CETIRIZINE STUDY 90CE16-0470

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
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II. ABSTRACT

A multicenter, double-blind, parallel group, placebo-controlled study was conducted to compare the efficacy and safety of 1.25 mg o.d., 2.5 mg o.d., and 5 mg o.d. doses of cetirizine. A secondary objective was to assess any differences in the effect of cetirizine between high weight (25 kg or more) and low weight (less than 25 kg) patients. Three hundred twenty-four (324) male or female patients, 6 to 11 years old, with a documented history of seasonal allergic rhinitis during the grass pollen season were enrolled in the study. Allergy to grass 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) of at least moderate severity.

The 324 patients were classified by initial weight (264 patients 25 kg or greater and 60 patients less than 25 kg). In each weight group, patients were randomly assigned to one of the treatment groups for the four week study period. Three hundred seven (307) patients were evaluable for efficacy analyses. All but one patient (who did not take study medication) were evaluable for safety analyses.

Thirty-three patients (33/324; 10.2%) discontinued prior to completing four weeks of treatment: 8/84 patients (9.5%) on placebo, 9/80 (11.2%) on 1.25 mg cetirizine, 9/79 (11.4%) on 2.5 mg cetirizine, and 7/81 (8.6%) on 5 mg cetirizine. The most common reasons for premature discontinuation were: intercurrent illness (8/33; 24.2%); protocol violation (9/33; 27.3%) and insufficient clinical response (8/33; 24.2%).

The treatment groups were generally comparable in baseline and demographic characteristics. Baseline mean total severity score ranged from 7.7 to 8.0 over the four treatment groups. These mean total symptom scores were not significantly different.

During the first week of treatment, mean patient assessment of total symptom score decreased by 0.8 in the placebo group, 1.1, 1.3, and 1.6 in the 1.25 mg, 2.5 mg, and 5 mg cetirizine groups, respectively. These treatment means were not significantly different, nor were the treatment means at any other week or when averaged over the four week treatment period. While the placebo, the 1.25 mg and the 2.5 mg groups showed steady improvement in total severity score from week 1 to week 4, no apparent time trend was found in the 5 mg cetirizine group.

Mean change from baseline total symptom severity score, as measured by the investigator, was comparable for all groups at each weekly visit. Over the 4 week study period, all four groups showed generally steady improvement.

Results of the analyses of high weight and low weight patients separately parallel the above findings, in the general absence of any significant differences among treatments at any timepoint.
The overall incidence of cetirizine patients with one or more adverse experiences was 17.6% (42/239). This incidence was similar to the 19% (16/84) frequency of adverse events seen in the placebo group. There were a total of 54 adverse experiences reported by the cetirizine treatment group compared to 20 reported by the placebo group. The most common adverse experience for both treatment groups was headaches: 7.9% (19/239) in cetirizine patients compared to 6% (5/84) in placebo patients. Somnolence occurred in 2.5% (6/239) of cetirizine patients and 1.2% (1/84) of placebo patients. The severity was generally mild to moderate for both treatments. The frequency of adverse experiences in each dosage group of cetirizine was 19.8% (16/81) for the 5 mg day, 16.5% (13/79) for 2.5 mg/day and 16.5% (13/79) for 1.25 mg/day. One cetirizine patient #90-N-0024-68, discontinued the study because of increased micturition frequency.

There were a total of 561 laboratory abnormalities for cetirizine treated patients and 190 for the placebo treated patients. Less than three percent (2.7%, 15/561) of the abnormal laboratory results in the cetirizine treatment group were clinically significant and possibly related to study drug. The placebo patients had 1.3% (2/190) such laboratory abnormalities.

This study indicates that cetirizine 1.25 mg to 5 mg. o.d. does not provide significant relief of the signs and symptoms of seasonal allergic rhinitis in the pediatric population. Cetirizine in this dose range is well tolerated.
III. OBJECTIVE

This multicenter, double-blind, parallel group, placebo-controlled study was conducted to compare the efficacy and safety of 1.25 mg o.d., 2.5 mg o.d., and 5 mg doses of cetirizine for seasonal allergic rhinitis over a one-month treatment period in children 6 to 11 years old. A secondary objective was to compare the effect of cetirizine between high weight (25 kg or greater) and low weight (less than 25 kg) patients.

