CETIRIZINE STUDY 91CE16-0573

A MULTICENTER DOSE RESPONSE STUDY OF THE SAFETY AND EFFICACY OF CETIRIZINE IN THE TREATMENT OF SEASONAL ALLERGIC RHINITIS IN CHILDREN 6 TO 11 YEARS OF AGE

FINAL STUDY REPORT

JULY 23, 1993
A multicenter, double-blind, parallel group, placebo-controlled study was conducted to compare the efficacy and safety of cetirizine 5 mg QAM and 10 mg QAM as treatment for seasonal allergic rhinitis in children 6 to 11 years old. Two hundred and nine (209) male or female patients, 6 to 11 years old, with a documented history of seasonal allergic rhinitis during the fall pollen season were enrolled in the study. Allergy to weed pollen was verified by skin (intradermal or prick) or RAST testing within two years prior to entry. Patients had a minimum total score of 6 (of a possible 18) on a four-point symptom rating scale (0-3; none to severe) of six rhinitis signs and symptoms at the initial visit. In addition, patients had at least two individual symptoms (one of which must have been nasal discharge or sneezing) rated as moderate or severe.

The 209 patients were stratified into two weight groups. In each weight group, patients were randomly assigned to one of the three treatment groups for the four week study period. Study drug was administered as an oral solution. An electrocardiogram (ECG) was to have been obtained at baseline and the end of week 2 visit; however, in some subjects the follow-up ECG was obtained at the end of week 3 or end of week 4 visits.

Two hundred and five (205) patients were evaluable for efficacy analyses; 66, 69 and 70 in the placebo, cetirizine 5 mg and cetirizine 10 mg groups, respectively. Of the efficacy evaluable patients, there were 165 in the high weight group (≥25 kg) and 40 in the low weight group (<25 kg). All 209 entered patients were evaluable for safety analyses.

Sixteen patients (16/209; 7.7%) discontinued prior to completing four weeks of treatment: 6 placebo patients (8.8%), 6 cetirizine 5 mg patients (8.7%) and 4 cetirizine 10 mg patients (5.6%). The most common reasons for premature discontinuation were: intercurrent illness (7/16; 43.7%); insufficient clinical response (3/16; 18.8%) and poor compliance (2/16; 12.5%).

The treatment groups were generally comparable in baseline and demographic characteristics, for the combined weight groups and for the low weight group. Small, statistically significant but clinically unimportant differences among the treatment groups in patient age, weight and systolic blood pressure were observed in the high weight group. Baseline mean total severity score for the combined weight groups ranged from 6.8 to 7.0 over the three treatment groups. These mean total symptom scores were not significantly different.

A preliminary analysis of weekly change from baseline symptom severity indicated that the cetirizine effect was not consistent between weight groups. At study weeks 2, 3 and 4 the positive cetirizine effects are limited to the high weight group. Since 80% of the efficacy
patients are from the high weight group, the results of the combined analysis of all evaluable patients reflect principally the positive results in this subgroup.

Among all efficacy-evaluable patients (high and low weight groups combined), cetirizine 10 mg was significantly more effective than placebo in reducing the summary score of patient-rated rhinitis symptoms (total symptom score), the primary efficacy parameter in this study. Cetirizine 10 mg provided greater reductions in patient-rated total symptom score than placebo at weeks 2 and 3 in the by-week analysis, and in the overall analysis of the entire 4-week period. Cetirizine 10 mg was also superior to cetirizine 5 mg in this measure at weeks 2 and 3 in the by-week analysis. Individual symptoms which were significantly reduced by cetirizine 10 mg versus placebo were ocular pruritus at weeks 1 and 3 in the by-week analysis and in the overall 4-week analysis and oral/nasal pruritus at week 3 in the by-week analysis. For some of these individual symptoms, cetirizine 10 mg was superior to 5 mg. Cetirizine 5 mg was not better than placebo in any individual symptom or the total symptom score, with the exception of sneezing at week 1 in the by-week analysis.

The significant differences between treatments in patient-rated total symptom score obtained in the high weight subgroup were the same as those among all efficacy-evaluable patients, except in the high weight group cetirizine 10 mg was also significantly better than 5 mg in this measure in the overall 4-week analysis. For individual symptoms, cetirizine 10 mg was significantly superior to placebo in the high weight group in the overall 4-week analysis for conjunctivitis, ocular pruritus and sneezing, and in some weeks of the by-week analysis for these symptoms and for oral/nasal pruritus. For most parameters for which cetirizine 10 mg was superior to placebo (except sneezing) it was also significantly better than cetirizine 5 mg. Among the few patients in the low weight group, there were no significant differences among treatments in any symptom or the total symptom score. There was insufficient data to draw conclusions about the efficacy of cetirizine relative to placebo in patients less than 25 kg in body weight.

