SYNOPSIS

INN: FEXOFENADINE

Study number: M016455O/3102

Study title: Evaluation of Efficacy and Safety of Fexofenadine Hydrochloride (MDL 16,455A) for Treatment of Pediatric Atopic Dermatitis (Double-blind, Randomized, Ketotifen Fumarate-controlled, Parallel Comparison)

CSR date: 4 November 2003

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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/3102

Title
Evaluation of Efficacy and Safety of Fexofenadine Hydrochloride (MDL 16,455A) for Treatment of Pediatric Atopic Dermatitis
(Double-blind, Randomized, Ketotifen Fumarate-controlled, Parallel Comparison)

Investigator(s), study site(s)
Hidemi Nakagawa, Professor, Department of Dermatology, Jichi Medical School
Masaru Iwasaki, Sponsor responsible medical officer, Aventis Pharma Ltd
Multi-center joint study (23 institutions)

Study duration and dates  from July 29, 2002 to December 25, 2002  Phase  Phase III

Objectives

•  Primary objective:
  - To investigate non-inferiority of fexofenadine hydrochloride 30mg (7-11 years old) and 60mg (12-15 years old) administered b.i.d. in comparison with ketotifen fumarate dry syrup in terms of efficacy for pediatric atopic dermatitis, based on the changes in itching scores obtained from patient diaries

•  Secondary objectives:
  - To evaluate safety of fexofenadine hydrochloride 30mg (7-11 years old) and 60mg (12-15 years old) administered b.i.d. for treating pediatric atopic dermatitis, using ketotifen fumarate dry syrup as control drug, based on the incidence of adverse events during the administration period of the investigational drug
  - To evaluate efficacy of fexofenadine hydrochloride 30mg (7-11 years old) and 60mg (12-15 years old) administered b.i.d. for treating pediatric atopic dermatitis, using ketotifen fumarate dry syrup as control drug, based on changes over time in itching scores obtained from patient diaries
  - To evaluate efficacy of fexofenadine hydrochloride 30mg (7-11 years old) and 60mg (12-15 years old) administered b.i.d. for treating pediatric atopic dermatitis, using ketotifen fumarate dry syrup as control drug, based on changes of rashes
  - To evaluate patients’ impressions obtained from questionnaire (effects of the drug during the administration period), using ketotifen fumarate dry syrup as control drug
Study design

Multi-center, double-blind, randomized, ketotifen fumarate-controlled, parallel comparison

Enrollment observation period (1W)

Comparison observation period (4W)

Enrollment

Allocation

Hospital visit

Hospital visit

Confirming inclusion/ exclusion

Reconfirming

criteria

Informed consent

Obtaining consent

Informing the Enrollment

Center

Blood/Urine samples

Blood/Urine samples

7-11 years old: fexofenadine hydrochloride 30 mg tablets b.i.d. (after breakfast and at bedtime) or ketotifen fumarate dry syrup 1 g b.i.d. (after breakfast and at bedtime)

12-15 years old: fexofenadine hydrochloride 30 mg tablets b.i.d. (after breakfast and at bedtime) or ketotifen fumarate dry syrup 1 mg b.i.d. (after breakfast and at bedtime)

Standard topical treatment (0.1% hydrocortisone butyrate cream)

Number of subjects planned

160 (Fexofenadine hydrochloride group: 80, Ketotifen fumarate group: 80)

Indication / Inclusion criteria

Subjects diagnosed with atopic dermatitis (7-15 years old) with average 2 or more itching score points for 3 days immediately before allocation. However, the subjects scoring 4 points every day for the entire 3 days were excluded.
Treatments

Investigational drug

<table>
<thead>
<tr>
<th>Drug code</th>
<th>30mg tablets</th>
<th>60mg tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>INN</td>
<td>MDL 16,455A</td>
<td>fexofenadine</td>
</tr>
<tr>
<td>JAN</td>
<td>Fexofenadine hydrochloride</td>
<td></td>
</tr>
<tr>
<td>Dosage</td>
<td>A dose of one tablet orally taken twice a day (after breakfast, before bedtime) for 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Dosage form</td>
<td>Film-coated tablets</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 containing no active ingredient and non-distinguishable in appearance from the investigational drug |
| Lot No.     | KB2000012   | KB2001050   |

Control drug

<table>
<thead>
<tr>
<th>Drug code</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>INN</td>
<td>ketotifen</td>
</tr>
<tr>
<td>JAN</td>
<td>Ketotifen fumarate</td>
</tr>
<tr>
<td>Dosage</td>
<td>A dose of 1g orally taken twice a day (After breakfast, before bedtime) for 4 weeks</td>
</tr>
<tr>
<td>Dosage form</td>
<td>Dry syrup</td>
</tr>
<tr>
<td>Lot No.</td>
<td>02043</td>
</tr>
</tbody>
</table>

Placebo for control drug

| Dosage form | Dry syrup containing no active ingredient and non-distinguishable in appearance from the control drug |
| Lot No.     | 02044 |

Efficacy data

Primary endpoint: itching scores
Secondary endpoints: conditions of rashes and patients’ impressions

Safety data

Primary endpoint: adverse events
Secondary endpoint: laboratory findings
Statistical procedures