IV. MATERIALS AND METHODS

A. Study Design

(1) Patient Population

This was a double-blind, parallel-group study of three hundred twenty-four (324) male and female patients between 6 and 11 years old with a documented history of seasonal allergic rhinitis confirmed with allergen sensitivity via RAST or skin tests. Patients were required to have a total symptom score of at least 6 (of a possible 18), based on six signs and symptoms of rhinitis, with at least two moderately severe symptoms (one of which was either nasal discharge or sneezing).

(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. Recent history of significantly abnormal renal, hematologic or hepatic 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 one week before and during the course of the study;

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

11. Use of an investigational drug during the month prior to entry, previous participation in a cetirizine study, use of astemizole within 2 months of study entry.

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

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

(3) Study Phases

This study utilized four treatment groups stratified by low and high weight groups in parallel fashion. The efficacy period was four weeks long. The study design is summarized in Figure A below.

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 for entry to the study were assigned to a treatment group according to the appropriate randomization schedule (either low weight, numbers 1 – 200, or high weight, numbers 201 – 700).

Study medication was taken each evening. The dose of study medication did not change over the treatment period. Parents were given three bottles and asked to see that the child took 1/4 tsp from Bottle A, 1/2 tsp from Bottle B, and 1 tsp from Bottle C.
B. Clinical Observations:

(1) Physical Examination

Prior to 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 2 years by the investigator).

(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.
Each evening, parent and child maintained 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.

(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. The assessments were rated as:

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

(4) Adverse Experiences

At each study visit (after 1, 2, 3 and 4 weeks of treatment), all adverse experience were recorded, including time of onset, severity, duration and relationship to study medication.

(5) Laboratory Data

The following laboratory tests were done at entry to and at the end of the study: hematocrit, hemoglobin, white blood cell count (WBC), red blood cell count (RBC), WBC differential, SGOT, SGPT, BUN, total bilirubin, serum creatinine, LDH and urinalysis. 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. (Appendix A.)

(2) Patient Diary Data

From the patient diary data, each symptom rating was reduced to a weekly mean severity according to:

\[
\text{mean severity for week } k = \frac{\text{sum of (daily severity)}}{\# \text{ of non-missing severities for that symptom-week}}, \quad K=1,2,3,4
\]

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.

(3) 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 above 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 nasal congestion.

The effect of cetirizine on seasonal allergic rhinitis was assessed using the mean change from baseline (day 1) total symptom score, as well as the severity of the individual symptoms of conjunctivitis, nasal congestion, nasal discharge, pruritus of oral/nasal mucosa, pruritus of eyes, and sneezing.

(4) Baseline Severity

For investigator assessments, baseline severity was taken as the rating given by the investigator, in conjunction with the patient, at the screening (day 1) visit.

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.

(5) Statistical Models

(a) Demographic and Baseline Characteristics

Comparability of the four 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 treatment, center, and weight-group, treatment-by-center, treatment-by-weight-group, and center-by-weight-group interaction effects. For each weight group separately, two way ANOVA were used. Comparability for the categorical parameters of race and sex were assessed by Cochran-Mantel-Haenszel tests for combined weight groups (with centers and weight groups as strata and each weight group separately with sites as strata).

Differences among the treatments for baseline symptom severity were evaluated using analyses of variance similar to those described above for demographic measures.

For these, and all other analyses, data from 3 centers (90N0017, 90N0020, 90N0030) were combined due to small enrollment in the low weight group, in order to avoid analytical difficulties resulting from 0 treatment-center cell frequencies. Patients in these centers were treated as though originating from a single site.

(b) Weekly Assessment of Symptom Severity

For each symptom and total symptom score, differences in mean change from baseline severity among the four treatments were assessed by analyses of covariance (ANACOVA). These assessments were made at each study week (weeks 1-4). The ANACOVA models included baseline (the covariate), treatment, center, weight-group, treatment-by-center, treatment-by-weight-group and center-by-weight-group interaction effects.

