2. SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Sponsor/Company</th>
<th>Individual Study Table Referring to Part of the Dossier</th>
<th>(For National Authority Use Only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer, Inc.</td>
<td></td>
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</tbody>
</table>

Name of Finished Product: Volume:
Name of Active Ingredient: Page:
cetirizine, pseudoephedrine

title of study: A Multicenter, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Zyrtec-D 12 Hour™ (Cetirizine HCl/Pseudoephedrine HCl) Versus Placebo in Patients with Seasonal Allergic Rhinitis and Concomitant Mild to Moderate Asthma

Investigators: William E. Berger, MD; Jonathan A. Bernstein, MD; Thomas B. Casale, MD; John J. Condni, MD; Diana L. Dickens, MD; Albert F. Finn, Jr., MD; Stanley P. Galant, MD; Marc F. Goldstein, MD; Gary N. Gross, MD; Robert E. Grubbe, MD; Edward M. Kerwin, MD; Kenneth Kim, MD; Craig Fred LaForce, MD; Lawrence P. Landwehr, MD; Lawrence V. Larsen, MD; William Lumry, MD; Clement A. Maccia, MD; Isaac R. Melamed, MD; Julian Melamed, MD; David L. Miller, MD; S. David Miller, MD; Don Q. Mitchell, MD; Dale Mohar, MD; John J. Murray, MD; Robert A. Nathan, MD; Anjuli S. Nayak, MD; Michael J. Noonan, MD; Andrew J. Pedinoff, MD; Frank J. Picone, MD; Warren W. Pleskow, MD; Stephen J. Pollard, MD; Bruce Prenner, MD; Gordon Raphael, MD; Paul Ratner, MD; Eric Schenkel, MD; Nathan D. Shultz, MD; Jeffrey Tillinghast, MD; John M. Weiler, MD; John A. Zora, MD; John F. Zwetchkenbaum, MD.

Study Centers:

Publication (reference): None

Study Period: 18 February 2002-19 July 2002
Phase of Development: 4

Date of first enrollment:
Date of last completed:
**Objective:** The primary objective of this clinical trial was to assess the efficacy and safety of Zyrtec-D 12 Hour™ versus placebo in subjects with seasonal allergic rhinitis who had concomitant mild to moderate asthma. The secondary objective was to evaluate the effects of Zyrtec-D 12 Hour™ on pulmonary function and asthma quality of life.

**Methodology:** This was a 5 week randomized, double-blind, parallel group, placebo-controlled, multicenter study of Zyrtec-D 12 Hour™ versus placebo in the treatment of subjects with seasonal allergic rhinitis who also suffer from concomitant mild to moderate asthma. This study was conducted in the United States during the Spring 2002 tree and grass allergy season. The study consisted of a one week screening phase, at the end of which subjects were randomized to one of the two treatment groups, Zyrtec-D 12 Hour™ or placebo. Subjects were followed for four weeks of treatment with a clinical follow-up every two weeks. Subjects were required to do home monitoring of peak expiratory flow rate (PEFR) and maintain diaries of allergic rhinitis and asthma symptoms as well as beta-agonist usage. Clinical evaluations also consisted of laboratory testing at Visit 1, administration of the Asthma Quality of Life Questionnaires (AQLQ) at Visits 2, 3, and 4, and routine spirometry at all visits.

**Number of Subjects (planned and analyzed):**

<table>
<thead>
<tr>
<th>Evaluation Groups</th>
<th>Cetirizine/pseudoephedrine</th>
<th>Placebo</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Entered Study</td>
<td>139</td>
<td>135</td>
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<tr>
<td>Completed Study</td>
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<td>113</td>
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<tr>
<td>Evaluated for Efficacy</td>
<td>139</td>
<td>134</td>
<td>273</td>
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<tr>
<td>Assessed for Safety</td>
<td>139</td>
<td>135</td>
<td>274</td>
</tr>
</tbody>
</table>

**Diagnosis and Main Criteria for Inclusion:** Male or female subjects (12 years or older) with a history and diagnosis of seasonal allergic rhinitis to a prevalent allergen (tree or grass) for at least two consecutive seasons, who also had a history and diagnosis of persistent mild to moderate asthma for at least six months before enrollment in this study.
**Name of Sponsor/Company**  
Pfizer, Inc.

**Name of Finished Product:**

**Name of Active Ingredient:**  
cetirizine, pseudoephedrine

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### Test Product, Dose and Mode of Administration, Batch Number:

- Cetirizine HCl 5 mg + Pseudoephedrine HCl 120 mg bid, tablet oral; Lot number 8309-G1, FID G01501AB

### Duration of Treatment:

There was a one-week screening phase and a four-week treatment phase.

