CETIRIZINE STUDY 89CK16-0411

A MULTICENTER STUDY OF THE SAFETY AND EFFICACY
OF CETIRIZINE IN THE TREATMENT OF SEASONAL ALLERGIC RHINITIS
IN CHILDREN 6 TO 11 YEARS OF AGE: COMPARISON WITH PLACEBO

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II. ABSTRACT

A multicenter, double-blind, placebo-controlled study was conducted to assess the efficacy and safety of cetirizine in children 6 to 11 years old with seasonal allergic rhinitis. The dose of cetirizine was 5mg QAM for patients weighing less than 25kg and 10mg QAM for heavier children. The treatment period was two weeks. A documented history of seasonal allergic rhinitis was required. All patients had a total severity score of 6 or more (of a possible 18) at entry to the study, based on six signs and symptoms of rhinitis as recorded in a daily diary. Each symptom was rated on a 4-point severity scale (0-3, none-severe). Two or more symptoms were at least moderately severe, including nasal discharge or sneezing. One hundred seventy-two (172) patients were randomly and evenly assigned to receive cetirizine or placebo. Thirteen patients in each treatment group weighed less than 25kg, and 73 patients in each group weighed at least 25kg. One hundred sixty-four (164) patients were evaluable for efficacy analyses. Two patients never took study medication, thus one hundred seventy (170) were evaluable for safety analyses.

Sixteen patients (9.3%) discontinued before completing the study: 9 patients (10.5%) on placebo and 7 patients (8.1%) on cetirizine. The most frequent reasons for premature discontinuation were intercurrent illness (7/16) and lack of efficacy (6/16). The treatment groups were comparable with respect to all demographic characteristics and baseline signs and symptoms of rhinitis. Initial mean total severity was 7.9 for placebo and 7.7 for cetirizine.

Cetirizine provided significant improvement in total severity of rhinitis over the first week of treatment (-1.4 for placebo, -2.4 for cetirizine; p=0.04). Cetirizine response was comparable to that of placebo during the second week of treatment. When averaged over both weeks, the difference between cetirizine and placebo approached significance (-1.5 for placebo, -2.3 for cetirizine; p=0.10). Significant improvements were observed 12 hours after the initial dose of study medication. Differences in mean improvement between cetirizine and placebo approached or attained statistical significance on each of the first seven days of treatment.

For individual symptoms, cetirizine provided significant improvement in pruritus of the oral/nasal mucosa during the first week (p=0.05) and when averaged over both weeks (p=0.03). No other individual symptoms showed significant improvement relative to placebo.

In children weighing at least 25kg, cetirizine provided significant improvement in total symptom severity throughout the study. Significant improvement occurred in conjunctivitis, pruritus of the eyes, pruritus of the oral/nasal mucosa and sneezing during the first week of treatment. Similar results were found in average response over both study weeks.
Among children weighing less than 25kg, no statistically significant differences between cetirizine and placebo were found. This was due primarily to the small number of low weight patients.

Asthmatic patients were included in both the cetirizine and the placebo groups (although the randomization was not stratified on such patients). Changes in asthma severity at the end of the study were similar between the cetirizine and the placebo groups. For asthmatics and for non-asthmatics, cetirizine provided significantly greater improvement than placebo in total severity during the first week of treatment.

Mean changes from entry weight, measured at the end of the study, were not different between cetirizine and placebo groups. However, among high weight patients only, the mean increase of 0.5 lbs in the cetirizine group was significantly greater than the mean of 0.3 lbs in the placebo group (p=0.02).

