinetics

Results are reported in “pharmacokinetic study of fexofenadine hydrochloride (MDL 16,455A) for the treatment of pediatric perennial allergic rhinitis in the Clinical trial: M016455O/3101”.

Conclusions

Fexofenadine hydrochloride 30mg (7-11 years old) and 60mg (12-15 years old) twice daily improved pediatric perennial allergic rhinitis in a non-inferior manner as compared with ketotifen fumarate. Fexofenadine was confirmed to be a safe drug, which caused significantly less sedation than ketotifen. No cardiovascular effects were observed.