SYNOPSIS

| Name of Company: | Pfizer Inc. | Individual Study Table Referring to Part of the Dossier |
| Name of Finished Product: | Zyrtec-D 12 Hour | (For National Authority Use only) |
| Name of Active Ingredients: | cetirizine-pseudoephedrine | |
| Title of Study: | A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multi-Center Study of the Efficacy and Safety of Cetirizine-Pseudoephedrine vs. Loratadine-Pseudoephedrine (Claritin-D® 12 Hour) vs. Placebo in the Treatment of Subjects Twelve Years and Older with Seasonal Allergic Rhinitis |
| Investigators and Study Centers: | 36 principal investigators from 36 centers were enlisted to participate in this study (See Section 16.4). |
| Publication (reference): | None |
| Date of first enrollment: | May 08, 2000 |
| Date of last completed: | July 29, 2000 |
| Phase of Development: | 3b |

Objective: The objective of this clinical trial was to assess the efficacy and safety of cetirizine-pseudoephedrine vs. loratadine-pseudoephedrine vs. placebo in the treatment of seasonal allergic rhinitis (SAR) in subjects 12 years and older.

Reason for Revision: This clinical study report (CSR) is identical to the original A3771001 report with regard to interpretation of the data and conclusions drawn from the data. The report was updated to correct the calculation of baseline symptom scores and the age group categorization. In the original CSR, the baseline calculation used scores for Days 0, -1, and -2 (where the baseline randomization visit is Day 1) to calculate the baseline. The new version of the report uses scores for Days 1, 0, and -1. The age group term for secondary analyses was also updated to a binary categorical variable (age group either adolescent or adult) rather than the actual age (continuous); this was originally done incorrectly and now reflects the analysis plan. Section 9.8.2 was also updated to reflect handling of missing data.

Methodology: This was a randomized, double-blind, double-dummy, parallel-group, placebo-controlled, multi-center study conducted in the United States during the Spring 2000 grass allergy season. Visit 1 consisted of the screening visit. If subjects qualified for study participation, they were enrolled in a seven-day single-blind placebo run-in period. Subjects qualified for randomization at Visit 2 if, on that day, their daily symptom diary cards included at least two symptoms with a score of $\geq 2$ on at least four days between Visit 1 and Visit 2. The symptoms scored were sneezing, runny nose, itchy nose, itchy eyes, watery eyes, postnasal drip, and nasal congestion. Nasal congestion must have been rated 1 or higher on at least 4 days between Visit 1 and Visit 2. Subjects were also required to have recorded in their diary a total rhinoconjunctivitis score of $\geq 6$ on any four days before Visit 2.

Subjects were randomized to receive either cetirizine-pseudoephedrine, loratadine-pseudoephedrine or placebo twice daily in a double-blind fashion (using a 1:1:1 ratio for
approximately two weeks. Subjects completed rhinoconjuctivitis symptom diary cards on a daily basis. Global evaluations, which included subject global evaluations of treatment effectiveness and treatment satisfaction, and an investigator symptom evaluation, were assessed at the completion of the study.

The primary efficacy endpoint for this study was the absolute change from baseline in Total Symptom Severity Complex (TSSC) scores (from the subject symptom diary). The TSSC score was the sum of seven individual symptoms (sneezing, runny nose, itchy nose, itchy eyes, watery eyes, postnasal drip, and nasal congestion).

**Methodology (con’t):** Secondary efficacy measures were the percent change from baseline in TSSC score from the subject symptom diary, change from baseline in the seven individual symptom scores from the subject symptom diary, change from baseline in the investigator’s assessment of subject symptoms as expressed by TSSC score, responder classification for TSSC scores, subject global evaluations of treatment effectiveness and treatment satisfaction, and investigator global evaluation.

Safety was assessed by summarizing the incidence of treatment-emergent adverse events (AEs), measurement of vital signs, physical examination findings, and concomitant medications.

**Number of Subjects (Planned and Analyzed):**
1300 planned; 1689 screened; 1094 randomized; 1087 treated

**Diagnosis and Main Criteria for Inclusion:**
- 12 years of age or older.
- Male; or female of non-childbearing potential (post-menopausal or documented as surgically incapable of conception); or female of childbearing potential who agreed not to become pregnant during the study. When sexually active, females of childbearing potential must have already been using oral contraceptives, Norplant®, or DepoProvera® injections, or have agreed to use at least any two of the following: a cervical barrier (diaphragm), spermicide, or condom. Females who were not sexually active must have agreed to use at least any two of the above barrier methods should they have become sexually active. Females between the ages of 12 and 18 years must have been using an acceptable form of birth control as described above for adults (not including barrier methods) if they were sexually active or became sexually active during the conduct of the study.
- Outpatient.
- Negative serum pregnancy test at Visit 1 (females only).
- History and diagnosis of SAR to grass.
- SAR to grass of such severity that it required pharmacologic therapy each year for the last two
consecutive years.