Twenty-seven of 84 (32.1%) cetirizine patients had adverse experiences compared to 18 of 86 (20.9%) placebo patients. Somnolence was more common in the cetirizine patients (7.1% or 6/84) than in the placebo treated group (1.2% or 1/86). The total number of adverse experiences reported by cetirizine patients was 39, while there were 29 total adverse experiences among the placebo patients. Headache was the most common adverse experience for both treatment groups; and occurred in 8.3% (7/84) of cetirizine patients and 9.3% (8/86) of placebo patients. Other adverse events occurring more frequently than 1.2% (1/84) were rash (3.6% or 3/84), nausea (3.6% or 3/84), nervousness (2.4% or 2/84) and abdominal pain (2.4% or 2/84) among the cetirizine group. The placebo group had one other adverse experience with an incidence greater than 1.2% which was nervousness (2.3% or 2/86). The severity was generally mild to moderate for both treatment groups. No patient discontinued from the study was due to an adverse experience.

There were 149 abnormal laboratory test results for cetirizine patients. Only 3 of the abnormal results (2.0%) were clinically significant and possibly related to study drug.

This study indicates that 10mg QAM cetirizine provides significant improvement in the total severity of seasonal allergic rhinitis in children weighing at least 25kg. Specifically, significant improvement in the individual symptoms of conjunctivitis, pruritus of the eyes, pruritus of the oral/nasal mucosa and sneezing were seen. Because of the small number of low weight patients, no conclusions can be made regarding the efficacy of 5mg QAM in this group.
III. OBJECTIVE

This placebo-controlled multicenter study was conducted to assess the efficacy and safety of cetirizine for the treatment of seasonal allergic rhinitis in children 6 to 11 years old. A secondary objective was to assess the efficacy of 5mg QAM cetirizine in children weighing less than 25kg and of 10mg QAM cetirizine in children weighing at least 25 kg.

IV. MATERIALS AND METHODS

A. Study Design

(1) Patient Population

This was a double-blind, parallel-group study of one hundred seventy-two (172) male and female patients 6 - 11 years old. All patients had a documented history of seasonal allergic rhinitis and a confirmed allergen sensitivity via RAST or skin tests. To qualify for entry, patients were required to have a total severity score of at least 6, based on six signs and symptoms of rhinitis. Each symptom was rated using a four-point scale described below (Section IV.B.2). At least two symptoms were moderately severe or severe, one of which was sneezing or nasal discharge.

Mild to moderate asthmatics were allowed to enter the study provided their baseline FEV1 was at least 75% of the predicted value, they had occasional bronchospasm reversible by inhaled beta-agonists and require no chronic medication other than theophylline, inhaled cromolyn or PRN inhaled bronchodilators.

(2) Patient Exclusion Criteria

Reasons for patient exclusion from the study were: an underlying disease that would interfere with the evaluation of the therapeutic response, a history of severe exacerbation of asthma during the ragweed-fall pollen season, a history of hypersensitivity to hydroxyzine or cetirizine, females who were post-menarchal, a history of significantly abnormal hematologic, renal or hepatic function tests, patients undergoing an escalating course of desensitization therapy for less than six months provided therapy shots were discontinued at least two weeks prior to entry, any concomitant disease requiring chronic medication (other than allowed asthma therapy), use of an antihistamine within 96 hours of entry, nasal cromolyn less than 7 days before entry, or nasal steroids less than 2 weeks before entry, use of any investigational drug within three months before entry, inability to understand the purpose of the study or otherwise make an informed judgement to participate, and/or an expectation of more than 2 days of travel during the study or other compliance problems.
(3) **Study Phases**

This study utilized two treatment groups in parallel fashion. The efficacy period was two weeks long. Patients visited the physician's office on the screening day and at the end of 1 week and 2 weeks of treatment. Table A outlines the study design.

(4) **Study/Rescue Medication**

Study medication was dispensed as 120 ml bottles identified with the patient number. The drug lot numbers used in this study are given in Table B.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetirizine</td>
<td>5mg/5ml</td>
<td>C9037</td>
</tr>
<tr>
<td>Placebo</td>
<td>-</td>
<td>C9040</td>
</tr>
</tbody>
</table>

Patients who weighed less than 25 kg took 1 tbsp (5 ml or placebo) each morning. Heavier patients (at least 25 kg) took 2 tsp (10 ml or placebo) each morning. No rescue medication was permitted in this study.
B. Clinical Observations

(1) Physical Examination

Before entry to the study, patients underwent a complete physical examination, including weight and laboratory determinations. Sensitivity to ragweed or fall pollen was documented by history and by RAST, prick or intradermal testing. Testing was required if not done within 2 years by the investigator.