In the analysis of investigator assessments of symptom severity, estimated effects were smaller and not as consistently significant across symptoms as in the analysis of patient symptom ratings. In the combined weight groups, the only significant differences between treatments were the following: cetirizine 10 mg was superior to placebo and cetirizine 5 mg in reducing ocular pruritus and oral/nasal pruritus at week 3 in the by-week analysis, and cetirizine 5 mg was significantly better than placebo in reducing sneezing at week 4 in the by-week analysis. As with the patient assessments the primary contribution to overall positive treatment effects was made by the high weight subgroup. In this group cetirizine 10 mg was superior to placebo in the by-week analysis in reducing the total symptom score at week 3, ocular pruritus at weeks 2 and 3 (and also in the overall 4-week analysis), nasal discharge at week 2 and sneezing at week 4. For some of the measures for which cetirizine 10 mg was significantly superior to placebo it was also significantly superior to cetirizine 5 mg. There were no significant differences among the treatments in the investigator symptom ratings in the low weight group. There were no significant differences among the treatments in the investigator's global assessment of the effectiveness of the study medication.
The most common adverse experience for both treatments was headache: 15.0% (21/140) in cetirizine patients compared with 18.8% (13/69) in placebo patients. None of the occurrences of headache were attributed by the investigator to study drug. Pharyngitis was reported in 10.0% (14/140) of cetirizine patients and 13.0% (9/69) of placebo patients. Abdominal pain was reported in 9.3% (13/140) of cetirizine patients, and was considered drug-related in two of these patients, in the investigator's judgement. The incidence of abdominal pain in the placebo group was 4.3% (3/69 patients reported this complaint). Overall, there were no pronounced differences in the incidence rates of adverse experiences in the cetirizine 5 and 10 mg dose groups. One patient in the cetirizine 5 mg group prematurely discontinued study participation due to an adverse experience, exacerbation of asthma, considered by the investigator to be of uncertain relationship to study drug administration. Another patient treated with 5 mg cetirizine had clinically significant and possibly drug-related abnormal laboratory test results for hematocrit and hemoglobin. These were thought by the investigator to be possibly due to mild iron deficiency anemia. There were no other clinically significant and possibly drug-related laboratory test abnormalities in any patient in the study.

Two hundred and two (202) of the 209 randomized patients provided sufficient ECG data for analysis. ECG data was analyzed by comparison among the treatments of change from baseline in the corrected QT interval (QTc), and by comparison of numbers of subjects in the three treatment groups in categories of percent increase from baseline in QTc (<5%, 5% to <10%, 10% to <20%, ≥20%). Analyses were performed on three subsets of patients: an endpoint analysis including all 202 patients of change from baseline to last ECG, an endpoint analysis of change from baseline to last ECG excluding patients whose last ECG was obtained more than 2 days after the last dose of study drug and an analysis of change from baseline to ECGs obtained 11-17 days after the start of the study (i.e., within ±3 days of the end of week 2 visit on day 14). Each of the analyses of mean change from baseline showed that cetirizine treatment did not result in statistically greater mean increases in QTc compared with placebo. None of the 202 patients had an increase of 20% or more from the baseline QTc. Furthermore, the number of patients with a 10% to 20% increase in QTc was comparable across treatment groups.

This study indicates that cetirizine 10 mg QAM provides significant relief of the signs and symptoms of seasonal allergic rhinitis in the pediatric population. Cetirizine 5 mg QAM did not appear to provide significant relief of seasonal allergic rhinitis in pediatric patients. Cetirizine in the dose range of 5 to 10 mg is well tolerated. Cetirizine in doses of 5 mg or 10 mg, compared to placebo, does not prolong the QTc interval in pediatric patients.
III. OBJECTIVE

This multicenter, double-blind, parallel group, placebo-controlled study was conducted to compare the efficacy and safety of 5 mg QAM and 10 mg QAM doses of cetirizine for seasonal allergic rhinitis over a four-week treatment period in children 6 to 11 years old.

IV. MATERIALS AND METHODS

A. STUDY DESIGN

(1) Patient Population

This was a randomized, double-blind, parallel-group, 12-center study of two hundred and nine (209) male and female patients between 6 and 11 years old with a documented history of seasonal allergic rhinitis during the fall pollen season confirmed with allergen sensitivity via RAST or skin tests. The RAST and/or skin tests must have been performed within two years of the start of the study. Patients were required to have a total symptom score of at least 6 (of a possible 18), based on the investigator rating of six signs and symptoms of rhinitis, with at least two symptoms rated as moderate or severe (one of which was required to be either nasal discharge or sneezing).

One of the 12 centers eligible to participate in this study did not enroll any patients (center No. 92N0034, Dr. Kaiser).