- History of positive response to antihistamine therapy for symptoms of SAR to grass.
- Documented SAR as confirmed by a recognized skin test (prick, intradermal (ID), or Multitest®) within the previous year to grass (Prick/Puncture wheal ≥ 3 mm, over the negative control; ID [up to concentration of 1:1000 w/v or 1000 PNU] wheal ≥ 5 mm, over the negative control).

### Diagnosis and Main Criteria for Inclusion (con’t):

- Subject diary documentation of rhinoconjunctivitis symptoms which must have included at least two of the seven symptoms with a score of ≥ 2 on at least four days between Visit 1 and Visit 2. The symptoms scored were sneezing, runny nose, itchy nose, itchy eyes, watery eyes, postnasal drip, and nasal congestion. Nasal congestion must have been rated 1 or higher on at least four days between Visit 1 and Visit 2.
- Subject diary documentation of a total rhinoconjunctivitis score of at least six on any four days before Visit 2.
- Someone from whom the principal investigator or study personnel would have expected conscientious cooperation over the duration of the study.
- Someone able to execute a written informed consent and/or assent at Visit 1.

### Test Product, Dose and Mode of Administration, Lot Numbers:

cetirizine-pseudoephedrine, 5 mg/120 mg, oral tablet, twice daily, Lot #8309-G1

doxepin, 10 mg, oral tablet, twice daily, Lot #ED-O-540-Z99

cetirizine-pseudoephedrine, oral tablet, twice daily, Lot #8304-G1

### Reference Therapy, Dose and Mode of Administration, Lot Numbers:

cetirizine-pseudoephedrine, 5 mg/120 mg, oral tablet, twice daily, Lot #8304-G1

doxepin, 10 mg, oral tablet, twice daily, Lot #ED-O-540-Z99

cetirizine-pseudoephedrine, oral tablet, twice daily, Lot #8304-G1

### Duration of Treatment:

Approximately three weeks (one week placebo run-in, followed by two weeks of randomized therapy).

### Criteria for Evaluation:

Samples analyzed included the intent-to-treat (ITT), efficacy analyzable (EA), completer, safety-analyzable, and all screened.

The ITT sample consisted of all subjects randomized to receive double-blind treatment who received at least one dose of study medication as determined by the Study Medication Record page of the case report form (CRF). These subjects must also have had at least one efficacy endpoint collected at baseline and post-baseline. All primary and secondary efficacy variables were analyzed for the ITT sample.

The EA sample consisted of all subjects in the ITT sample who met the prospectively defined criteria for efficacy evaluability, including: a) dosing compliance such that the subject did not miss more than 2 doses of study drug within a given week; and b) protocol compliance (i.e., no
major protocol violations). All primary and secondary efficacy variables were analyzed for the EA sample.

The completer sample consisted of all subjects in the ITT sample who did not prematurely withdraw from the study. All primary and secondary efficacy variables were analyzed for the completer sample.

The safety-analyzable sample consisted of all subjects randomized to double-blind treatment who received at least one dose of study medication as determined Study Medication Record page of the CRF. All safety (i.e., non-efficacy) data except for subject evaluation groups were based on the safety-analyzable sample.

The all-screened sample consisted of all subjects who signed an informed consent/assent form and were enrolled in the study at Visit 1, regardless of whether they met inclusion/exclusion criteria to be randomized at Visit 2. The summary table and subject data listing for subject evaluation groups was based on the all-screened sample.
**Name of Company:** Pfizer Inc.  
235 East 42nd Street  
New York, NY 10017

**Name of Finished Product:** Zyrtec-D 12 Hour

**Name of Active Ingredients:** cetirizine-pseudoephedrine

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**Statistical Methods:** All statistical tests related to treatment effect were two-sided and conducted at the 0.05 significance level. All linear model hypothesis testing was performed using SAS Type III sums of squares. Treatment group differences for all categorical data were analyzed by the Cochran-Mantel-Haenszel (CMH) test stratifying by center. Treatment group differences for ordinal variables were tested using the row mean scores test. All other treatment group differences were tested using the general association test. All categorical data was summarized by the number and percentage of subjects within each treatment group.

The primary analysis model for continuous variables was an analysis of covariance (ANCOVA) model with treatment and center as main effects and baseline value as a covariate. A secondary ANCOVA model was used with treatment-by-center interaction considered as an exploratory effect. In addition, two exploratory ANCOVA models were fitted including the randomization stratification variable, age group (adolescents or adults). Baseline continuous variables were analyzed by an analysis of variance (ANOVA) model with main effects treatment and center.

