CETIRIZINE STUDY 87CE16-0262

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 CHLORPHENIRAMINE

Summary of Studies: #87-N-0012, 87-N-0013,
87-N-0014, 87-N-0015
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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 CHLORPHENIRAMINE

II. ABSTRACT

A multicenter, two-week, third-party blinded, parallel group study of one hundred eighty-eight (188) patients was conducted to compare the safety and efficacy of cetirizine QAM, cetirizine BID and chlorpheniramine TID regimens. Patients were 6-11 years old with a history of seasonal allergic rhinitis, documented by skin or RAST tests. At entry, patients were classified as low weight (less than 25kg) or high weight (at least 25 mg). Patients were randomly assigned to receive cetirizine QAM (5mg/day for low weight, 10 mg/day for high weight patients), cetirizine twice daily (2.5 mg BID for low weight, 5 mg BID for high weight patients) or chlorpheniramine 2 mg TID. To qualify for entry, patients had a total rhinitis severity score of at least 6 (of a possible 18) based on six signs and symptoms of rhinitis. Each symptom was rated using a four-point severity scale (0-3, none - severe). Of the 188 patients, 186 were evaluable for efficacy and all were evaluable for safety. The three treatment groups were comparable with respect to baseline symptom severity and demographic characteristics. Mean total severity score (excluding nasal congestion) at entry was 5.8 for all groups.

Patients recorded their rhinitis severity twice-daily in a diary. Averaged over the two weeks of treatment and over AM/PM evaluation times, the group mean changes from baseline total severity were -2.5 for cetirizine QAM, -2.6 for cetirizine BID and -2.6 for chlorpheniramine TID. These mean changes were not significantly different (p=0.91). The mean changes from baseline after the first twelve hours of treatment were -1.6 for cetirizine QAM, -2.1 for cetirizine BID and -1.2 for chlorpheniramine, indicating a rapid onset of action for all treatments. These means were not significantly different. No significant differences among the treatments were found for individual symptoms. Analyses of severity over each week of treatment confirmed the comparable, positive effects of the three treatments.

The results for investigator ratings of severity parallel those of the patient assessments described above.

One hundred seventeen (117) mild to moderate asthmatics were enrolled in the study. For these patients, there were no significant differences among the treatments in the investigator assessment of asthma severity. In all treatment groups, asthmatics had significantly greater mean improvement in total rhinitis severity score than non-asthmatics.

Among patients receiving cetirizine 10 mg/day, those on the QD regimen had more adverse experiences overall (23/55 patients or 41.8%) compared with those on the BID regimen (17/54 or 31.5%). Somnolence appeared more common among 10 mg/day patients taking a BID regimen (7/54 or 13.0%) than among those taking 10 mg QD (2/55 or 3.6%). Among all cetirizine patients, 42/125 (33.6%) reported an adverse experience. A total of 59 adverse experiences was reported by cetirizine patients. Twenty-four (24) of 63 chlorpheniramine patients (38.1%) reported a total of
37 adverse experiences. The most common adverse experience among cetirizine patients was abdominal pain, reported by 12/125 patients (9.6%); the incidence of abdominal pain in the chlorpheniramine group was 4.8% (3/63 patients reported abdominal pain). Somnolence was equally common in both drug groups, reported by 10/125 cetirizine patients (8.0%) and by 5/63 chlorpheniramine patients (7.9%).

Adverse experiences occurring among cetirizine patients with an incidence greater than 1.6% (i.e., reported by more than two patients) were fatigue (4.0% incidence), and nausea and headache (3.2% each). Compared with the cetirizine group, incidence of fatigue and headache were greater in the chlorpheniramine group (6.3% each), nausea was less common (1.6% incidence). One adverse experience (1.7%) in the cetirizine groups was severe, while 8.1% were severe among patients who received chlorpheniramine. In a separate analysis comparing the incidence of sedation among the cetirizine QAM, cetirizine BID and chlorpheniramine patients, no statistically significant differences were observed among the groups. No patients prematurely discontinued participation in this trial due to the occurrence of an adverse experience.