(2) Patient Exclusion Criteria

Reasons for patient exclusion from the study were:

1. An underlying disease that would interfere with the evaluation of the therapeutic response;

2. Patients with any clinically significant concomitant disease;

3. Patients with severe exacerbation of asthma during the pollen season;

4. A history of allergic reaction to hydroxyzine or cetirizine;

5. Post-menarcheal female patients;

6. Patients with significantly abnormal renal, hematologic or hepatic function tests;

7. Patients undergoing an escalating course of desensitization or who have been on a stable regimen for less than 6 months;
8. Patients who were not capable of understanding and accepting the reasons for their participation in the study;

9. Patients who could not discontinue nasal decongestants for 24 hours, antihistamines for 48 hours or cromolyn sodium for two weeks before and during the course of the study;

10. Administration of oral steroids or astemizole within two months of study entry;

11. An inability to stop inhaled, intranasal or topical steroids for two weeks prior to and for the duration of the study;

12. Use of an investigational drug during the month prior to entry or previous participation in a cetirizine study;

13. Patients who expected to be away for more than one or two days during the study period or who presented other compliance problems;

14. Intention to donate blood during or four weeks after the study.

(3) Study Treatment

This study utilized three treatment groups stratified by low and high weight groups in parallel fashion. High weight was defined as 25 kg (55 lbs) or greater; low weight as less than 25 kg. The efficacy period was four weeks long. The study design is summarized in the diagram on the following page.

Documentation of a history of seasonal allergic rhinitis and sensitivity to grass pollen was obtained at the baseline visit, and baseline signs and symptoms were recorded. Patients who qualified entered the study and were randomized to the three treatment groups.

Study medication, in the form of an oral solution, was taken each morning of the study, at 10 AM. The first dose of medication was to be taken at the study site if the visit occurred before 10 AM. If the visit occurred after 10 AM, the first dose was to be taken the following morning. The dose of study medication did not change over the treatment period. Parents were given two bottles and asked to see that the child took 1 tsp from Bottle A and 2 tsp from Bottle B each morning.
B. CLINICAL OBSERVATIONS

(1) Physical Examination

At entry to the study (day 1), patients underwent a complete physical examination, including weight and specimens for laboratory evaluation. History of seasonal allergic rhinitis was documented, and allergy to grass pollen was confirmed by performing RAST or intradermal skin tests (if not done within the previous 2 years by the investigator). The complete physical examination was repeated at the end of the study.

(2) Signs and Symptoms

At entry to the study (day 1), and after 1, 2, 3 and 4 weeks of treatment, the investigator recorded the severity of: sneezing, nasal discharge, pruritus of the eyes, pruritus of the oral and/or nasal mucosa, conjunctivitis, and nasal congestion.

At day 1, a total symptom severity score was calculated as the sum of the severities of all signs or symptoms noted above. This score was used to determine if the patient met the entry criteria. The total symptom score used in the efficacy analysis excluded nasal congestion (refer to Section V.C).

Each morning during the study, parent and child completed a daily diary of the severity of each symptom over the 24 hours prior to each dose of study medication. Severity was rated using the same scale as above. The diary was to be completed immediately prior to the AM dose. This applied to all doses including the initial dose (i.e., first diary entry was made prior to administration of first dose).

(3) Global Evaluations

At the end of the four week treatment period, the investigator made an overall assessment of the effect of therapy, in conjunction with the patient and parent but without referring to the diary cards.
(4) Adverse Experiences

At each study visit (after 1, 2, 3 and 4 weeks of treatment), the investigator recorded all adverse experiences, including time of onset, severity, duration and relationship to study medication. The patient diary included sheets for recording of adverse experience data. The investigator included the adverse experiences noted in the diaries in the weekly visit adverse experience record.

(5) Laboratory Data

The following laboratory tests were done at entry to and at the end of the study: CBC (including platelet count) with differential, serum chemistries (including total bilirubin, SGOT, SGPT, creatinine and BUN) and urinalysis. Laboratory test results falling outside of the normal range were reviewed by the investigator for clinical significance and relationship to study medication.

(6) Electrocardiogram

A 12-lead electrocardiogram was to have been obtained at baseline and at the end of week 2 visit.
V. STATISTICAL METHODS

A. EFFICACY EVALUABLE ANALYSES

Patients were blindly evaluated for eligibility and compliance to the protocol. The analyses and conclusions were based on data from patients determined to be evaluable for efficacy.

Only four patients were non-evaluable for efficacy analysis.

B. PATIENT DIARY DATA

Total symptom scores were computed for each diary day in which at least three severities (exclusive of nasal congestion) were present. Daily total symptom scores were used to compute weekly mean total scores by the above formula.

C. EFFICACY PARAMETERS

The primary efficacy parameter was the patient assessment of total symptom score, defined as 5 times the mean of the severity of all signs and symptoms listed in Section IV.B.2, excluding nasal congestion. Severity of nasal congestion was not included in the total since the literature on allergic rhinitis indicates that antihistamines do not control nasal congestion.

The effect of cetirizine on seasonal allergic rhinitis was assessed using the mean change from baseline (day 1) in patient-rated total symptom score, as well as the mean change from baseline in severity of the individual symptoms of patient-rated conjunctivitis, nasal congestion, nasal discharge, pruritus of oral/nasal mucosa, pruritus of eyes, and sneezing.
Other measures of treatment efficacy were the change from baseline with respect to the investigator assessment of severity of each symptom and total symptom score and the investigator's global evaluation of therapeutic effect.

D. BASELINE SEVERITY

For patient diary data, baseline severity was taken as the rating given by the patient at the initial diary entry (day 1). These day 1 scores were omitted from calculation of week 1 mean symptom severities.