All efficacy data were tabulated in summary tables and listed in subject data listings. There was one baseline visit (Visit 2) and two treatment evaluation periods (Visits 3 and 4) during the double-blind treatment phase of the study, during which multiple diary cards were completed.

For the efficacy endpoints derived from the subject diary, each efficacy sample was analyzed for the following time points during the double-blind treatment phase: the weekly averages for Week 1 and for Week 2, overall (defined as the average of all post-baseline observations), and at endpoint (defined as the last available post-baseline observation). The ITT sample was considered the primary analysis sample, and Week 2 was considered the primary analysis time point.

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**Summary - Conclusions**

**Efficacy Results:** The results of this study showed that both cetirizine-pseudoephedrine and the active comparator loratadine-pseudoephedrine were statistically significantly better at reducing symptoms associated with SAR than placebo. There was not a statistically significant difference between the cetirizine-pseudoephedrine and loratadine-pseudoephedrine treatment groups. Subjects within both the cetirizine-pseudoephedrine and loratadine-pseudoephedrine treatment groups experienced improvement in TSSC scores at Week 2 that were statistically significantly greater than improvements at this timepoint in the placebo group.

The results of all other secondary analyses were consistent with these primary results for all time points and for the EA and completer samples.

**Safety Results:** A total of 351 treatment-emergent (all causalities) AEs were reported by 256 (23.6%) subjects during the study. The incidence of treatment-emergent AEs was
slightly higher in subjects receiving active drug, with 8588 (24.0%) cetirizine-pseudoephedrine-treated subjects and 96 (26.72%) loratadine-pseudoephedrine-treated subjects reporting AEs compared with 72 (19.9%) placebo-treated subjects. Although the majority of treatment-emergent AEs were mild or moderate in severity, 10 (2.7%) subjects in the cetirizine-pseudoephedrine group, 18 (5.0%) subjects in the loratadine-pseudoephedrine group, and 11 (3.0%) subjects in the placebo group reported severe treatment-emergent AEs.

Headache was the most frequently reported treatment-emergent AE reported by 6 (1.6%) subjects in the cetirizine-pseudoephedrine treatment group, 16 (4.5%) subjects in the loratadine-pseudoephedrine treatment group, and 11 (3.0%) of subjects in the placebo treatment group. Two (0.6%) subjects in the loratadine-pseudoephedrine treatment group and 5 (1.4%) subjects in the placebo group had severe headache. One (0.3%) subject in the cetirizine-pseudoephedrine group, 3 (0.8%) subjects in the loratadine-pseudoephedrine group, and 2 (0.6%) subjects in the placebo group had headaches that were considered to be treatment-related.

Treatment-emergent AEs affecting the respiratory system occurred in 23 (6.3%) subjects in the cetirizine-pseudoephedrine group, 10 (2.8%) subjects in the loratadine-pseudoephedrine group, and 18 (5.0%) subjects in the placebo group.

Of the 351 treatment-emergent AEs, 164174 (49.0%) (49.6%) were considered to be treatment-related. The incidence of treatment-related AEs was: 54 (14.8%) subjects in the cetirizine-pseudoephedrine group, 54 (15.0%) subjects in the loratadine-pseudoephedrine group, and 20 (5.5%) subjects in the placebo group.

One placebo subject (0.3%) had his/her dose reduced or temporarily discontinued due to an AE. Eight (2.2%) subjects in the cetirizine-pseudoephedrine group, 4 (1.1%) subjects in the loratadine-pseudoephedrine group, and 7 (1.9%) subjects in the placebo group discontinued from the treatment phase of the study due to an AE. Of these, one (0.3%) subject in the cetirizine-pseudoephedrine group discontinued due to somnolence; two subjects in the loratadine-pseudoephedrine (0.6%) group discontinued because of somnolence, and one subject in the placebo (0.3%) group discontinued due to insomnia.

There were no SAEs or deaths reported or entered into Pfizer’s early alert safety database.
Conclusion: The results of this study demonstrated that both cetirizine-pseudoephedrine (5 mg/120 mg) and loratadine-pseudoephedrine (5 mg/120 mg) provided effective symptomatic relief in adults with SAR. In addition, subjects treated with either cetirizine-pseudoephedrine or loratadine-pseudoephedrine reported significant improvement in individual rhinoconjunctivitis symptoms compared to those treated with placebo throughout the treatment period (p<0.001) in the TSSC score. These effects were consistent across the ITT, EA, and completer samples.

Cetirizine-pseudoephedrine was well tolerated during the study. There were no clinically significant laboratory evaluations, vital signs, or physical examination abnormalities during the study.

during the study. A clinical review of vital sign and of physical examination data showed no clinically meaningful changes during the study.