(2) Signs and Symptoms

At each visit the investigator recorded the severity of sneezing, nasal discharge, pruritus of the eyes, pruritus of the oral/nasal mucosa, conjunctivitis and nasal congestion.

The severity of each sign or symptom was rated as:

0 None (not present at all)
1 Mild (just noticeable and not troublesome)
2 Moderate (frequently/definitely present and annoying)
3 Severe (continuously present and interferes with normal daily functions or sleep).

A total symptom severity score was calculated from the severities of the symptoms noted above, excluding nasal congestion. Nasal congestion was excluded because antihistamines have been shown to lack decongestant activity.

Patients maintained a daily diary. Each morning before medication and in the evening, the parent and child discussed and recorded the severity of sneezing, runny nose/post nasal drip, itchy eyes, itchy nose, mouth or throat, red, teary eyes or swollen eyelids, and stuffy nose. Severity was rated using the same scale as above.

(3) Global Evaluations

At the end of the two weeks of treatment or at discontinuation, the investigator made an overall assessment of the effect and toleration of therapy. Efficacy was rated as:

0 (Completely ineffective)
1 (Slightly effective, but not sufficient)
2 (Quite effective; symptoms under good control)
3 (Extremely effective; symptoms absent or negligible)

Tolerance for the drug was rated as:

0 (Side effect(s) required discontinuation of therapy)
1 (Side effect(s) bothersome, but tolerable)
2 (Side effect(s) noted, but not bothersome)
3 (No side effects noted)
(4) **Symptoms of Asthma**
At the end of each week of treatment, the investigator rated the severity of asthma for patients with this condition. The severity was rated as:

1. Much worse than usual
2. Slightly worse than usual
3. Same as usual
4. Slightly better than usual
5. Much better than usual

(5) **Pulmonary Function Testing**
At entry to the study (day 1) and at the end of each week of treatment, the investigator performed spirometry and recorded the peak flow, FEV1, FEF 25-75 and FVC.

(6) **Adverse Experiences**
At each study visit, all volunteered or observed adverse experiences were noted. For each adverse experience, time of onset, duration, severity and relationship to study medication were recorded.

(7) **Laboratory Data**
The following laboratory tests were done at entry to and at the end of the study: CBC, SGOT, SGPT, BUN, creatinine and total bilirubin. Results falling outside of the normal range were reviewed by the investigator for clinical significance and relationship to study medication.

V. **STATISTICAL METHODS**

(1) **Efficacy Evaluable Analyses**
Patients were blindly evaluated for eligibility and compliance to the protocol. The primary analyses and conclusions were based on data from patients determined to be evaluable for efficacy. To assess any possible exclusion biases, an intent-to-treat analysis was also performed. (See Appendix C.)
(2) **Efficacy Parameters**

The primary efficacy parameter was total symptom severity, based on the diary records of severity of all signs and symptoms given in IV. B.2. other than nasal congestion. Severity of nasal congestion was not included in the total since the literature on allergic rhinitis indicates that antihistamines do not control congestion. Secondary parameters were the individual symptoms of sneezing, nasal discharge, pruritus of the eyes, pruritus of the oral/nasal mucosa, conjunctivitis, and nasal congestion.

The effect of cetirizine on seasonal allergic rhinitis was assessed via the mean change from baseline total symptom severity relative to placebo.

(3) **Patient Diary Data**

For each patient, a weekly AM and PM mean severity for each symptom was calculated. For each time of day, the weekly mean severity was computed as the sum of the severity scores at that time of day divided by the number of days of diary data for the week. In cases of less than 2 days of diary data in a given week, the mean severity was not calculated. Weekly total AM and PM severity were based on all symptoms other than nasal congestion. Non-missing data for at least 3 symptoms, exclusive of nasal congestion, were required in computing the total.