For investigator assessments, baseline severity was taken as the rating given by the investigator, in conjunction with the patient, at the screening visit.

E. ECG MEASUREMENTS

The measured QT interval was corrected for heart rate using Hodges' Formula: QTc = QT + 1.75*(HR-60). The change from baseline to end of treatment heart rate (HR) and QTc, as well as QT uncorrected, was analyzed comparatively between treatments to determine the effect of cetirizine on these ECG parameters. A positive change indicates an increase over the baseline value. (QT was also corrected for heart rate using the traditionally accepted Bazett's Formula: QTc=QT/(Sqrt(60/HR)). This correction was also analyzed and presented for reference purposes. However, based on empirical validation of the formulas, Hodges Formulas is deemed to be more appropriate.)

F. STATISTICAL MODELS

(1) Demographic and Baseline Characteristics

Comparability of the treatment groups with respect to demographic characteristics was assessed using analyses of variance for quantitative parameters (age, weight, height, pulse, systolic and diastolic blood pressure, temperature and duration of illness). The models included terms for center, treatment and the treatment-by-center interaction. Differences among treatments for baseline symptom severity were assessed in the same manner. Comparability for the categorical parameters of race and sex were assessed by Cochran-Mantel-Haenszel tests with centers as strata. This was done for weight groups combined and also separately.

(2) Analysis of Symptom Severity by Week

For each symptom and the total symptom score as rated by either the patient or investigator, differences in mean change from baseline severity were compared among treatments by analyses of covariance. Analyses were performed separately for each study week utilizing all evaluable data available. The number of patients in each analysis varies according to the pattern of missing or non-evaluable responses. Patients who discontinued treatment early due to insufficient clinical
response were included in the analyses of weeks subsequent to discontinuation with their final severity scores carried forward.

A preliminary analysis was performed to assess the effect of weight stratification on patient response. The statistical model included terms for baseline (the covariate), weight group, treatment and the weight-by-treatment interaction. Since the distribution of weight groups was very unbalanced among centers -- two centers did not enroll any low weight patients and one enrolled only two -- a center term was not included in the statistical model. This analysis indicated that treatment differences were dependent on patient weight group (see Table 14) after study week 1.

(3) Repeated Measures Analysis of Symptom Severity

Repeated measures analyses of covariance over study weeks were also conducted employing the multivariate repeated measures methodology of SAS PROC GLM. The statistical model included the effects of baseline, center, treatment, study week and all the first and second order interactions of the main effects. Consistent with a multivariate approach to repeated measures, patients who did not have complete data for all study weeks were excluded from these analyses. Patients discontinued early due to insufficient clinical response were treated as complete patients with their final severity ratings carried forward to the subsequent weeks, and were included in the repeated measures analyses.

(4) Statistical Computations and Statistical Significance

All statistical analyses were performed using the Statistical Analysis System (SAS) software package, Version 6.04. PROC GLM Type III sums of squares were computed for all the effects in the models, and adjusted treatment means are the LSMEANS produced by PROC GLM.

The overall treatment effect in the model was declared statistically significant if the p-value for the associated F-ratio is less than or equal to .05. Pairwise comparisons of adjusted treatment means (adjusted for baseline differences and
center differences) were made using the two-sided protected least significant difference test at the .05 level of significance for each comparison. Interaction effects were declared statistically significant if the associated p-value is less than or equal to .10.

(5) Global Evaluations

Differences in the distribution of the global evaluations of therapy among the treatment groups were analyzed using the general association version of the Cochran-Mantel-Haenszel test with study centers as strata. Overall differences among treatments were declared statistically significant if the associated p-value was less than or equal to .05.

(6) Analysis of Heart Rate and QT Interval

Mean changes for HR, QT and QTc(Hodges and Bazett) were compared among treatment groups using standard one-way analysis of covariance procedures. Observed mean changes were adjusted for differences in baseline values. The treatment effect was declared statistically significant if the computed F-ratio was greater than or equal to the 5% critical value. Following a significant F-ratio, pairwise comparisons of adjusted treatment means were made using the Least Significant Difference at the nominal .05 level of significance.

In addition to the analysis of mean change from baseline, the percent increase from baseline for QTc was categorized as less than 5%(including decreases), 5 to less than 10%, 10 to less than 20%, and over 20% in order to determine the incidence of clinically significant increases. Increases in QTc of 20% or greater are considered clinically significant. The distribution of percent increase was compared between treatments using the Mantel-Haenszel statistic (with two degrees of freedom and assuming equally spaced, integer scoring of the categories) produced by SAS PROC FREQ. Overall treatment differences were declared statistically significant if the computed statistic was greater than or equal to the 5% critical value of the Chi-square distribution. Pairwise comparisons of treatments were made using pairwise Mantel-Haenszel statistics at the nominal 5% level of significance whenever the overall statistic was significant.
VI. RESULTS