This study demonstrates that cetirizine 5-10 mg/day given once-daily (QAM) or twice-daily in divided doses (BID) is safe and as effective as chlorpheniramine 2 mg TID in children 6-11 years of age in the treatment of seasonal allergic rhinitis. Cetirizine 10 mg/day in children weighing at least 25 kg provides comparable rhinitis relief to that of 5 mg/day in children weighing less than 25 kg.
III. OBJECTIVE

The primary objective of this multicenter study was to compare the safety and efficacy of a regimen of cetirizine QAM, BID and chlorpheniramine 2 mg TID in the treatment of seasonal allergic rhinitis in children 6 to 11 years of age.

Secondary objectives were to investigate whether response to treatment was similar for two weight classes (patients weighing no more than 25 kg and those weighing at least 25 kg) and for asthmatics and non-asthmatics.

IV. MATERIALS AND METHODS

A. Study Design

(1) Patient Population

This was a 4-center, 2-week, randomized, third-party-blinded study with three parallel treatment groups. Patients were initially classified according to body weight as less than 25 kg or greater than or equal to 25 kg. Within each weight class patients were randomized to receive either cetirizine once daily (5 mg QAM for patients less than 25 kg in weight; 10 mg QAM for patients greater than or equal to 25 kg), cetirizine twice-daily (2.5 mg BID for patients less than 25 kg in weight; 5 mg BID for patients greater than or equal to 25 kg) or chlorpheniramine 2 mg TID, (regardless of weight).

One hundred and eighty-eight (188) patients 6 to 11 years of age, males and females, entered the trial. All patients had a documented history of seasonal allergic rhinitis during the grass pollen season. The allergy to grass pollen was verified for each patient by skin (intradermal or prick) or RAST testing, within two years of the start of the study. Entering patients were required to score a total of 6 or greater (of a maximum severity rating of 18) in the investigator's baseline assessment of six rhinitis symptoms (using a scale of 0=none, 1=mild, 2=moderate, 3=severe), including sneezing, nasal discharge, pruritus of the eyes, pruritus of the oral or nasal mucosa, symptoms of conjunctivitis and nasal congestion. In addition, patients were required to have at least two symptoms rated of moderate or greater severity, one of which must be sneezing or nasal discharge. Patients with mild to moderate asthma could be entered, if they had a baseline FEV1 of at least 75% of the predicted value; experienced occasional bronchospasm reversible by inhaled beta-agonists; required no chronic medication other than theophylline, inhaled cromolyn, or PRN inhaled bronchodilators; and had not been treated with oral beta-agonists or short-term steroid therapy within two months of the start of the study.

(2) Patient Exclusion Criteria

Patients were excluded if they had a concomitant disease which would interfere with the evaluation of response to therapy, a history of severe exacerbation of asthma during the pollen season or a
history of hypersensitivity to cetirizine, hydroxyzine or chlorpheniramine. Female patients who had reached menarche were excluded. Other reasons for excluding patients from the study are listed in the protocol (Appendix A).

(3) Study Phases

This study utilized three treatment groups in parallel fashion. The efficacy period was two weeks long. Table A outlines the study design:

**TABLE A. General Study Design**

<table>
<thead>
<tr>
<th>Week:</th>
<th>0</th>
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<tr>
<td>Low Weight</td>
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<td>High Weight</td>
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<td>x</td>
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</table>

x = Patient Visit

(4) Study Medication

All patients received a morning dose of medication before breakfast, those in the cetirizine BID group also received a dose approximately 12 hours later, and those in the chlorpheniramine TID group also received a dose in the afternoon and at bedtime. Cetirizine was administered in a clear 2.5 mg/5 ml solution, and chlorpheniramine was administered in a blue-green 2 mg/5 ml solution. Drug assignment and dispensing was performed by a third party (the study nurse) who did not participate in any of the efficacy or safety evaluations. The medications were packaged with standard double-blind labeling, although the treatments were distinguishable because of differences in the number of daily doses and in the color and texture of the drug solutions.
B. Clinical Observations

1. Physical Examination

A medical history was obtained at baseline (day 1 of study), and a physical exam was performed at baseline and at the end of the study (end of week 2). During the baseline visit documentation of sensitivity to grass pollen was obtained by performing RAST, prick or intradermal testing, if these had not been performed by the investigator within two years.