### Reference Therapy, Dose and Mode of Administration, Batch Number:

- Placebo bid, tablet oral; Lot number 8304-G1, FID G02115AA

### Criteria for Evaluation:

**Efficacy:** Efficacy evaluations for this study included Subject and Investigator evaluations of allergic rhinitis and asthma symptoms, pulmonary function testing, AQLQ, Subject and Investigator Global Evaluation of effectiveness of study medication, and a rating of the willingness of the subject to take the study medication again. The primary efficacy parameter was the Allergic Rhinitis Total Symptom Severity Complex (TSSC) score.

**Safety:** Safety evaluations included monitoring adverse events, physical examination findings, clinical laboratory data, and subject discontinuations and use of concomitant medications.

### Statistical Methods:

Approximately 616 subjects were to be randomized into the study at 44 centers with the expectation that a minimum of 262 subjects per treatment group (Zyrtec-D 12 Hour™ or placebo) would complete the study.

Continuous variables were analyzed by means of analysis of covariance (ANCOVA), and categorical variables by means of Cochran-Mantel-Haenszel (CMH) tests. All statistical tests were two-sided and statistical significance was declared at the 0.05 level for treatment effects. Demographic and safety data were summarized with descriptive statistics using the current version of Pfizer Worldwide Safety Standards (WSS) and Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) terminology.
### SUMMARY – CONCLUSIONS

**Efficacy Results:** Cetirizine/pseudoephedrine treatment reduced allergic rhinitis and asthma symptoms in subjects in this study. For allergic rhinitis symptoms, the overall mean TSSC score for combined measurements in the cetirizine/pseudoephedrine group was 42.3% below baseline, a statistically significant (p < 0.001) reduction in score that was 18.7% greater than the reduction observed in the placebo group. Mean decreases in TSSC score from baseline to Week 4 and Week 4/LOCF were somewhat larger than mean changes from baseline to Week 2. Statistically significant differences between the cetirizine/pseudoephedrine and placebo groups were observed for each of the individual symptom measurements of allergic rhinitis TSSC—sneezing, runny nose, itchy nose, post-nasal drip, and nasal congestion. Reductions in asthma symptom severity combined scores in the cetirizine/pseudoephedrine group were also statistically significant in comparison with the placebo group in the change from baseline to Week 2 in morning scores (p = 0.002) and in the change from baseline to Week 2 and Week 4/LOCF in evening scores (p < 0.001 and p = 0.007, respectively). In measures of individual asthma symptoms—wheezing, coughing, shortness of breath, and chest tightness—statistically significant differences (p < 0.001 to p = 0.033) in measures of asthma symptoms at both daily timepoints, at both post-baseline timepoints, were observed (exceptions: morning wheezing, shortness of breath at Week 4/LOCF, and chest tightness at Week 4/LOCF).

Results of secondary, subjective analyses offered additional support for the effectiveness of cetirizine/pseudoephedrine in reducing the symptoms of allergic rhinitis and asthma. The percentage of subjects in the cetirizine/pseudoephedrine group reporting improvement in allergic rhinitis symptoms was higher than in the placebo group (50.4% vs 22.5%, respectively), a difference that was consistent with the investigator’s assessment (cetirizine/pseudoephedrine: 48.9%; placebo: 22.7%), and that was statistically significant (p < 0.001). The difference between the treatment groups in subjects who reported improvement in asthma symptoms was also substantial and statistically significant (cetirizine/pseudoephedrine: 37.8%; placebo: 24.6%; p < 0.021). The investigator’s assessment of improvement in asthma symptoms was consistent with the subject’s assessment in the cetirizine/pseudoephedrine group (35.6%), but not in the placebo group.
(12.5%) (p < 0.001), indicating that placebo subjects perceived more improvement in their asthma symptoms than did the investigators.

The percentage of subjects in the cetirizine/pseudoephedrine group reporting satisfaction with the treatment of allergic rhinitis symptoms was higher than in the placebo group (68.1% vs 37.7%, respectively), and the difference was statistically significant (p < 0.001). A similar, but smaller, difference between treatment groups in satisfaction with the treatment of asthma symptoms (cetirizine/pseudoephedrine: 61.5%; placebo: 45.0%; p < 0.006) symptoms was observed. Interestingly, the percentages of subjects who reported satisfaction with treatment were higher in both treatment groups than the percentages of subjects who reported major or moderate improvement in allergic rhinitis symptoms. The majority of subjects in the cetirizine/pseudoephedrine group (67.4%) reported a willingness (definite or probable) to take the study medication again, compared with 48.8% of the subjects in the placebo group (p = 0.003).