A. PATIENT CHARACTERISTICS

(1) Patient Population

Sixty-eight (68) patients were randomized to the placebo treatment group, and 69 and 72 to the cetirizine 5 mg and 10 mg treatment groups, respectively (Table 1). Sixty-six of 68 placebo patients were evaluable for efficacy, as were 69 of 69 cetirizine 5 mg patients and 70 of 72 cetirizine 10 mg patients. Two placebo patients and two cetirizine 10 mg patients were not evaluable for any efficacy parameters. The two excluded placebo patients (and reason for exclusion) were 92N0036-293 (protocol violation of bilateral polyposis at baseline) and 92N0040-220 (withdrawn after one dose due to ECG abnormality at baseline). The excluded cetirizine 10 mg patients were 92N0037-30 (medication dispensing error, discussed below) and 92N0043-167 (received only one dose of study medication and refused to take any further doses).
(2) Baseline and Demographic Characteristics

Mean age in the placebo and cetirizine 5 and 10 mg groups for high weight patients was 9.3, 9.6 and 8.9 years, respectively; mean weight in these groups was 83.6, 81.5 and 77.5 lbs, respectively. Mean systolic blood pressure ranged from 101.6 to 104.8 mmHg among the three groups for high weight patients. None of these differences were clinically important. There were no significant differences among the treatments in these characteristics in the low weight group.

Summary statistics for baseline symptom severity ratings are presented in Table 6D. There were no statistically significant differences among the treatments with respect to the baseline severity of any symptom. Baseline mean total symptom score for the combined weight groups ranged from 6.8 to 7.0.

B. EFFICACY

(1) Patient Diary Data - Assessment of Weight Effect on Response

As stated previously in the description of statistical methods (Section V), a preliminary analysis of weekly change from baseline symptom severity indicated that the cetirizine effect was not consistent between weight groups. Table 14 presents a summary by week of adjusted treatment means within each weight stratum along with p-values for the weight-by-treatment interaction. At study weeks 2, 3 and 4 the interaction was statistically significant with respect to the total symptom score, and indicates that positive cetirizine effects are limited to the high weight group.
Because of this dependence of drug effect on patient weight, the primary analysis (described in the next section) of change from baseline severity was conducted separately for each of the weight groups in addition to the analysis for the combined study group. Since 80% of the patients are from the high weight group, the results of the combined analysis reflect principally the positive results in this subgroup.

(2) Patient Diary Data - Primary Analysis of Improvement in Rhinitis Severity for Weight Groups Combined

Among all evaluable patients the improvement in total symptom score for cetirizine 10 mg was significantly greater than that of both placebo and cetirizine 5 mg at study weeks 2 and 3. Differences between cetirizine 5 mg and placebo with respect to total symptom score were not statistically significant at any study week.

With respect to individual symptoms, cetirizine 10 mg was significantly more effective than placebo at study week 1 and 3 in reducing severity of ocular pruritus and also significantly more effective than 5 mg at week 3. Cetirizine 10 mg also provided significantly greater reductions in oral/nasal pruritus versus 5 mg at weeks 2 and 3 and versus placebo at week 3. Cetirizine 5 mg provided significantly greater reductions in sneezing at week 1 than placebo.

The mean reduction in severity of ocular pruritus and the total symptom score over the entire four week treatment period (obtained from the repeated measures analysis on complete patients) was significantly greater for cetirizine 10 mg as compared to that of placebo, and for mean severity of ocular pruritus and oral/nasal pruritus cetirizine 10 mg provided significantly greater relief than cetirizine 5 mg. The treatment-by-week interaction was not statistically significant for any symptom, indicating that treatment effects are consistent over study weeks.

Except for one analysis (conjunctivitis at week 2), the treatment-by-center interaction was not statistically significant, indicating consistency of treatment effects across study centers. Therefore, the results stated above based on
treatment differences pooled across centers require no qualification. Statistical analyses separately by study center are contained in Appendix B.

(3) Patient Diary Data - Primary Analysis of Improvement in Rhinitis Severity For Weight Groups Separately

Tables 8A, 8B and 8C.1-4 present summaries of the analyses of patient symptom ratings for the subgroup of high weight patients, and Tables 9A, 9B and 9C.1-4 present the same for the low weight group. Complete details of these analyses are provided in Appendix A.

As shown in Table 8A, among the high weight patients, cetirizine 10 mg provided significantly greater reductions in total symptom score compared to placebo and cetirizine 5 mg at study weeks 2 and 3. With respect to individual symptoms, cetirizine 10 mg provided significantly greater relief compared to placebo of ocular pruritus at every study week, of conjunctivitis and oral/nasal pruritus at study weeks 2 and 3, and of sneezing at weeks 1 and 2. Compared to cetirizine 5 mg, the mean reductions in symptom severity were significantly greater for cetirizine 10 mg with respect to conjunctivitis and oral/nasal pruritus at study weeks 2 and 3, and with respect to ocular pruritus at weeks 1, 2 and 3. The reduction in severity of sneezing at week 1 was the only symptom for which cetirizine 5 mg was significantly better than placebo.