2. Signs and Symptoms

At baseline, at the end of week 1 and at the end of the study, the investigator rated the severity of six symptoms of allergic rhinitis. The symptoms were sneezing, nasal discharge (rhinorrhea, post-nasal discharge), pruritus of the eyes, pruritus of the oral and/or nasal mucosa, signs and symptoms of conjunctivitis (red/teary eyes, lid edema, "cobblestoning") and nasal congestion. The severity of each sign/symptom was rated according to the following four-point scale:

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)

On each study day, once in the morning and once in the evening, the patients rated the severity of the six symptoms of rhinitis identified above using the scale identified above. The patients were provided with diary cards on which they recorded these daily symptom ratings.

3. Global Evaluation

At the end of the study, the investigator performed a global evaluation of the efficacy and toleration of the study medication, using the following four-point scales:

Efficacy

0 = completely ineffective
1 = slightly effective, but not sufficient
2 = quite effective; symptoms under good control
3 = extremely effective; symptoms absent or negligible

Toleration

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 the end of week 1 and at the end of the study, patients were asked by the investigator if they had any adverse experiences to report. All volunteered or observed adverse experiences were recorded, including time of onset, severity and duration. For each adverse experience, the investigator made an assessment of any possible relationship to the administered study medication.

7. Clinical Laboratory Tests

Clinical laboratory tests were performed at baseline and at the end of the study. These consisted of a CBC with differential (including platelet count) and blood chemistries (including total bilirubin, SGOT, SGPT, creatinine and BUN). The investigator evaluated all post-treatment laboratory test abnormalities for clinical significance and relationship to study medication. The abnormal results were later computer categorized according to the following codes:

1 = baseline value abnormal
2 = deviation insignificant
3 = single abnormal value
4 = normal with continued therapy
9 = clinically significant and possibly related to study medication

A Pfizer physician reviewed these computer printouts in a blinded fashion. Based on this review, abnormalities were left as category 9 or recategorized to one of the following:

5 = documented laboratory error
6 = likely due to concurrent illness
7 = likely due to concurrent medication
8 = clinically insignificant or not due 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. Because only two patients were non-evaluable, and no data were obtained for these patients, an intent-to-treat analysis was not performed.

(2) Efficacy Parameters

The primary efficacy parameter was total symptom severity score, 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 and of chlorpheniramine on seasonal allergic rhinitis was assessed via the mean change from baseline total symptom severity score.

(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 was 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 symptom severity recorded in the patient 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 day 1 visit. The severity of nasal congestion was excluded from the total symptom score.

(5) Statistical Models

(a) Demographic and Baseline Characteristics

Comparability of the three treatment groups for demographic characteristics was assessed using two-way analyses of variance (ANOVA) for age, weight and duration of rhinitis.
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, with centers as strata.

Comparability of the quantitative parameters within low and high weight groups individually was assessed via linear contrasts in above mentioned two-way ANOVA's. For categorical parameters, CMH tests were performed on each weight group separately.

Treatment differences in baseline symptom severity were evaluated using two-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.

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 III(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.

SAS Type I tests of baseline effect and Type III tests for all other model effects were used to determine statistical significance.
(c) **Global Evaluations of Efficacy and Tolerance**

Differences in the distribution of global evaluations of efficacy and of tolerance between the 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.

(f) **Pulmonary Function Data**

Differences in group mean change from baseline pulmonary function were assessed at each study week. Analyses of covariance were used, including baseline (the covariate), treatment, center, asthma class (present or absent) and all interactions.