Repeated measure analyses of covariance incorporating all weekly data were also conducted, employing the multivariate repeated measures methodology of SAS Proc GLM. Consistent with a multivariate approach to repeated measures, patients who did not have complete data for the four week treatment period were excluded from these models, except for discontinuations due to inadequate response as discussed in (7) below.

Prior to implementing the ANACOVA models described above, 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. In cases of statistically significant differences among the treatments, subsequent pairwise comparisons were made using the protected least significant difference test.

(c) Global Evaluations

Differences in the distribution of global evaluations of therapy among the three treatment groups were analyzed using the general association version of the Cochran-Mantel-Haenszel test, with study sites as strata.
(6) Regression analyses of adjusted mean change in total severity score versus the natural logarithm of dose were carried out for patient assessments and investigator assessments at each study week. The models included baseline as a covariate, log(dose) of cetirizine and center effects. Adjusted placebo mean total severity was subtracted from each active group to accommodate data in the log-based scale. Lack of fit tests were performed to assess the appropriateness of the linear regressions.

(7) 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 were included in the weekly analyses prior to the time of discontinuance and excluded from the repeated measures analyses. In the "intent-to-treat" analysis, patients who discontinued due to lack of efficacy, had their final weekly mean severity values carried forward to subsequent weeks and included in the weekly and the repeated measures analyses.

(8) Analyses by Study Center

For each study center, analyses of patient assessments, investigator assessments and global evaluations were conducted. Analyses of covariance were used for symptom assessments and Cochran-Mantel-Haenszel tests for global evaluations. The analyses of covariance were the same as those described in V.5b above except that center and center by effect interactions were not included. Cochran-Mantel-Haenszel tests used weight groups as strata. Consistent with the methods employed in the pooled analysis, centers 90N0017, 90N0020 and 90N0030 were combined and treated as a single center.

(9) Statistical Significance

Result of the overall comparisons of treatment effects, pooled over centers, were considered statistically significant provided a p-value of 0.05 or less obtained. For pairwise comparisons of treatments, both the F-ratio from the analysis of covariance and the individual pairwise p-value were required to be 0.05 or less for the difference to be considered statistically significant. All pairwise comparisons were based on '2-sided' alternative hypotheses. In tests of interaction effect, including those for homogeneity of covariate slopes, a p-value of at most 0.10 was considered statistically significant, owing to the relatively small number of patients for the treatment-center and treatment-weight group combination and consequently low statistical power.

(10) Statistical Software

All statistical analyses were performed using the Statistical Analysis System (SAS) software package, Version 6.04.
VI. RESULTS

A. PATIENT CHARACTERISTICS

(1) Patient Population

Eighty-four (84) patients were randomized to the placebo treatment group, and 80, 79, and 81 were randomized to the 1.25 mg, 2.5 mg and 5 mg cetirizine groups respectively. Of these patients, 82 placebo patients were evaluable for efficacy, as were 73 1.25 mg cetirizine patients and 75 2.5 mg cetirizine patients and 77 5 mg cetirizine patients (Table 1A). The number of patients entered and evaluable at each week of the treatment period is presented in Table 1B.

Seventeen (17) patients were not evaluable for efficacy (9 due to protocol violations, 3 due to poor compliance, 2 were ineligible, 2 lost to follow-up, and 1 withdrew consent). Of these patients, two were in the placebo group, seven in the 1.25 mg cetirizine group, and four each in the 2.5 mg and 5.0 mg cetirizine groups. (Table 2A).

Twelve evaluable patients had one or more non-evaluable study days (Table 2B). Investigator assessments of rhinitis severity were non-evaluable at one weekly visit for six evaluable patients, and at two weekly visits for one patient. In all cases these patients had an insufficient number of evaluation days in the week. (Table 2C).