In the repeated measures analysis of change in symptom severity over the 4-week treatment period (Table 8A), cetirizine 10 mg significantly reduced total symptom score compared to placebo and cetirizine 5 mg. For the individual symptoms of conjunctivitis, ocular pruritus and sneezing, cetirizine 10 mg was statistically significantly more effective in reducing severity relative to placebo, and compared to cetirizine 5 mg the mean reductions over four weeks were significantly greater with respect to ocular pruritus and oral/nasal pruritus. Sneezing was the only symptom for which cetirizine 5 mg significantly reduced the mean severity over the four weeks of treatment.

In the repeated measures analysis for the high weight group, the treatment-by-week interaction was statistically significant for the total symptom score and also for severity of conjunctivitis (Table 8B). At each study week all three treatments showed reduction in total symptom severity. The cetirizine effect was always positive for both doses with 10 mg providing greater symptom reduction than 5 mg, but the magnitude of the effects vary from week to week.
(4) **Investigator Assessments - Improvement in Rhinitis Symptom Severity**
Cetirizine 10 mg provided significantly greater reduction in nasal discharge than placebo at week 2. Significantly greater reductions in oral/nasal pruritus severity occurred in the cetirizine 10 mg group compared with the cetirizine 5 mg group at week 3. With respect to total symptom score, cetirizine 10 mg produced significantly greater symptom reduction than placebo at week 3 and relative to cetirizine 5 mg was significantly better at both week 2 and 3. Both cetirizine 10 mg and 5 mg were significantly more effective in reducing severity of sneezing compared to placebo at week 4. The treatment-by-center interaction was statistically significant with respect to severity of conjunctivitis, ocular pruritus and nasal discharge and also for the total symptom score for at least one study week in each case (Table 11B). Statistical analyses separately by study center are contained in Appendix B.

In the repeated measures analyses for the high weight group (Table 11A), the treatment effect over the 4-week study period indicated that cetirizine 10 mg significantly reduced only ocular pruritus compared with placebo and cetirizine 5 mg. The treatment-by-week interaction was significant for conjunctivitis, oral/nasal pruritus and the total symptom score, and the treatment-by-center interaction was statistically significant only for severity of conjunctivitis (Table 11B).

Among the low weight group no statistically significant cetirizine effects were observed in the investigators symptom ratings (Table 12A). Again as with the patients’ assessments, the direction of differences from placebo were not consistently positive for the cetirizine groups.

(5) Investigators’ Global Evaluations of Treatment Effectiveness

There were no statistically significant differences among treatments with respect to these distributions combined across weight groups, and this result was consistent for each weight group separately.

C. SAFETY

(1) Adverse Experiences
The most common adverse experience for both treatments was headache: 15.0% (21/140) in cetirizine patients compared with 18.8% (13/69) in placebo patients. None of the occurrences of headache were attributed by the investigator to study drug. Pharyngitis was reported in 10.0% (14/140) of cetirizine patients and 13.0% (9/69) of placebo patients. Abdominal pain was reported in 9.3% (13/140) of cetirizine patients, and was considered drug-related by the investigator in two of these patients. The incidence of abdominal pain in the placebo groups was 4.3% (3/69 patients reported this complaint). The next most common complaint in the cetirizine group was coughing, with an incidence of 8.6% (12/140 patients), similar to the 8.7% incidence (6/69 patients) in the placebo group. Epistaxis was reported by 7.1% of cetirizine patients (10/140); 4.3% (3/69) placebo patients had this adverse experience. Among cetirizine patients, bronchospasm occurred with an incidence of 5.7% (versus 7.2% in the placebo group) and vomiting with an incidence of 4.3% (versus 2.9% in the placebo group). Five cetirizine patients each (3.6% of the total) reported the following adverse experiences: diarrhea, nausea, respiratory disorder, fever and pain. These adverse experiences each had an incidence of 1.4% in the placebo group, with the exception of nausea (2.9% placebo incidence) and respiratory disorder (7.2% placebo incidence). Conjunctivitis and edema each had an incidence of 4/140 cetirizine patients (2.9%); the respective placebo incidence rates were 4.3% and zero. Hyperkinesia, dyspepsia and fatigue each had an incidence of 3/140 cetirizine patients (2.1%); the respective placebo incidence rates were zero, 1.4% and 4.3%. The remaining adverse experiences were reported by two or fewer cetirizine patients each.

The majority of cetirizine adverse experiences were mild (Table 16). Of the 157 adverse experiences reported by cetirizine patients, 60.5% (95/157) were mild, 26.1% (41/157) were moderate and 12.7% (20/157) were severe. Severity was not specified for one of the 157 cetirizine adverse experiences. For the placebo patients the distribution was 59.1% (42/71) mild, 33.8% (24/71) moderate and 7.0% (5/71) severe. Of the 21 occurrences of headache in the cetirizine patients, 9 were mild, 10 were moderate and 2 were severe. Seven (7) of the 13 complaints of headache in the placebo group were mild and 6 were moderate; none were severe. Of the 14 occurrences of pharyngitis in the cetirizine patients, 8 were mild, 3 were moderate and 3 were severe. The severity distribution of
the 9 placebo complaints of pharyngitis was mild - 5, moderate - 2, severe - 2. Of the 13 instances of abdominal pain in the cetirizine group, 10 were mild, 3 were moderate and none were severe. Of the 3 instances of abdominal pain in the placebo group, 2 were mild, one was moderate and none were severe.