(g) **Analysis by Body Weight Class**

For patient ratings, and for investigator ratings of rhinitis, treatment response to body weight class (less than 25 kg and at least 25 kg) was assessed at each study week. Analyses of covariance were used, including baseline severity, (the covariate), treatment, center, weight group and all interactions.

Pairwise comparisons of treatment response within each weight group were conducted using linear contrasts from the models described above. In keeping with the pre-planned nature of the comparisons, differences were considered statistically significant irrespective of the treatment-by-weight group interaction test results. These comparisons are presented in Appendix C, Tables C.5.1-C.6.7 and D.3.1-D.4.7.
(h) **Analysis of Asthmatic Class**

For patient ratings and for investigator ratings of rhinitis, treatment response by asthmatic class (present or absent) was assessed at each study week. Analyses of covariance were used, including baseline severity (the covariate), treatment, center, asthmatic class (present or absent) and all interactions.

(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 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) **Analysis by Study Center**

For patient assessments, investigator assessments and global evaluations of efficacy, statistical analysis of data from each study center were performed. The models were similar to those of the pooled analysis except that the "center" main effect and all "center-by-effect" interaction were removed.

(8) **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.

(9) **Statistical Software**

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

VI. **RESULTS**

A. **Patient Characteristics**

(1) **Patient Population**

One hundred eighty-eight (188) patients were enrolled in the study. Sixty-three (63) patients were randomized to the cetirizine QAM and to the chlorpheniramine groups and 62 patients to the cetirizine BID group.
(2) **Demographic and Baseline Characteristics**

Mean ages ranged from 8.6 years to 9.1 years over the treatment groups. Mean duration of allergy was 5.8 years in the cetirizine QAM group, 5.7 years in the cetirizine BID group and 5.2 years in the chlorpheniramine group. There were approximately twice as many males as females in each treatment group. Most patients (161) were high weight (at least 25mg), with the remaining 25 patients classified as low weight (less than 25kg). One hundred seventeen (117) patients were asthmatics, while the other 69 patients did not have asthma. No statistically significant differences in demographic parameters were found among the treatment groups (Table 5).

Baseline mean total severity, as rated by the patient, was 5.8 for each of the treatment groups. These means do not include nasal congestion, thus are less than the minimum of 6 (based on all symptoms) needed to qualify for entry to the study. No significant differences in treatment group means were found in total severity or in the severity of any individual symptom (Table 6). No statistically significant treatment-by-center interactions were found for any parameter.

Group mean investigator ratings of initial severity were generally greater than those rendered by the patient and parent prior to the first dose of medication. Initial total severity ranged from 7.6 to 7.9 among the three treatments. The treatment groups were comparable with respect to investigator rating of initial severity and in pulmonary function parameters (Table 7.)

**B. EFFICACY**

(1) **Efficacy Evaluable Analyses**

The comparison of cetirizine and chlorpheniramine regimens was based on 186 evaluable patients. Since no data were available for the two invaluable patients, an "intent-to-treat" analysis would duplicate that of evaluable patients. Therefore, no "intent-to-treat" results are presented in this report.
(2) Patient Diary Data - Improvement in Rhinitis Signs and Symptoms

Significantly greater mean improvement was seen during week 2 than week 1. These weekly changes were smallest in the cetirizine QAM group (-2.28 for week 1 vs. -2.65 for week 2). Weekly changes in the cetirizine BID and chlorpheniramine groups were the same (-2.33 vs. -2.94 for cetirizine BID and -2.18 vs. -2.79 for chlorpheniramine). This difference in treatment response over the study weeks was not statistically meaningful, as seen in the test of week-by-treatment interaction (p=0.36).

Mean changes for individual symptoms were similar (within 0.2) among the treatment regimens at each week and then averaged over the treatment period. No significant differences among treatments were found.

No statistically significant treatment-by-center interactions were found for any symptom or for total symptom score. This indicates that the pattern of improvement among treatment regimens was similar over the four study centers.