Thirty-three patients (33/324; 10.2%) discontinued prior to completing four weeks of treatment: 8/84 patients (9.5%) on placebo, 9/80 (11.3%) on 1.25 mg cetirizine, 9/79 (11.4%) on 2.5 mg cetirizine, and 7/81 (8.6%) on 5 mg cetirizine. The most common reasons for premature discontinuation were: intercurrent illness (8/33); protocol violation (9/33) and insufficient clinical response (8/33). (Tables 3 and 4).

In the intent to treat analysis, eight patients who discontinued due to insufficient clinical response prior to completing the study had their final symptom severity data 'carried forward' to subsequent weeks (Table 5).

(2) Baseline and Demographic Characteristics

Mean baseline and demographic characteristic of the treatment groups are presented in Tables 6A - 6C. For the combined weight groups, baseline mean systolic blood pressure was significantly different (p = 0.046) among the treatment groups ranging from 96.4 mmHg for the 2.5 mg cetirizine group to 99.7 mmHg for the 1.25 mg cetirizine group. Among high weight group subjects duration of illness differed significantly (p = 0.013) among the four treatment groups (ranging from 4.3 years for those subjects receiving placebo to 5.4 years for those receiving 1.25 mg cetirizine). For the combined weight groups baseline nasal congestion was significantly different among the treatment groups (ranging from a mean symptom severity score of 2.0 for placebo subjects to 2.3 for those subjects receiving 1.25 mg cetirizine). The significant difference in baseline mean nasal congestion was due primarily to the relatively high mean value (2.3) of the 1.25 mg group. The range of means (2.0 to 2.3) was not clinically significant. Further, the 1.25 mg group did not have the largest mean decreases from baseline (Table 9) as would be expected, given the
correlation between baseline and change from baseline values. Therefore, no adjustments (beyond those of the analysis of covariance) were made to the analysis of nasal congestion.

The four treatment groups were comparable with respect to all other demographic, physical examination characteristics, and baseline signs and symptoms of rhinitis. Baseline mean total symptom score ranged from 7.7 (1.25 mg cetirizine) to 8.0 (5 mg cetirizine). Statistically significant treatment-by-center interactions were found at baseline for duration of rhinitis.

B. EFFICACY

(1) Patient Diary Data - Improvement in Rhinitis Symptom Severity

No statistically significant differences in adjusted mean change from baseline total symptom score were found at any week or when averaged over the four week treatment period. Similarly, no significant difference among treatments were found in the adjusted mean changes from baseline of any individual symptom.

The analysis of low weight and high weight patients separately found no significant differences among treatment groups for any individual symptom or for total symptom severity at any time point.

No significant treatment-by-center or treatment-by-weight-group interactions were found, indicating a similar response among treatment groups over the study centers and weight groups.
With the exception of conjunctivitis at week 4 (p = .05), covariate slopes were homogeneous for all symptoms at all weeks, consistent with the expected tendency for patients with higher than average baseline severity to have greater than average decrease from baseline.

The repeated measures analyses indicated significant treatment-by-week interactions for nasal congestion, oral/nasal pruritis, nasal discharge, conjunctivitis, and total symptom score. These significant interactions are reflected in the differential slopes of the treatment groups over time seen in Figures 1A and 4A, 4B, 4D, and 4E.

(2) Investigator Assessments - Improvement in Rhinitis Symptom Severity

Adjusted mean decreases in total symptom severity occurred in all treatment groups at study weeks 1-4 and when averaged over the four week treatment period. The magnitude of improvement in each group generally increased over time. Adjusted mean changes over the four weeks of treatment were -3.9 for the placebo group, -3.6 for the 1.25 mg cetirizine group, -3.9 for the 2.5 mg cetirizine group, and -3.6 for the 5 mg cetirizine group. No dose-related trends were evident at any study week or averaged over weeks.

No statistically significant differences in adjusted mean change from baseline total symptom severity were found at any week or when averaged over the four week treatment period. Similarly, no significant differences among treatments were found in the adjusted mean changes from baseline of any individual symptom.
The repeated measures analyses indicated no significant treatment-by-week interactions.