As shown in Table 17, 36 of 69 cetirizine 5 mg patients (52.2%) reported an adverse experience; 35 of 71 cetirizine 10 mg patients (49.3%) reported an adverse experience. With the exception of headache, the most common cetirizine adverse experiences (occurring in > 5 patients for both doses combined) had approximately the same incidence or a lower incidence in the 10 mg group compared with the 5 mg group. Headache occurred in 13% (9/69) of cetirizine 5 mg patients and in 16.9% (12/71) of cetirizine 10 mg patients. Overall, there were no pronounced differences in the incidence rates of adverse experiences in the two cetirizine dose groups.

As shown in Table 18, there was a small decline in the percentages of cetirizine patients reporting adverse experience over the four weeks of the study: week 1 - 29.3%, week 2 - 28.8%, week 3 - 24.3%, week 4 - 22.9%. Headache appeared more common during the first week (10.0% incidence) than during the remaining three weeks (2.9-4.3% incidence). Abdominal pain declined after the first week, when the incidence was 5.7%. During the remaining three weeks the incidence of abdominal pain was 0.7-3.1%. Epistaxis also declined, from 4.3% during the first week to 0.8-2.9% over the remaining weeks. The incidence of coughing rose during the study, from 2.9% in week 1 to 6.9% in week 4. The incidence of bronchospasm was higher in weeks 3 and 4 (3.8-4.4%) compared with weeks 1 and 2, when the incidence of this complaint was zero and 1.4%, respectively. In the placebo group, the percentage of patients reporting adverse experiences did not change markedly during the study intervals (20.6-23.2% over the four weeks). Of the individual adverse experiences in the placebo group, headache declined from the week 1 incidence of 11.6% to 6.1% at week 2 and 3.1-3.2% at weeks 3-4. The incidence of pharyngitis in the placebo patients was low at week 1 (1.4%), and became higher as the study progressed (week 3-4 incidence of 6.2-6.3%). As in the cetirizine patients, coughing in the placebo group was more common as the study progressed (1.4% in week 1, 4.8% in week 4).

One patient in the study, who received cetirizine 5 mg, prematurely discontinued study participation due to an adverse experience.
None of the adverse experiences which occurred during this study met the FDA definition of a "serious" adverse experience.

(2) Clinical Laboratory Tests

Laboratory tests were obtained at baseline and at the end of the study. Table 19 is a frequency distribution, for each laboratory test, of the total number of patients with an abnormality in that test during the study, and the abnormality category (1-9) into which the abnormality for that patient was placed. Results for the two treatments (cetirizine and placebo) are presented on separate pages. The categorization system is described on the first pages of Data Listing 7 (Appendix C), which presents all laboratory data obtained for all patients in the study. The total number of abnormalities classified in Category 9 ("clinically significant and possibly related to study drug") was 2 among the cetirizine patients and was zero in the placebo group. Both Category 9 abnormalities (one in hematocrit, one in hemoglobin) were in the same cetirizine patient, who is briefly described below.
Two hundred two (202) patients had an ECG evaluation at baseline and during treatment. The distribution of the number of patients with follow up ECGs by the day of occurrence was as follows: 4 patients on day 10 or less; 121 patients on days 11 - 17; 23 patients on days 18 - 22; 40 patients on days 23 - 27; and 14 patients on day 28 or greater (Table 20). Thus, there were 81 patients with ECGs performed on days other than the 14 ± 3 day window and 121 patients with ECGs obtained according to protocol.

There were no clinically significant abnormal ECGs that lead to a change in treatment nor any arrhythmia during the study. A data listing for each patient may be found under Data Listing 8 in Appendix C.

ECG intervals were determined using the digitizing tablet and cross hair cursor. The methods are provided in Appendix F (ECG Interval Digitizing Protocol).

Analyses were performed for three subsets of patients: an endpoint analysis including the 202 patients with baseline and on/post treatment ECG; an endpoint analyses excluding patients with ECGs recorded more than 2 days after the last dose; and patients with ECGs recorded after 11 - 17 days of treatment (i.e., within ±3 days of the end of week 2 visit on day 14). Analysis of the heart rate, QT, corrected QT (QTc), and per cent change in QTc were performed for each subset. There was no statistically significant changes in the heart rate for any of the time periods. Therefore, this discussion will focus on the QTc results.

Table 21 shows the analysis of the adjusted mean QTc change from baseline for the endpoint ECGs. The Hodges adjusted mean QTc change from baseline within the placebo treated patients was 2.44. The adjusted change from baseline for 5 mg and 10 mg cetirizine patients was -5.09, and 6.79, respectively. The difference across treatment groups was statistically significant (p<0.001). Pairwise comparison of the mean adjusted QTc showed cetirizine 5 mg to be
significantly less than both placebo and cetirizine 10 mg. Cetirizine 10 mg was not significantly different from placebo.

