**SYNOPSIS**

<table>
<thead>
<tr>
<th>Name of Company:</th>
<th>Pfizer, Inc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>235 East 42nd Street</td>
<td>New York, NY 10017</td>
</tr>
<tr>
<td><strong>Name of Finished Product:</strong></td>
<td><strong>Zyrtec</strong></td>
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<tr>
<td><strong>Name of Active Ingredient:</strong></td>
<td>Cetirizine HCl</td>
</tr>
<tr>
<td><strong>Title of Study:</strong></td>
<td>A Randomized, Double Blind, Parallel Group, Placebo Controlled, Multi-Center Study of the Efficacy and Safety of Zyrtec® (Cetirizine HCl) Syrup vs. Claritin® (Loratadine) Syrup vs. Placebo in the Treatment of Children with Seasonal Allergic Rhinitis</td>
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<td><strong>Investigators and Study Centers:</strong></td>
<td>Seventy-one Principal Investigators participated in this study (See Appendix 16.1.4).</td>
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<tr>
<td><strong>Publication (reference):</strong></td>
<td>None</td>
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<tr>
<td><strong>Date of first subject enrollment:</strong></td>
<td>29 March 2001</td>
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<tr>
<td><strong>Date of last subject completed:</strong></td>
<td>25 July 2001</td>
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<tr>
<td><strong>Introduction:</strong></td>
<td>Zyrtec® and Claritin® are prescription antihistamines commonly used to treat seasonal allergic rhinitis (SAR) in pediatric patients who are 6 to 11 years of age. Both drugs received approval for use in pediatric populations based on the Pediatric Rule of 1994, which extrapolated data from adult studies to children. Although both agents have been studied extensively in adults, there is a paucity of comparative efficacy data in this pediatric age group.</td>
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<td><strong>Objectives:</strong></td>
<td>The objective of this clinical trial was to assess the efficacy and safety of cetirizine HCl syrup vs. loratadine syrup vs. placebo syrup in the treatment of SAR in children 6 to 11 years old.</td>
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<td><strong>Methodology:</strong></td>
<td>This was a randomized, double-blind, parallel-group, placebo-controlled, multi-center study of children with SAR conducted during the Spring tree and grass allergy season. Subjects qualified for randomization if the diary cards included (1) symptom scores of 2 for at least 2 of the following 4 rhinoconjunctivitis symptoms on 4 or more days: sneezing, runny nose, itchy eyes, and watery eyes; and (2) a total rhinoconjunctivitis (or Total Symptom Severity Complex [TSSC]) score of 5 on any 4 days. The TSSC score was expressed as the sum of the 4 individual symptoms scores recorded in the daily diary cards for the following symptoms: sneezing, runny nose, itchy eyes, and watery eyes. Subjects were randomized to receive 1 of 3 treatments in a double-blind fashion using a 1:1:1 allocation ratio: cetirizine HCl syrup and placebo loratadine syrup; loratadine syrup and placebo cetirizine HCl syrup; or cetirizine placebo syrup and loratadine placebo syrup.</td>
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Final: 18 July 2002
Name of Company: Pfizer, Inc.  
235 East 42nd Street  
New York, NY 10017  
Name of Finished Product: Zyrtec®  
Name of Active Ingredient: Cetirizine HCl  

<table>
<thead>
<tr>
<th>Individual Study Table</th>
<th>When Referring to Part of the Dossier</th>
<th>(For National Authority Use only)</th>
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<tbody>
<tr>
<td>Volume:</td>
<td>Page:</td>
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Number of Subjects (Planned and Analyzed): 1100 planned; 1536 screened; 683 randomized; 231 (33.8%) randomized to the cetirizine HCl treatment group, 221 (32.4%) to the loratadine treatment group, and 231 (33.8%) to the placebo treatment group.

Diagnosis and Main Criteria for Inclusion:
- Male or female; 6 to 11 years of age;
- Females who reached menarche either before or during the study, agreed to use acceptable methods of birth control (oral contraceptives or Norplant®) if they became sexually active;
- Outpatient;
- History and diagnosis of SAR to a prevalent allergen (grass or tree);
- SAR to a prevalent allergen (grass or tree) of such severity that it required pharmacologic therapy each year for the last 2 consecutive years (including the present year);
- Documented SAR to a prevalent allergen (grass or tree) as confirmed by a recognized skin test within the previous 15 months;
- A written informed assent must have been provided by the subject and a written informed consent must have been provided by the parent/legal guardian at Visit 1.