In each AQLQ domain measure, the increases (higher scores indicating better quality of life) from baseline to both post-baseline timepoints were larger in the cetirizine/pseudoephedrine group than in the placebo group, and, with one exception (emotional function at Week 4/LOCF), the differences between the cetirizine/pseudoephedrine group and the placebo group were statistically significant (p < 0.001 to p = 0.023). In this study, the mean differences between the cetirizine/pseudoephedrine group and the placebo group in changes from baseline to Week 2 and Week 4 did not meet the minimum important difference (MID) guideline in any of the AQLQ domains.

Results of pulmonary function tests (FEV1, FVC, and PEFR) showed similar, small increases in both treatment groups over the course of the study. The mean decrease in MDI total daily use at the end of the study in the cetirizine/pseudoephedrine group (31.6%) was approximately twice as large as the decrease observed in the placebo group (14.6%).
Safety Results: One serious adverse event, viral meningitis in a placebo subject, was reported during this study. A total of 235 subjects completed the study. Thirty-nine subjects discontinued from the study; of these, 9 in the cetirizine/pseudoephedrine group and 8 in the placebo group discontinued due to treatment-emergent adverse events, the majority of which were exacerbation of asthma. Four subjects in the cetirizine/pseudoephedrine group discontinued due to adverse events considered by the investigator to be related to study drug; no subjects in the placebo group discontinued due to treatment-related adverse events. The number of subjects who experienced adverse events and the total number of adverse events were higher in the cetirizine/pseudoephedrine group than in the placebo group. However, the majority of adverse events were mild or moderate in severity and were characteristic of those previously observed with the use of cetirizine/pseudoephedrine. The most commonly occurring adverse events were exacerbation of asthma (20 cetirizine/pseudoephedrine subjects, 14.4%; 14 placebo subjects, 10.4%) and somnolence (8 cetirizine/pseudoephedrine subjects, 5.8%; 1 placebo subject, 0.7%). The incidences of somnolence in the cetirizine/pseudoephedrine group were considered to be treatment-related. Changes in vital signs, physical examinations, and laboratory results (collected on limited basis) were minor.

Conclusions: Study A3771007 was designed to assess the efficacy and safety of cetirizine/pseudoephedrine versus placebo in subjects with allergic rhinitis who had concomitant mild to moderate asthma and to evaluate the effects of cetirizine/pseudoephedrine on pulmonary function and asthma quality of life.

This was a 5-week randomized, double-blind, parallel group, placebo-controlled, multicenter study of cetirizine/pseudoephedrine versus placebo in the treatment of subjects with seasonal allergic rhinitis who also suffer from concomitant mild to moderate asthma. This study was conducted during the Spring 2002 tree and grass allergy season. Subjects received 5 mg/120 mg cetirizine HCl/pseudoephedrine HCl or placebo twice daily for 4 weeks. Efficacy evaluations for this study included subject and investigator evaluations of allergic rhinitis and asthma symptoms, pulmonary function testing, AQLQ, Subject and Investigator Global Evaluation of effectiveness of study medication, and a rating of the
willingness of the subject to take the study medication again. The primary efficacy parameter was the allergic rhinitis TSSC score. Safety evaluations for this study included monitoring adverse events, vital signs measurements, and subject discontinuations and use of concomitant medications. Demographic and baseline characteristics were comparable in the two treatment groups. Fewer subjects than expected were enrolled in this study due to the difficulties encountered in recruiting qualified subjects.

Two hundred seventy-four subjects were randomized in this study—139 subjects received cetirizine/pseudoephedrine and 135 subjects received placebo. Subjects in this study had a primary diagnosis of seasonal allergic rhinitis and a secondary diagnosis of asthma. The median duration of therapy for subjects in this study was 28 days.

Cetirizine/pseudoephedrine treatment reduced allergic rhinitis and asthma symptom scores in subjects in this study. Substantial, statistically significant differences in favor of cetirizine/pseudoephedrine were observed in subject and investigator evaluations of allergic rhinitis and asthma symptoms and in subject satisfaction with treatment. Results of pulmonary function tests (FEV1, FVC, and PEFR) showed similar, small increases in both treatment groups over the course of the study. The mean decrease in MDI total daily use at the end of the study in the cetirizine/pseudoephedrine group was approximately twice as large as the decrease observed in the placebo group.

Cetirizine/pseudoephedrine was well tolerated. One serious adverse event, viral meningitis in a placebo subject, was reported during this study. Ten subjects in each study group discontinued due to an adverse event, the majority of which were treatment-emergent exacerbation of asthma. Four subjects in the cetirizine/pseudoephedrine group discontinued due to adverse events considered by the investigator to be related to study drug; no subjects in the placebo group discontinued due to treatment-related adverse events. The majority of adverse events were mild or moderate in severity.

**Date of the Report:** 22 October 2003