Mean daily symptom severities were calculated as the average of the AM and PM mean severities of that symptom.

(4) **Baseline Severity**

For patient diary data, baseline symptom severity was taken as the severity of that symptom recorded in the diary before the first dose of study medication. For investigator severity assessments, baseline symptom severity was taken as the rating given by the investigator at the screening visit. The severity of nasal congestion was excluded from the total symptom score.

(5) **Statistical Models**

(a) **Demographic and Baseline Characteristics**

Comparability of the two treatment groups (cetirizine and placebo) for demographic characteristics was assessed using two-way analyses of variance (ANOVA) for age, weight (males and females separately, and all patients combined), height, pulse, blood pressure, temperature and respiration. The ANOVA models included treatment, center, and treatment-by-center interactions. For the categorical parameters of race, sex and presence of asthma, the Cochran–Mantel–Haenszel (CMH) test was used.

Comparability of the quantitative parameters within low and high weight groups individually was assessed via two-way ANOVA's as described above. For categorical parameters, CMH tests were performed on each weight group separately.
Treatment differences in baseline symptom severity were evaluated using three-way ANOVA models similar to those described above.

(b) **Weekly Assessment of Symptom Severity**

Differences in mean change from baseline severity between active and placebo treatments were assessed by analyses of covariance (ANACOVA). Each symptom and total symptom score were analyzed. These assessments were made at the end of study week 1 and 2 for both patient and investigator evaluations. The ANACOVA models included baseline (the covariate), treatment, center, weight and all interaction effects.

Assessment of treatment mean differences for low and for high weight patients was conducted using linear contrasts in the models just described. Treatment comparisons within weight groups were planned in the study design. Consistent with their "pre-planned" nature, these comparisons were declared significant when appropriate, irrespective of the results of the test for treatment-by-weight group interaction.

Repeated measure analyses of covariance incorporating data from both weeks were also conducted. These models included baseline, treatment, center, weight, week and all interaction effects. Consistent with a multivariate approach to repeated measures, patients who did not complete the two weeks of treatment were excluded from these models, except where the discontinuations were due to inadequate response. (See V(6) below.)

Results for each weight group separately were obtained via linear contrasts in the repeated measure models described above.

Before implementing the ANACOVA models, preliminary models including baseline-by-treatment effects were run to assess homogeneity of covariate slopes. Based on the general lack of significant effects, these terms were deleted from the models to allow proper estimation of other model effects.

Type I tests of baseline effect and Type III tests for all other model effects were used to determine statistical significance. (See V (8) below.)

(c) **Global Evaluations of Efficacy and Tolerance**

Differences in the distribution of global evaluations of therapy between the two treatment groups were analyzed using the general association version of the test. Study site and weight group were the strata. CMH distributional differences for low and high weight groups separately were assessed using CMH tests of each weight group, using centers as strata.

(d) **Evaluation of Asthma Severity**

Differences in the distribution of asthma severity were assessed via the general association version of the CMH test, with centers and weight groups as strata. Distributional differences for low and high weight groups separately were assessed using CMH tests of each group, using centers as strata.
(e) **Analysis of Efficacy by Day**

Differences in group mean change from baseline severity of each symptom and total symptom score were assessed daily during the first week of treatment. Analysis of covariance models were implemented for each day. The models included baseline (the covariate), treatment group, center, weight group and all interactions. Results for the weight groups separately were based on linear contrasts in the analysis of covariance models just described.

(6) **Missing Data/Discontinued Patients**

Patients for whom baseline severity was missing for any symptom were excluded from all analyses of that symptom. Patients who discontinued prematurely during the efficacy period for reasons other than lack of efficacy were included in the weekly analyses before the time of discontinuance and excluded from the repeated measures analyses. For patients who discontinued prior to the week 2 visit due to lack of efficacy, their final mean severity values were carried forward to later weeks and included in the weekly and the repeated measures analyses.