Test Product and Reference Therapy:
Subjects randomized to receive cetirizine HCl syrup also received placebo syrup; subjects randomized to receive loratadine syrup also received placebo syrup; and both placebo syrups were received by subjects randomized to receive placebo.

Duration of Double-Blind Treatment: 2 weeks

Criteria for Evaluation:
The primary efficacy endpoint was the change from baseline to the Overall endpoint in the subject 24-hour reflective TSSC.
Secondary efficacy measures included the following:
- Subject 24-hour reflective TSSC, with and without stuffy nose score.
- Instantaneous TSSC, with and without stuffy nose score.
- Individual rhinoconjunctivitis symptoms (reflective and instantaneous).
- Parent/legal guardian evaluation of subject's rhinoconjunctivitis symptoms.
- Investigator evaluation of subject's rhinoconjunctivitis symptoms.
- Parent/legal guardian overall personal satisfaction.
- Subject with/without the parent or legal guardian global evaluation of treatment.
- Investigator global evaluation of the effectiveness of treatment.
Parent/legal guardian response on the Parental Burden Questionnaire.

Safety measures included the incidence and severity of treatment-emergent adverse events (AEs), vital signs, concomitant medications, and physical examination findings. Clinical laboratory evaluation was not required for this study.

Statistical Methods: All statistical tests related to treatment effect were 2-sided, and statistical significance was declared at the 0.05 probability level. Least squares means (LSMeans) were used to estimate treatment effect. Populations analyzed included the Full Analysis (intent-to-treat [ITT]) Set (FAS), Per-Protocol Set (PPS), Safety-Analyzable Set, and All-Screened Analysis Set. Demographic and baseline data for all subjects in the Safety-Analyzable Set were summarized and listed.

The effects of treatment at the Overall and all other analysis Time Points were assessed using ANCOVA models. The main effects model contained terms for treatment and Investigator site, with baseline TSSC value as a covariate. The LSMeans and standard errors were based on the main effects model.

Methods of analysis of secondary efficacy data included analysis of covariance (ANCOVA) models and CMH row mean scores tests.

Analysis of drug safety included the incidence of treatment-emergent AEs, concomitant medications, vital signs, and physical examination findings for the Safety-Analyzable Set.

Efficacy Results:

Primary Efficacy Endpoint
For the FAS and PPS, cetirizine HCl-treated subjects had statistically significantly greater reductions from baseline to the Overall Time Point in 24-hour reflective TSSC scores than placebo-treated subjects:
- FAS: LSMean changes of -2.1 and -1.6, respectively; \( P=0.006 \).
- PPS: LSMean changes of -2.3 and -1.7, respectively; \( P=0.003 \).

In the PPS, the cetirizine HCl group was also statistically significantly more efficacious than the loratadine group: LSMean changes of -2.3 and -1.9, respectively \( (P=0.048) \). The difference between the loratadine and placebo groups was not statistically significant for the FAS or PPS.

Secondary Efficacy Endpoints
For the FAS and/or PPS, cetirizine HCl was more effective than placebo for the following endpoints:
- 24-hour reflective TSSC plus stuffy nose: \( P=0.011 \) at Overall Time Point for the FAS, and \( P=0.005 \) for the PPS.
- Instantaneous TSSC: \( P=0.014 \) at Overall Time Point for the FAS, and \( P=0.005 \) for the PPS.
For the PPS, cetirizine HCl was also more effective than loratadine for these variables:
  - 24-hour reflective TSSC: \( P=0.048 \) at Overall Time Point.
  - 24-hour reflective TSSC plus stuffy nose: \( P=0.033 \) at Overall Time Point.
  - Investigator-assessed TSSC: \( P=0.041 \) at Overall Time Point.
  - Parental Burden Questionnaire item, “How much did your child’s allergies interfere with your ability to be productive at work?”: \( P=0.031 \) at Overall Time Point.