- Efficacy
  Efficacy was mainly analyzed in PPS (per protocol set).
  **Primary efficacy variable:**
  - The primary efficacy variable is the change from pre-treatment in the mean of daily itching scores. Analysis of covariance (ANCOVA) was employed, using the change in the mean of daily itching scores as dependent variable and pre-treatment value and age group as covariates; one-sided 95% confidence interval of the point estimate for the difference in the means of two groups was obtained. Non-inferiority was claimed when the upper limit of the 95% confidence interval excluded 0.37.
  **Secondary efficacy variables:**
  - Means of weekly and daily itching scores and the changes in the means of weekly and daily itching scores
  - Conditions of rashes
  - Patients’ impressions
  - Changes in mean itching scores, conditions of rashes and patients’ impressions by age group (7-11, 12-15 years old)

- Safety
  Safety was analyzed in safety analysis population.
  **Primary safety variable:**
  - The incidence based on TEAE (Treatment Emergent Adverse Event) was compared between the two groups by Fisher’s exact test with two-sided 5% level of significance.
  **Secondary safety variables:**
  - TEAEs possibly related to study medication
  - Sedative-related adverse events (Important secondary safety variable)
  - Laboratory findings
  - TEAE, Sedative-related adverse events and Laboratory findings of age group (7-11, 12-15 years old).

Interim analysis

No interim analysis was performed.

Results - Study subjects and conduct

All of the 190 subjects who submitted informed consent were enrollment, and 174 were allocated to groups. Of 174 subjects treated with the investigational drugs, 172 were FAS (full analysis set), 162 were PPS (per protocol set) and 174 were safety analysis population. Eight cases were discontinued after allocation; 4 cases of them were discontinued due to adverse events and 4 cases due to protocol violation.

No significant differences were observed in background factors (sex, age, height and weight) between the two PPS groups.
### Breakdown of subjects

<table>
<thead>
<tr>
<th>All allocated to groups</th>
<th>Fexo group (fexofenadine hydrochloride)</th>
<th>Keto group (ketotifen fumarate)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total 7-11 years old 12-15 years old Total</td>
<td>7-11 years old 12-15 years old Total</td>
</tr>
<tr>
<td>All allocated to groups</td>
<td>174 55 28 83</td>
<td>56 35 91</td>
</tr>
<tr>
<td>Safety analysis population</td>
<td>174 55 28 83</td>
<td>56 35 91</td>
</tr>
<tr>
<td>FAS</td>
<td>172 53 28 81</td>
<td>56 35 91</td>
</tr>
<tr>
<td>PPS</td>
<td>162 51 26 77</td>
<td>53 32 85</td>
</tr>
</tbody>
</table>

### Results - Efficacy

**Primary efficacy variable:**

Non-inferiority of the Fexo group to the Keto group in the primary efficacy variable, namely, changes in mean itching scores was demonstrated. The point estimate and the upper limit of the one-sided 95% confidence interval of the treatment difference in mean itching scores between the Keto and the Fexo groups were 0.050 and 0.185 according the analysis of covariance model, therefore the non-inferiority limit (0.37) was not included. The mean changes in itching scores were –0.50 in the Fexo group and –0.58 in Keto group.

**Secondary efficacy variables:**

- Itching scores (weekly, daily) of the Fexo group decreased over time after the start of administration of investigational drugs, in the same manner as the itching scores of the Keto group.

- Rash conditions of the Fexo group were improved at 2 weeks and 4 weeks, in a similar manner as the Keto group. Between group comparison in improvement at 2 weeks and 4 weeks was examined by Mantel-Haenszel test, and no significant difference was observed (p=0.6358, p=0.6964).

In the Fexo group, 15.6% (12/77) of subjects said “much improved” and 41.6% (32/77) said “improved” at 4 weeks. In the Keto group, 10.6% (9/85) of subjects said “much improved” and 36.5% (31/85) said “improved” at 4 weeks. The frequency distribution was compared with that of the Keto group by Mantel-Haenszel test, and no significant difference was observed (p=0.2439).

Changes in mean itching scores, evolution of itching scores over time (weekly, daily), evolution of rash conditions and patients’ impressions were not different between two age groups (7-11, 12-15 years old).
Results - Safety

Primary variable:
Incidence of TEAEs was 30.1% (25/83) in the Fexo group and 31.9% (29/91) in the Keto group. No significant differences were observed by Fisher’s exact test between the two groups (p=0.7452).

Secondary variables:
The incidence of TEAEs possibly related to study medication was 10.8% (9/83) in the Fexo group and 13.2% (12/91) in the Keto group, and no significant difference was found by Fisher’s exact test between the two groups (p=0.6487). No TEAEs possibly related to study medication were observed in 5% or more subjects. The most frequent TEAEs possibly related to study medication was somnolence (Fexo: 3 cases (3.6%), Keto: 4 cases (4.4%)).

The incidence of sedative-related TEAEs and the incidence of sedative-related TEAEs possibly related to study medication were 6.0% (5/83) and 3.6% (3/83), respectively, in the Fexo group, and 5.5% (5/91) and 4.4% (4/91), respectively, in the Keto group. No significant differences were observed between the two groups (p= 1.0000 for each). Somnolence was the only sedative-related TEAE in both groups.

There were no significant differences between the two groups concerning the incidence of abnormalities in any of laboratory findings. There was no difference between the two groups.

Conclusions

The results of the study demonstrated that fexofenadine hydrochloride 30mg (7-11 years old) and 60mg (12-15 years old) b.i.d were not inferior to ketotifen fumarate in improving pruritus of atopic dermatitis. No differences were observed between the safety of fexofenadine hydrochloride and ketotifen fumarate.