With the exception of conjunctivitis (red teary eyes or swollen eyelids), baseline-to-improvement correlations were similar among treatment groups for each symptom and for total symptom score, indicative of the expected tendency for patients with greater than average baseline severity to have greater than average improvement.

3. Patient Diary Data - AM/PM Severity Ratings

A comparison of AM and PM ratings is given in Table 9. Graphical comparisons are in Figures 3A and 3B. Details of the statistical analyses are given in Appendix C, Tables C.3.1-C.4.7.

As seen in Table 9, significant differences were found between AM and PM changes from baseline for total severity and most individual symptoms. In the cetirizine QAM and BID groups, improvement was consistently greater at the PM time than the AM time. The AM to PM differences for patients on chlorpheniramine were small.
and did not exhibit a consistent pattern of greater improvement at one timepoint. This lack of similar treatment response over the two measurement times was statistically significant for total severity (treatment-by-time p=0.07), runny nose/post-nasal drip (treatment-by-time p=0.09), and stuffy nose (treatment-by-time p=0.01).

Interpretation of these results is complex due to the study design. For patients receiving cetirizine QAM, the AM measurement was approximately 24 hours after the last dose of study medication. For cetirizine BID patients, these measurements were approximately 12 hours post-dose. The greatest differences between AM and PM means occurred in the cetirizine QAM group. However, similar yet smaller diminished improvements were seen in the cetirizine BID group. This may indicate a diurnal effect which is obscured in the chlorpheniramine group due to the TID dosing regimen. Since baseline severity was measured in the morning only and there was no placebo group, this study does not allow a separate assessment of diurnal and durational effects. Thus, a causal inference for either effect is precluded.

4. Patient Diary Data - Analysis by Study Day

After the first twelve hours of treatment, the mean improvement from baseline was -1.6 for cetirizine QAM, -2.1 for cetirizine BID and -1.2 for chlorpheniramine (Figure 3B). These improvements indicate a rapid onset of relief for all treatments. Over the first week of treatment, no significant differences among the treatments were found. This comparability is consistent with the by-week results described above.

5. Investigator Assessments - Improvement in Rhinitis Symptom Severity

The effect of cetirizine and of chlorpheniramine on symptom improvement, as rated by the investigator, was more positive than as judged by the patient. Mean improvement in total severity averaged over two weeks of treatment was -3.5 for cetirizine QAM, -3.6 for cetirizine BID and -3.8 for chlorpheniramine. No significant differences were found among treatments at either week or over the treatment period except for pruritus of the oral/nasal mucosa at week 2. In this instance, the mean improvement in the cetirizine QAM group (-0.71) was significantly less than that of the cetirizine BID group (-1.01). The mean improvement for the
chlorpheniramine Group (-0.88) was not significantly different from either cetirizine mean. This indicates that the study is not sufficiently sensitive to determine which cetirizine regimen is comparable to chlorpheniramine.

As was found in the patient assessments, significant differences in improvement between week 1 and week 2 occurred in total severity and all symptoms other than sneezing and conjunctivitis. In all cases, the week 2 mean improvements were greater than the week 1 improvements.

6. Global Evaluation of Treatment

Treatment was rated "quite effective" or "extremely effective" in 53% of patients in the cetirizine QAM group, 42% of patients in the cetirizine BID group and 50% of the patients in the chlorpheniramine group. There were no significant differences in the distribution of ratings of efficacy or of tolerance among the three treatments.

7. Pulmonary Function Tests

The pattern of mean changes over the treatment groups was not consistent over the four centers, as evidenced by the statistically significant treatment-by-center interactions in peak flow, FEV1, and FEF 25-75. Small reductions in these parameters were found in the cetirizine groups and larger changes in the chlorpheniramine group at center 87-N-0015. This pattern was not evident in the other three centers. (Although treatment means by center are not presented in this report, they can be obtained from the data provided in Data Listing 6.)