(7) **Statistical Significance**

Results of the overall comparisons of treatment effects, pooled over centers, were considered statistically significant provided a p-value of 0.05 or less obtained. The same level of significance was used for treatment comparisons within each weight group. In tests of interaction effects, including those for homogeneity of covariate slopes, a p-value of at most 0.10 was considered statistically significant. The choice of a higher type I error rate was due to the relatively small number of patients for each interaction effect combination and consequently low statistical power.

(8) **Statistical Software**

All statistical analyses were performed using the Statistical Analysis System (SAS) software, version 5.18.

**VI. RESULTS**

**A. PATIENT CHARACTERISTICS**

(1) **Patient Population**

Eighty-six (86) patients were randomized to receive cetirizine and 86 to receive placebo. In each group, 73 patients weighed at least 25kg (high weight) and 13 weighed less than 25kg (low weight). Eighty-one cetirizine patients and eighty-three placebo patients were evaluable for efficacy. Thirty-three cetirizine patients (38%) and 35 placebo patients (41%) were asthmatics (Table 1a). The number of patients entered and evaluable at each week of the treatment period is presented in Table 1b.
Sixteen (16) patients discontinued before completing two weeks of treatment (Table 3). The distribution of reasons for premature discontinuation is presented in Table 4. The most frequent reasons for discontinuation were intercurrent illness (7 patients) and lack of efficacy (6 patients).

For statistical analysis, the three patients who discontinued due to lack of efficacy had their final symptom severity data 'carried forward' to subsequent weeks (Table 5). These severities were included in the weekly assessment of treatment response.

(2) Initial Symptom Severity and Demographic Characteristics

Mean initial severity and demographic characteristics (obtained at the screening visit) are presented in Table 6. As seen in the table, the treatment groups were comparable with respect to all characteristics. No statistically significant treatment differences in initial mean symptom severity were found.

No significant differences in mean initial symptom severity or in demographic characteristics were found in the low weight and high weight groups. Mean differences which approached significance occurred among high weight patients for sneezing (1.68 for placebo, 1.89 for cetirizine; p=0.058) and for conjunctivitis (1.10 for placebo, 0.85 for cetirizine; p=0.061). In the high weight group, the percentage of non-whites randomized to placebo was somewhat larger than that of cetirizine (15% vs. 7%, respectively; p=0.093).

Mean initial total severity was 7.9 in the placebo group and 7.7 in the cetirizine group. Among low weight patients, mean initial total severity was 7.8 for placebo and 7.6 for cetirizine. For high weight patients, the means were 8.0 for placebo and 7.7 for cetirizine.

No significant treatment-by-center or treatment-by-weight interactions were found. This indicates the active-to-placebo differences were consistent across the study centers and the high and low weight groups. (While the interaction test results are not included in Table 6, they may be reproduced from the date in Appendix E.)
B. EFFICACY

(1) Patient Diary Data - Improvement in Rhinitis Signs and Symptoms

No statistically significant differences in mean change from baseline total symptom severity were found among the low weight patients. Cetirizine effects on total severity (as measured by the difference between active and placebo group means) were smaller in this group than those of the high weight group described above. Averaged over the two weeks of treatment, the mean improvement in total severity among low weight patients was 1.5 for placebo and 2.3 for cetirizine.

For individual signs and symptoms, no statistically significant differences between cetirizine and placebo groups were found except for pruritus of oral/nasal mucosa in week 1 and averaged over both weeks (p=0.05). Among high weight patients, cetirizine improvements were significantly greater than placebo for conjunctivitis (weeks 1, 2 and overall), pruritus of the eyes (week 1 and overall), pruritus of the oral/nasal mucosa (week 1 and overall) and sneezing (week 1 and overall). In the low weight group, comparable response between the active and placebo groups was found in all parameters. The placebo response was generally greater among low weight patients than in the high weight group.