Safety Results:
Of the 683 subjects who were randomized, 677 subjects received study medications. A total of 191 treatment-emergent (all causalities) AEs were reported by 145 (21.4%) subjects during the double-blind treatment phase of the study. The incidence of treatment-emergent AEs was similar among treatment groups, with 45 (19.7%) cetirizine HCl-treated subjects, 48 (21.8%) loratadine-treated subjects, and 52 (22.7%) placebo-treated subjects reporting AEs.

The treatment-emergent AEs that were reported with the highest frequency were headache and pharyngitis. Headache was reported in 8 (3.5%) subjects in the cetirizine HCl treatment group, 8 (3.6%) subjects in the loratadine treatment group, and 7 (3.1%) subjects in the placebo treatment group. Pharyngitis was reported in 8 (3.5%) subjects in the cetirizine HCl treatment group, 6 (2.7%) subjects in the loratadine treatment group, and 8 (3.5%) subjects in the placebo treatment group.

Of the 191 treatment-emergent AEs, 35 (18.3%) were considered treatment-related. The incidence of treatment-related AEs for each treatment group was as follows: 11 (4.8%) subjects in the cetirizine HCl treatment group, 10 (4.5%) subjects in the loratadine treatment group, and 6 (2.6%) subjects in the placebo treatment group.
A total of 22 subjects discontinued from the study due to treatment-emergent AEs: 6 (2.6%) subjects in the cetirizine HCl treatment group, 9 (4.1%) subjects in the loratadine treatment group, and 7 (3.1%) subjects in the placebo treatment group. Two of these 22 subjects were discontinued due to treatment-emergent, treatment-related AEs (1 [0.4%] subject in the cetirizine HCl treatment group and 1 [0.5%] subject in the loratadine treatment group). No deaths or SAEs were reported or entered into Pfizer's early alert safety database.

Conclusion:
The objective of this study was to assess the efficacy and safety of cetirizine HCl syrup versus loratadine syrup versus placebo syrup in the treatment of SAR in children 6 to 11 years old.

This comparative trial of 677 treated pediatric subjects aged 6 to 11 years with SAR revealed that cetirizine HCl was statistically significantly better than placebo in the treatment of SAR.

On 10 primary and secondary efficacy parameters described below, the cetirizine group was statistically significantly more efficacious than placebo. The cetirizine group was also statistically superior to loratadine on 3 of the parameters.

For the FAS, cetirizine HCl-treated subjects had statistically significantly greater reductions from baseline to the Overall Time Point in 24-hour reflective TSSC scores than placebo-treated subjects (P=0.006). Cetirizine HCl-treated subjects had statistically significantly greater improvements compared to placebo in the following secondary efficacy variables: TSSC plus stuffy nose (P=0.011), Instantaneous TSSC (P=0.014) (both at the Overall Time Point), Investigator-assessed TSSC (P=0.001) (at the Endpoint Time Point), and Parent-assessed TSSC (P=0.018) (at the Overall Time Point).

Results were similar for the PPS. Cetirizine HCl-treated subjects also had statistically significantly greater improvements at the Overall Time Point than loratadine-treated subjects in the following secondary efficacy variables: TSSC (P=0.048), TSSC plus stuffy nose (P=0.033), and Investigator-assessed TSSC (P=0.041).

Of the 10 parameters in which cetirizine was superior to placebo, loratadine was statistically significantly better than placebo in only 3 parameters: Investigator-assessed TSSC in the FAS (P=0.021), Parent-assessed TSSC in the FAS (P=0.038), and Parent-assessed TSSC in the PPS (P=0.036).
Cetirizine HCl was well tolerated during the study. The incidences of treatment-emergent AEs; treatment-emergent, treatment-related AEs; and treatment-emergent AEs leading to discontinuation were similar between treatment groups. Somnolence was reported in 3 (1.3%) subjects in the cetirizine HCl treatment group. No deaths or SAEs were reported or entered into Pfizer's early alert safety database. There were no clinically significant vital signs or physical examination abnormalities during this study.

In conclusion, cetirizine HCl was effective in the treatment of SAR and both cetirizine HCl and loratadine were safe and well-tolerated in children 6 to 11 years old.

Date of Report: Final: 18 July 2002