8. Investigator Assessment of Asthma Severity

After one week of treatment, most patients (61%-74%) had asthma severity the "same as usual" while 26%-28% were rated "slightly better" or "much better" than usual. The differences in distribution of ratings were not significant. At the end of the second week, the percentage of "slightly better" or "much better" patients were 43%, 21% and 31% in the cetirizine QAM, BID and chlorpheniramine groups, respectively. The asthma severity distribution for cetirizine QAM showed greater improvement than
chlorpheniramine (43% vs. 31% slightly or much better and 6% vs. 13% slightly or much worse). For cetirizine BID, a less variable distribution was found, with 21% slightly or much better and 0% slightly or much worse. Differences in the distribution of severity among the three treatments approached significance (p=0.064).

9. **Rhinitis Severity by Body Weight Class**

Low weight patients received cetirizine 5mg/day in a single or a divided dose depending on treatment group. High weight patients received 10mg/day of cetirizine.

Generally, the high weight patients had less improvement than the low weight patients, irrespective of treatment group. However, these differences were not statistically significant.

In general, comparable effects of the three treatments were found in the high weight and in the low weight groups (Appendix C, Tables C.5.1-C.5.7 and Tables D.3.1-D.3.7.)

The results of the analysis of investigator assessments by weight group paralleled those of the patient assessments described above.

10. **Comparison of Asthmatics and Non-Asthmatics**

In general, asthmatic patients had significantly greater improvement than non-asthmatics in total severity and in all symptoms except itchy eyes and sneezing. The pattern of response among the treatment groups was similar for asthmatics and non-asthmatics, as indicated by the lack of statistically significant asthmatic-by-treatment interactions other than sneezing at week 2.

These results indicate that cetirizine and chlorpheniramine provide greater improvement of rhinitis symptoms for asthmatics than non-asthmatics. Due to the non-randomized nature of these subgroup, this conclusion should be interpreted cautiously.
11. Results by Study Center

The results at each center parallel those of the pooled analysis. Cetirizine QAM and BID provided comparable improvement to that of chlorpheniramine TID. Generally, the improvement during week 2 was greater than that of week 1. Unlike the pooled analysis, these weekly differences were not statistically significant, due primarily to the small sample sizes and consequently low statistical power.

C. SAFETY

1. Adverse Experiences

A summary of the incidence of all adverse experiences which occurred during the study is presented in Tables 22-30B. All reported adverse experiences have been included regardless of their severity or relationship to study drug. The adverse experiences were categorized by WHO dictionary preferred terminology. If a patient reported a specific adverse experience on more than one occasion, it is recorded as one adverse experience. Appendix D is a listing of all adverse experiences occurring in the study, by individual patient.

Table 22 presents the incidence of adverse experiences during the trial separately for chlorpheniramine patients, for all cetirizine patients combined, and for cetirizine patients taking each of the four possible cetirizine dose regimens (5 mg QAM, 10 mg QAM, 2.5 mg BID, and 5 mg BID). Among patients receiving cetirizine 10 mg/day, those on the QD regimen had more adverse experiences overall (23/55 patients or 41.8%) compared with those on the 5 mg BID regimen (17/54 or 31.5%). Somnolence appeared more common among 10 mg/day patients following a BID regimen (7/54 or 13.0%) than among those taking 10 mg QD (2/55 or 3.6%).

Because of the small number of cetirizine 5 mg/day patients (8 each on the QD and BID regimens), and because of the variety of dosing regimens used, all cetirizine patients are combined into one group for the remainder of this review of adverse experience incidence rates.