(3) Global Evaluation of Treatment

A summary of the investigators' global assessment of therapy is presented in Table 11 and mean global ratings are given in Figure 2. Treatment was rated "extremely effective" by 21%, 11%, 12%, and 14% of the placebo, 1.25 mg, 2.5 mg, and 5 mg cetirizine, respectively. The differences in distribution of global assessments were not statistically significant for the combined weight groups, or for either weight group separately.

(4) Dose Response Analyses

No statistically significant dose response was evident, indicating the models adequately described the observed data. Lack of fit for these models is non-significant, indicating the models adequately described the observed data. These dose response relationships are plotted along with the observed means in Figures 3A-4D.

(5) Body Weight

A summary of group mean weight at the start and at the end of the treatment period is presented in Table 13, along with a statistical comparison of the treatment groups. All treatment groups and treatment-by-weight groups show average increases in weight during the four week course of the study. There was no significant difference in change in weight among treatment groups across weight groups. However, among those subjects in the high weight group the change in weight among the treatment groups is statistically significant (p = .033). Weight gains in the high weight group averaged 0.34 kg, 0.27 kg, 0.16 kg, and 0.53 kg, for the placebo, 1.25 mg, 2.5 mg, and 5 mg cetirizine groups, respectively.

(7) Intent-to-treat analysis

Despite the small percentage of non-evaluable patients (17/324; 5.2%), an intent-to-treat analysis was conducted which included all patients who received one or more dose of double-blind medication irrespective of evaluability. The results of these analyses are presented in Appendix A, Tables 1-8. These results do not differ substantially from those of the evaluable patients discussed above.
C. SAFETY

(1) Adverse Experiences

A summary of the incidence of all adverse experiences during the study is presented in Tables 26-33B. 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 specific adverse experience on more than one occasion, it is recorded as one adverse experience. Appendix D is a listing, by individual patients, of all adverse experiences occurring in the study.

Table 26 presents the summary of all adverse experiences and relationship to study drug. The overall incidence of adverse experiences for patients taking cetirizine was 17.6% (42/239 patients). This incidence approximates the 19% (16/84) incidence of adverse experiences seen in the placebo treatment group. The total number of adverse experiences reported by cetirizine patients was 54, while the placebo patients reported a total of 20. Five of the 54 (9.3%) total cetirizine adverse experiences were reported as related to drug compared to 2 of 20 (10%) for placebo.

The most common adverse experience for both treatment groups was headaches: 7.9% (19/239) in cetirizine patients compared with 6% (5/84) in placebo patients. None of the headaches were related to study drug. Somnolence was reported in 2.5% (6/239) of cetirizine patients and 1.2% (1/84) of placebo patients. Other adverse experiences occurring in more than one cetirizine patient were fatigue (1.7%), dyspepsia (1.3%), nausea (1.3%), vomiting (0.8%), abdominal pain (0.8%) and epistaxis (0.8%). Compared with the cetirizine group, the placebo patients had 2.4% incidence of fatigue, nausea and abdominal pain, 1.2% vomiting, and 1.2% epistaxis; no dyspepsia was reported.

The severity of adverse experiences in all patients is presented in Table 27. The majority of cetirizine adverse experiences were mild. Of the 54 patients, 66.7% (36/54) were mild, 27.8% (15/54) were moderate, and 5.6% (3/54) were severe. For the placebo group the distribution was 80% (16/20) mild and 20% (4/20) moderate; no severe adverse experiences were reported. Of the 19 cetirizine cases of headache, 12 were mild, 5 were moderate and 2 were severe. Five of the 6 cases of somnolence in the cetirizine group were mild and 1 was moderate in severity.

Table 28 presents the incidence of adverse experiences during the study for each of the 3 cetirizine dosage groups (1.25 mg, 2.5 mg and 5 mg daily). The incidence of patients with adverse experiences for cetirizine doses was: 19.8% (16/81) for 5 mg/day; 16.5% (13/79) for 2.5 mg/day; and 16.5% (13/79) for 1.25 mg/day. These incidences are similar to the placebo incidence of 19% (16/84). For the most common adverse experiences the incidence of headache was 6.3%, 7.6% and 9.9% for cetirizine 1.25 mg, 2.5 mg and 5 mg, respectively and were similar to placebo (6.0%). For somnolence, the incidence was 1.3%, 2.5% and 3.7% for the 1.25, 2.5 and 5 mg cetirizine groups, respectively compared with 1.2% in the placebo group.
Headache was the most common adverse experience for both weight groups with an occurrence of 7.1% (14/196) and 11.6% (5/43) for high weight and low weight cetirizine children, respectively compared with 7.5 and 0% in the high and low weight placebo groups. The incidence of somnolence in the high and low weight cetirizine groups was 2.6% and 2.3%, respectively compared with 1.5% and 0% in the placebo groups.