No significant treatment-by-center interactions were found, indicating a similar response between treatment groups over the six study centers (Table 7b). No significant treatment-by-weight group interactions were found, indicating the effect of cetirizine relative to placebo was similar for low and for high weight patients. In general, covariate slopes were homogeneous over the treatment groups and study weeks, consistent with the expected tendency for patients with higher than average baseline severity to have greater than average decreases from baseline (Table 7b).
The magnitude of symptom improvement associated with cetirizine was generally similar (within 0.1 for individual symptoms) between low weight and high weight groups. This indicates that the increased dose administered to high weight patients was compensated for on average by their increased weight. The observed comparability of cetirizine and placebo among low weight patients is due in part to a generally greater placebo response and consequently smaller treatment mean differences. However, the small size of the low weight group (12 placebo and 9 cetirizine patients) is the primary explanation for the lack of statistical significance. Because of this, clinically important cetirizine effects may be present, but obscured by the imprecision of the observed means.

(2) Analysis by Day for Study Week 1

In particular, significantly greater improvement was seen in the cetirizine group 12 hours after the initial dose of study medication.

(3) Investigator Assessments – Improvement in Rhinitis Symptom Severity

Mean symptom severity and adjusted mean changes from baseline for each treatment group is summarized in Table 8a, while the analysis of covariance results are presented in Table 8b. Additional detail (group standard deviations and baseline means) is provided in Table 10.

The effect of cetirizine on total symptom score, as rated by the investigator, was more positive than as judged by the patient. In particular, improvement in total symptom severity was significantly greater for cetirizine than for placebo at week 2 and over both weeks (p=0.02), and at week 1 and overall among high weight patients (p=0.02 and p=0.03, respectively). Active-to-placebo differences approached significance in the high weight group at week 2 (p=0.10) and in the low weight group at week 2 (p=0.07) and overall (p=0.09).

For individual symptoms, differences which approached or attained statistical significance were found in pruritus of the eyes for both weight groups combined, in sneezing among high weight patients and in pruritus of the eyes among low weight patients.

Therapeutic response between the treatment groups was similar over the study centers, as no significant treatment-by-center interactions were found. Active-to-placebo differences were similar between high and low weight groups, consistent with the lack of significant treatment-by-weight group interactions. Covariate slopes were homogeneous over the treatment groups at all weeks for all symptoms except nasal congestion (p=0.05 for week 1 and p=0.09 for the average of week 1 and 2).
(4) **Global Evaluation of Treatment**

A summary of the investigator assessment of efficacy and tolerance is presented in Tables 11A and 11B, respectively.

For both weight groups combined, the percentage of patients whose treatment was rated 'definitely improved' or 'highly effective' was 32% for placebo and 44% for cetirizine. The corresponding percentages for the low weight group were 36% for placebo and 44% for cetirizine, and for the high weight group, 31% for placebo and 42% for cetirizine.

No significant differences in the distribution of global evaluations of efficacy or of tolerance were found between cetirizine and placebo groups for both weight groups combined, or for either group separately.

(5) **Comparison of Asthmatics and Non-Asthmatics**

Tables 12a and 12b summarize the analysis of improvement in the signs and symptoms of rhinitis for asthmatics and non-asthmatics for study weeks 1 and 2. Assessments of asthma severity are given in Table 12c for each study week.

Among non-asthmatic patients, the improvement in total severity due to cetirizine was significantly greater than that of placebo at week 1 (1.0 for placebo vs. 2.3 for cetirizine; p<0.01). For asthmatic patients, the corresponding mean improvements were 1.6 for placebo and 2.7 for cetirizine (p=0.04). No significant differences were found at week 2 for either patient group.

For non-asthmatics, improvements relative to placebo for individual symptoms which approached or attained significance were found in conjunctivitis (week 1), nasal congestion (week 2), pruritus of the eyes (week 1), post-nasal discharge (weeks 1 and 2), pruritus of the oral/nasal mucosa (week 1) and sneezing (week 1). In the asthmatic group, significant or near significant improvements relative to placebo were found in conjunctivitis (weeks 1 and 2), nasal congestion (week 2), pruritus of the eyes (weeks 1 and 2) and pruritus of the oral/nasal mucosa (week 1).