There were 33.6% (42/125) of cetirizine patients reporting an adverse experience (Table 22). The total number of adverse experiences reported by cetirizine patients was 59. Twenty-four (24) of 63 chlorpheniramine patients (38.1%) reported a total of 37 adverse experiences. The most common adverse experience among cetirizine patients was abdominal pain, reported by 12/125 patients (9.6%). The incidence of abdominal pain in the chlorpheniramine group was 4.8% (3/63). As a result of the frequency of abdominal pain, a decision was made to remove sorbitol from the syrup formulation and replace it with sugar in all future formulations.
Somnolence was equally common in both drug groups, reported by 10/125 cetirizine patients (8.0%) and by 5/63 chlorpheniramine patients (7.9%). Other adverse experiences occurring among cetirizine patients with an incidence greater than 1.6% (i.e., reported by more than two patients) were fatigue (4.0% incidence), and nausea and headache (3.2% each). Compared with the cetirizine group, the incidence of fatigue and headache were greater in the chlorpheniramine group (6.3% each), but nausea was less common (1.6% incidence).

The severity of adverse experiences among cetirizine and chlorpheniramine treated patients is presented in Table 23. Only one of 59 (1.7%) adverse experiences reported by cetirizine-treated patients was severe. Patient #013-104 entered the study with a severe cough. The cough lasted five days and did not require additional therapy. The patient did not have a history of asthma and pulmonary function tests performed during this study were normal. The patient completed the study.

All other adverse experiences were mild or moderate. In the chlorpheniramine group 91.9% (34/37) of the adverse experiences were reported as mild to moderate in severity and 8.1% (3/37) were reported as severe.

With respect to individual symptoms, ten of the 12 (83.3%) reports of abdominal pain were mild in the cetirizine group, 2/12 (16.7%) were moderate, none were severe. Each of the ten (100%) reports of somnolence in the cetirizine group were mild. Mild/moderate ratios for the three remaining cetirizine adverse experiences reported with an incidence greater than 1.6% were as follows: fatigue - 3 mild/2 moderate, headache - 2 mild/2 moderate and nausea - 4 mild/0 moderate.

Table 24 presents adverse experiences reported during the study among cetirizine and chlorpheniramine patients by the following intervals: days 1-7, days 8-14, and day 15 and greater. Since this is a 2-week trial, the first two intervals are of principal interest. In the cetirizine group, the incidence of patients reporting any adverse experience was similar in week 1 (25.6%) and week 2 (21.1%). Most of the common individual adverse experiences demonstrated a slight decline in incidence during the second week. Exceptions to this observation were headache, for which 3 of the 4 total reports occurred in the second week; and nausea, where all of the 4 reports occurred in the first week.

In a separate analysis, presented in Table 25, comparing the incidence of sedation among the cetirizine QAM, cetirizine BID and chlorpheniramine groups (4.8%, 11.3% and 6.4% respectively), no statistically significant differences were observed among the treatments in the incidence of this adverse experience.
The overall frequency of adverse experiences for high weight children (Table 26A) tested with cetirizine was 36.7% (40/109) which was higher than the frequency of adverse experiences in low weight children (Table 26B) treated with cetirizine, 12.5% (2/16). The frequencies of adverse experiences in chlorpheniramine treated patients were 38.9% (21/54) and 33.3% (3/9) for high weight and low weight groups respectively. There were no statistically significant differences within weight treatment groups comparison nor between high and low weight treatment groups comparisons.

Two or more patients reported the following adverse experiences in the high weight group: abdominal pain 11% (12/109), somnolence 8.3% (9/109), fatigue 4.6% (5/109), headache 3.7% (4/109), nausea 3.7% (4/109), dizziness 1.8% (2/109), increased appetite 1.8% (2/109), vomiting 1.8% (2/109), conjunctivitis 1.8% (2/109), dyspepsia 1.8% (2/109), and epistaxis 1.8% (2/109) for the cetirizine treated patients; and somnolence 7.4% (4/54), fatigue 7.4% (4/54), headache 7.4% (4/54), abdominal pain 5.6% (3/54), hyperkinesis 3.7% (2/54), diarrhea 3.7% (2/54), rash 3.7% (2/54) and cramps 3.7% (2/54) for the chlorpheniramine treatment group. There were no adverse experiences in the low weight group, for both drugs, reported by 2 or more patients.