The adjusted mean QTc change from baseline, using the Bazett equation, was 3.44 for the placebo treatment group, -4.71 for the 5 mg cetirizine treatment group and 9.61 for the 10 mg cetirizine treatment group as shown in Table 21. The difference across treatment groups was statistically significant (p=0.002). Cetirizine 5 mg was significantly less than placebo and cetirizine 10 mg based on pairwise comparison. Cetirizine 10 mg was not significantly different from placebo.

The adjusted change from baseline for the ECGs obtained within two days of the last dose showed a statistically significant difference for the Hodges QTc (p<0.001) and Bazett QTc (p=0.002) as seen in Table 22. The values were 2.05, -4.74, and 7.61 for placebo, 5 mg and 10 mg cetirizine, respectively, using the Hodges equation. Adjusted mean change for placebo and cetirizine 10 mg were both significantly different from that of cetirizine 5 mg. Using the Bazett equation, the values were 2.95, -4.27, and 10.53 for placebo, 5 mg and 10 mg cetirizine, respectively. The adjusted mean change for cetirizine 5 mg was significantly less than cetirizine 10 mg. Pairwise comparison of the adjusted change for the placebo and 10 mg cetirizine treatment groups was not statistically significant for both the Hodges and Bazett QTc calculations (p > 0.05).

The Hodges adjusted mean QTc change from baseline for days 11 to 17 showed differences between treatment groups. As shown in Table 23, the Hodges adjusted mean QTc change from baseline was 1.37 for the placebo treatment group, -5.13 for the 5 mg cetirizine treatment group, and 5.90 for patients treated with 10 mg of cetirizine (p=0.018). Pairwise comparison showed the QTc for cetirizine 5 mg was significantly less than cetirizine 10 mg (p ≤ 0.05), but there was no difference between placebo and cetirizine 10 mg. The adjusted change using the Bazett equation was 2.13, -3.40 and 9.63, for the placebo, 5 mg cetirizine and 10 mg cetirizine treatment groups.

None of the patients had an increase in QTc, using the Hodges equation, greater than or equal to 20% (Table 24). The highest percent change (17.1%; 368 msec to 431 msec) from baseline occurred in a patient treated with 5 mg of cetirizine, 920040-219 (Data listing 8 Appendix C). Among patients with endpoint ECGs, the number of patients with an increase in QTc (Hodges) between 10 to 20% over the baseline value was 3 (4.4%), 4 (6.2%), 1 (1.5%) for placebo, 5 mg, and 10 mg cetirizine treated patients, respectively (Table 24). The differences among treatments with respect to the distribution of percent changes as shown in Table 24 were not statistically significant. These data do not suggest a clinically significant increase in QTc in cetirizine treated pediatric patients.

The results of the analysis using the Bazett equation showed no significant difference between treatment groups (Table 25). There were six (8.7%) placebo patients, five (7.7%) patients treated with 5 mg cetirizine and eight (11.8%) patients treated with 10 mg cetirizine who had an increase in QTc between 10%
to 20%. Patient 92N0042-183 received placebo and had the largest (19.8%; 352 msec to 404 msec) change from baseline.

The distribution of percent changes in Hodges QTc and Bazett QTc for ECGs obtained within two days of the last dose is shown in Tables 26 and 27, respectively. This analysis is consistent with the results of the endpoint analysis.

When the number of patients with ECGs at baseline and days 11 -17 were evaluated for percentage QTc change, there was no statistically significant difference with the Hodges QTc (p=0.636) and the Bazett QTc (p=0.483) as shown in Tables 28 and 29, respectively.

In summary, the analysis of all ECGs and those ECGs obtained within two days of the last administered dose showed that mean changes in QTc associated with cetirizine treatment were not statistically significantly greater than the changes observed in the placebo group. As compared to placebo, cetirizine did not lead to a statistically significant increase in QTc after 11 -17 days of treatment. None of the 202 patients had an increase of 20% or more from the baseline QTc. Furthermore, the number of patients with 10% to 20% increase in QTc was comparable across treatment groups. Thus, these data show that cetirizine in doses of 5 mg or 10 mg, compared to placebo, does not prolong the QTc interval in pediatric patients.

VII. CONCLUSIONS

Based on this double-blind study of 209 patients with seasonal allergic rhinitis, it may be concluded that:

1. cetirizine 10 mg QAM provides significant improvement in the signs and symptoms of rhinitis over 4 weeks of treatment,

2. cetirizine 5 mg QAM does not provide significant improvement in the signs and symptoms of rhinitis over 4 weeks of treatment,

3. there is insufficient data to draw conclusions on the efficacy of cetirizine 10 mg relative to placebo in lower weight patients (<25 kg),

4. cetirizine 5 mg QAM and 10 mg QAM in children aged 6-11 years is safe and well tolerated,

5. cetirizine in doses of 5 mg or 10 mg, compared to placebo, does not prolong the QTc interval in pediatric patients.