In investigator ratings of asthma severity among asthmatic patients, there were no statistically significant differences in the distribution of ratings between cetirizine and placebo patients at week 1 or at week 2 (Table 12c). Thus, cetirizine did not affect asthma symptoms in patients with mild asthma.

Due to the non-randomized nature of the asthmatic/non-asthmatic groups, the above results should be interpreted cautiously. Although the groups appear comparable with respect to concomitant factors, the absence of randomization precludes a causal inference.
(6) **Body Weight**

A summary of group mean weight at the start and the end of the treatment period is presented in Table 13, along with a statistical comparison of the treatment groups for both weight groups combined and for each weight group separately.

Clinically unremarkable weight gains occurred in both the cetirizine and the placebo groups. Among high weight patients combined, the mean weight gains of 0.3kg for placebo and 0.5kg for cetirizine were not significantly different (p=0.42). The corresponding means among low weight patients were 0.6kg for placebo and 0.3kg for cetirizine (p=0.02).

(7) **Pulmonary Function Tests**

Pulmonary function parameters are presented by treatment group and weight group in Table 14, along with the results of the statistical analysis.

No significant differences in treatment group means were found for any pulmonary parameter. Significant (p≤0.001) differences between high and low weight patients occurred in all parameters. The high weight group had higher mean FEV1, FEF25-75 and FVC in both the active and placebo treatment groups reflecting the increased pulmonary capacity that is expected in physically developing children. Mean differences among study weeks were significant for FEF25-75 due to a decreasing trend in the means over time. These changes were small and clinically insignificant. The FEV1 remained unchanged during the study period (p=0.074).

(8) **Comparison of AM and PM Diary Data**

A summary of the statistical analysis of AM and PM mean changes from baseline symptom severity is presented in Table 15 by weight group.

No statistically significant differences were found between AM and PM means at week 1 or week 2. Further, no significant interactions of time of day-by-treatment or time of day and weight group were found (Table 15). Accordingly, the AM and PM values were combined to give a daily mean value in the analyses described in (3) above.

Generally, the group mean changes for PM data (12 hours post-dose) were greater than the AM mean changes (24 hours post-dose). The differences were not statistically significant, as noted above. These small changes in AM and PM relief are consistent with 24 hour control of rhinitis.
(10) **Intent-to-treat analysis**

Despite the small percentage of non-evaluable patients (8/172; 4.7%), an intent-to-treat analysis was conducted which included all patients who received one or more doses of double-blind medication irrespective of evaluable. The results of these analyses are presented in Tables 1–7(c) of Appendix C. These results do not differ substantially from those of the evaluable patients discussed above.

C. **SAFETY**

(1) **Adverse Events**

A summary of the incidence of all adverse experiences during the study is presented in Tables 22–26B. All reported adverse experiences have been included regardless of their severity or relationship to study drug. The adverse experiences were categorized by the WHO dictionary preferred terminology. If a patient reported a specific adverse experience on more than one occasion, it is reported as one adverse experience. Appendix E gives a listing of all adverse experiences occurring in the study, by individual patient.

Table 22 presents the incidence of adverse experiences and relationship to study drug for cetirizine and placebo. Twenty-seven cetirizine patients (27/84 or 32.1%) had a total of 39 adverse experiences, which was greater than the 29 total adverse experiences reported by 18 placebo patients (18/86 or 20.9%). There was a higher incidence of somnolence in the cetirizine study group (6/84 or 7.1%) as compared to the placebo group (1/86 or 1.2%) at a p=0.052 level of significance. Seven of the 39 (18%) cetirizine adverse experiences were noted by the investigators as related to study drug and four of those seven adverse experiences were somnolence. The other 3 adverse experiences reported as related to study drug were nausea, nervousness and hyperkinesia. The placebo group (13.8% or 4/29) had headache, hyperkinesia, diarrhea and hypokinesia attributed to study drug.