The severity of adverse experiences for high and low weight patients is shown in Tables 27A and 27B, respectively. All of the three adverse experiences reported for low weight patients were mild (2) or moderate (1). Only one (2.5%; 1/40) adverse experience among the high weight children (Patient #013-14) was severe and this patient was previously discussed.

The summaries of all adverse experiences by cetirizine regimen for each weight grouping are shown in Tables 28A and 28B. Within the high weight group, 31.5% (17/54) of the 5 mg BID treated patients reported adverse experiences and 41.8% (23/55) of the 10 mg QAM treated patients reported adverse experiences. The frequency of specific adverse experiences reported were similar with the exception of somnolence. Somnolence was reported by 13% (7/54) of the 5 mg BID treated patients and 3.6% (2/55) of the 10 mg QAM treated patients (p=0.08). The frequency of abdominal pain was similar for both treatment groups with reporting frequencies of 11.1% (6/54) and 10.9% (6/55) for the 5 mg BID and 10 mg QAM treatment groups, respectively.
The low weight children received 5 mg QAM or 2.5 mg BID of cetirizine (Table 28B). There were 25% (2/8) and no (0/8) patients reporting adverse experiences for children treated with 5 mg QAM and 2.5 mg BID of cetirizine, respectively. Among the patients taking a total of 5 mg daily (1 teaspoon per day) there were no complaints of abdominal pain as compared to the children taking 10 mg daily (2 teaspoons per day).

Table 29A and 29B presents the adverse experiences occurring during intervals of continuous therapy for each weight group. Of the cetirizine high weight patients 27.5% (30/109), 23.4% (25/107) and 15.6% (14/90) reported adverse experiences during days 1-7, days 8-14 and 15 days or greater respectively. There were 12.5% (2/16), 6.3% (1/16) and 0% patients with adverse experiences during the same time periods for low weight cetirizine treated patients. The differences between weight groups were not statistically significant.

The chlorpheniramine high weight treatment group did not differ from the high weight cetirizine patient adverse event frequency during the same intervals of continuous treatment (Table 30A). The frequencies of adverse events reported by chlorpheniramine treated high weight patients were 29.6% (16/54), 28.3% (15/53) and 9.3% (4/43) during days 1-7, days 8-14 and day 15 or greater. Among the chlorpheniramine low weight patients 11% (1/9), 33.3% (3/9) and 42.9% (3/7) reported adverse experiences during days 1-7, days 8-14, or 15 days or greater respectively (Table 30B). The low weight chlorpheniramine treatment group was not significantly different from the low weight cetirizine treated patients.

No patients prematurely discontinued participation in this trial due to the occurrence of an adverse experience. However, patients 014-110 and 014-111 randomized to cetirizine and chlorpheniramine treatments, respectively, developed upper respiratory infections and discontinued therapy.

2. Clinical Laboratory Tests
Among the three cetirizine 10 mg QAM patients, abnormalities were recorded in a total of five tests, of which two were SGOT, two were SGPT and one was creatinine. Among the five cetirizine 5 mg BID patients, abnormalities were recorded in a total of six tests, of which two were SGOT and four were SGPT. None of these abnormalities were considered clinically significant by the investigators.

VII. CONCLUSIONS

Based on this study of one hundred eighty-eight pediatric patients with seasonal rhinitis, it may be concluded that:

(1) cetirizine 5–10mg given once daily and twice daily provides improvement in rhinitis signs and symptoms comparable to that of chlorpheniramine 2mg TID,

(2) cetirizine and chlorpheniramine have a rapid onset of action, with clinically significant improvement within 12 hours of the first dose,

(3) low weight patients had greater improvement than high weight patients (although the differences were not statistically significant). This indicates that the increase in body weight more than compensated for the increase in dose from 5mg to 10mg daily.

(4) patients with asthma had significantly better improvement in rhinitis symptoms than non-asthmatics,

(5) cetirizine in once daily and divided doses (BID) is safe and well-tolerated in a pediatric population.