The severity of adverse experiences was mild to moderate for both weight groups (Tables 31A, 31B). One low weight patient reported a severe headache and two severe events (headache and dry mouth) were reported in the high weight group.

The 5 mg dose of cetirizine accounted for 13 patients reporting adverse experiences while there were 8 and 6 patients in the 2.5 mg and 1.25 mg treatment groups, respectively, for high weight children. The reverse case was seen in the low weight children with 7, 5, and 3 patients reporting adverse events for 1.25 mg, 2.5 mg and 5 mg, respectively (Tables 32A and 32B). The frequency of adverse events reports during week 1, 2, 3, 4 or greater was 5.6% (11/196), 6.8% (13/192), 8.1% (15/186) and 4.9% (9/182) for the high weight children treated with cetirizine; and 27.9% (12/43), 19% (8/42), 9.8% (4.41) and 5.1% (2/39) for the low weight children treated with cetirizine.

One patient in this study withdrew because of an adverse intolerable experience. Patient #90-N-0024-68 was randomized to 1.25 mg/day of cetirizine. The patient complained of frequency of urination after 6 days of study drug treatment. The symptoms persisted and the patient discontinued the study after 12 days of treatment. Two urinalyses were normal. The frequency of micturition persisted 1 week after stopping cetirizine, then resolved.
(2) **Clinical Laboratory Tests**

Laboratory tests were obtained at baseline and at the end of the study. Among 229 cetirizine patients, there were 561 abnormal values (Table 34). The elevation of eosinophils, which occurs in allergic patients, accounted for 20.5% (115/561) of these laboratory abnormalities. Fifteen of the 561 (2.7%) laboratory abnormalities reported in cetirizine patients were Category 9 (i.e. clinically significant and possibly related to study drug). For the placebo patients, two of 190 (1.1%) laboratory abnormalities were Category 9 as shown in Table 34.

The incidence of Category 9 laboratory abnormalities for cetirizine treated patients was: 2/229 (0.9%) hematocrits, 3/229 (1.3%) white blood cell count, 3/229 (1.3%) SGOT, 4/229 (1.8%) SGPT and 1/229 (0.4%) total bilirubin. Two non-required lab tests, 1 LDH and 1 GGT, were obtained to evaluate elevated transaminase in patient #90-N-0030-603 and #90-N-0024-430, respectively. Both lab test results were above normal and category 9 abnormalities. There were one SGOT and one SGPT (1%) Category 9 laboratory abnormality in the placebo treatment group.

One patient discontinued the study because of an abnormal laboratory result. Patient #90-N-0018-280 had a baseline SGOT of 46 units (normal 7-40 units). After seven days of 5 mg daily cetirizine therapy, the SGOT was 62 units; cetirizine therapy was discontinued 4 days later. A repeat value 1 day after therapy was discontinued was 46 units. The investigator was uncertain as to the cause of this abnormality. All other liver function tests (SGPT and bilirubin) remained within normal limits.
VIII. CONCLUSIONS

Based on this double-blind study of 324 patients with seasonal allergic rhinitis, it may be concluded that:

(1) cetirizine 1.25 mg - 5 mg o.d. does not provide significant improvement in the signs and symptoms of rhinitis over 4 weeks of treatment,

(2) similar lack of effect in this dose range was found in low weight (less than 25 kg) and in high weight (at least 25 kg) patients,

(3) differential improvement in rhinitis severity was not dose-related,

(4) cetirizine 1.25 mg - 5 mg o.d. in children aged 6-11 years is safe and well tolerated.