The severity of adverse experiences were generally mild to moderate for both cetirizine and placebo (Table 23). Ninety-two percent (36/39) of the adverse experiences in the cetirizine group and 97% (28/29) of the placebo treatment group's adverse experiences were mild or moderate symptoms. The 3 (3/39 or 7.7%) severe adverse experiences associated with cetirizine were somnolence, nervousness and depersonalization. One placebo patient reported severe fatigue.
Table 24 presents the incidence of adverse experiences by dose. Of the 84 cetirizine treated patients, 11 patients took 5 mg and 73 patients were treated with 10 mg. The incidence of patients adverse experiences was 36.4% (4/11) for the 5 mg group and 31.5% (23/73) for the 10 mg group. The majority of the adverse experiences (34/39 or 87.2%) in patients taking cetirizine were seen in the 10 mg dosing group; this is not remarkable since only 11 of 84 cetirizine treated patients received 5 mg.

Adverse experiences occurring during 1-7 days, 8-14 days or 15 days or more of continuous dosing with cetirizine or placebo are displayed in tables 25A and 25B respectively. The incidence of patients reporting adverse experiences was similar for each time period for the cetirizine treatment group (23.8%, 16.9%, and 21.4% for day 1-7, days 8-14 and day 15 or greater respectively). For the placebo group, the incidence of patients reporting adverse experiences was 16.3%, 14.3% and 11.4% respectively for the same time periods. Somnolence resolved after the first week of cetirizine treatment and none of the 6 patients complained of somnolence during day 8 or later. The other adverse experiences remained stable or resolved after the first week. No patient discontinued from the study due to the occurrence of an adverse experience.

(2) Clinical Laboratory Tests

Laboratory tests were obtained at baseline and at the end of the study. Of 82 cetirizine patients with complete laboratory data, 149 test results were abnormal (Table 26A). Only 3 of 149 (2.0%) of the abnormal values were clinically significant and possibly related to study medication (Category 9).

Patient 161 had baseline neutrophil count of 47% (45-75 normal) and lymphocyte count of 41% (18-46 normal). The neutrophil count was 31% and the lymphocyte count was 62% at the end of the study. Subject 194 had an increase in the SGOT from 26 to 43 units (normal 10-37).

Placebo patients' lab data showed 163 abnormalities for 86 patients (Table 26A). Three of 163 (1.8%) were judged clinically significant and possibly related to study drug. Patient 120 had an elevation of the SGOT from 26 to 79 units (normal 0-45) and SGPT from 11 to 67 units (0-50 normal). Patient 125 had an increase in the SGOT from 32 to 60 U/L (0-45 normal).

Listings of individual patient laboratory test results that are category 9 abnormalities are provided in Table 26B. All patient laboratory results are displayed in Appendix E.

VII. CONCLUSIONS

Based on this double-blind study of 172 pediatric patients with seasonal allergic rhinitis, it may be concluded that:

(1) in patients weighing at least 25kg, 10mg cetirizine provides significant improvement in average total symptom severity over two weeks of treatment. Significant improvement was found in the individual symptoms of conjunctivitis, pruritus of the eyes, pruritus of the oral/nasal mucosa and sneezing.
(2) Cetirizine provides significant improvement in the total symptom severity within 12 hours of initial dosing and significant or nearly significant improvement throughout the first week of therapy. These improvements are due primarily to the high weight patients who received 10mg cetirizine.

(3) 5mg cetirizine in patients weighing less than 25kg did not provide significant improvement relative to placebo. Due to the small size of this group and subsequently low statistical power, the effectiveness of the 5mg dose for low weight patients has not been established.

(4) Among mild asthmatic patients, cetirizine did not significantly affect the severity of their asthma over the two weeks of treatment.

(5) Differences in mean improvement between PM data (12 hours post-dose) and AM data (24 hours post-dose) were non-significant, consistent with 24 hour control of rhinitis.

(6) Cetirizine is safe and well tolerated by children 6 - 11 years of age.