SUMMARY

ZENECA INC

FINISHED PRODUCT: **ACCOLATE™**

ACTIVE INGREDIENT(S): **ZAFIRLUKAST (ICI 204,219)**

Trial title (number): A Randomized, Double-blind, Parallel-group Trial to Compare the Safety and Effectiveness of Zafirlukast (Accolate) vs Loratadine vs Placebo in Subjects with Seasonal Allergic Rhinitis: A Day-in-the-Park Trial (9188IL/0124)

Clinical phase: III

First patient entered: 1 August 1995 **Last patient completed:** 27 August 1995

Principal investigator and location: PPD PPD
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Publications: None at time of report preparation

OBJECTIVES: To compare the effect of oral zafirlukast, loratadine, and placebo on daily signs and symptoms of acute seasonal allergic rhinitis, as assessed by diary cards; to determine the onset of action of oral zafirlukast during periods of peak pollen exposure; to determine the safety and tolerability of oral zafirlukast as compared to loratadine and placebo

METHODS

Design: Two-day, single-center, randomized, double-blind, double-dummy, parallel comparison of zafirlukast, loratadine, and placebo

Population: Approximately 160 men and women, aged 12 to 70, with a documented history of seasonal allergic rhinitis requiring treatment during the ragweed season during 2 of the preceding 3 years and verification of ragweed allergy

Key inclusion criteria: Demonstrated symptoms of allergic rhinitis or conjunctivitis or both as manifested by two symptoms greater than or equal to 2 (mild to moderate) or one symptom greater than or equal to 3 (moderate to severe) during a 3-hour qualification period

Key exclusion criteria:

(a) Chronic sinusitis requiring antibiotic treatment

(b) Treatment with corticosteroids, astemizole, cromolyn, nedocromil sodium, theophylline, or antihistamines other than chlorpheniramine or pseudoephedrine, or vaccination with hepatitis B surface antigen within the specified time periods

Dosage: Three weeks before Trial Day 1, all patients switched from their usual regimen of allergy medications to short-acting antihistamines or decongestants or both. On Trial Day 1, patients were supplied with tablets and capsules; depending on their randomization group, they received: (a) zafirlukast 20 mg BID; or (b) zafirlukast 80 mg BID; or (c) placebo; or (d) loratadine 10 mg (QD). Patients were instructed to take their assigned trial medication on Trial Days 1 and 2.

Batch numbers:

- 20-mg zafirlukast tablets (formulation CCI , batch CCI , lot CCI)
- zafirlukast-matching placebo tablets (formulation CCI , batch CCI , lot CCI)
- capsules, each containing a 10-mg loratadine tablet; capsules not backfilled (formulation CCI , batch CCI , lot CCI)
- loratadine-matching capsules, each containing a placebo tablet that was similar to but not identical with a loratadine tablet; capsules not backfilled (formulation CCI , batch CCI , lot CCI)

Key assessments:

Efficacy: After patients received trial medication, allergic symptoms were collected by having patients complete symptom-score diary cards on an hourly basis while at the park and continue documentation at home at 1830, 2030, and 2230. Allergy symptoms included: nasal - runny, stuffy, sneezing, itchy (including throat and palate); and non-nasal - itchy, teary, red eyes. Additionally, patients completed a global efficacy assessment at the end of the trial.

Safety: Safety was assessed by monitoring adverse events. Results of clinical laboratory tests, vital signs measurements, electrocardiography (ECGs), and physical examinations were evaluated at screening.

Statistical considerations: The symptoms-score diary-card data were analyzed in the framework of an analysis of covariance (ANCOVA) model for a randomized, parallel group design. Pairwise comparisons between each active dose group and the placebo group and between each of the zafirlukast dose groups and the loratadine group were performed within the ANCOVA framework, as well as a contrast analysis testing linear trend with dose among the zafirlukast dose groups and the placebo group. All statistical analyses of diary data were performed on two patient populations: the intention-to-treat (ITT) population, which consisted of all randomized patients, and the per-protocol (PP) population, which excluded patients with major protocol violations.

Survival analysis methodology was used to assess differences among treatments with respect to the time of onset of action.

Chi-square tests of independence and logistic regression were used to assess pairwise treatment group differences and linear trend with dose, respectively, for patients' global evaluations of efficacy.

RESULTS

Demography: A total of 183 patients (120 women [66%] and 63 men [34%], with a mean age of 26.1 years [range PPD through PPD years]) with allergic rhinitis were enrolled in the trial; 179 patients (98%) completed both days of treatment.

Efficacy: In the ITT analysis of stuffy nose scores, patients treated with zafirlukast 80 mg showed statistically significantly greater improvement than placebo-treated patients for two of the hourly in-the-park diary assessments on Trial Day 2. The assessment of linear dose response was also statistically significant at these time points. In addition, comparison of the 80-mg treatment group versus the placebo-treatment group and assessments of linear dose response approached statistical significance for the following two summary time points: (1) average of all in-the-park assessments on Trial Day 2 (830 through 1630) and (2) average of all Trial Day 2 time points (830 through 2230). During the evening of Trial Day 2, the mean stuffy nose scores in the zafirlukast 80-mg treatment group continued to show approximately the same level of improvement from baseline as was seen in the park on Trial Day 2; however, the placebo effect increased slightly and statistical significance was not achieved. The results of the PP analysis supported the ITT analysis, with the p-values for the aforementioned summary time points achieving statistical significance in favor of the zafirlukast 80-mg treatment group. The zafirlukast 20-mg treatment group was not statistically significantly different from the placebo treatment group for any time point in the analysis of stuffy nose scores.

The ITT analyses showed no statistically significant differences between either zafirlukast treatment group and the placebo treatment group in runny nose scores, sneezing scores, itchy nose, throat, palate scores, itchy, watery eyes scores, total symptoms scores, or total nasal symptoms scores. In the PP analyses, the zafirlukast 80-mg treatment group showed a statistically significantly greater improvement than the placebo treatment group in runny nose scores for one time point on Trial Day 1 and in total nasal symptoms scores for one time point on Trial Day 1. The assessment of linear dose response was statistically significant at only two hourly timepoints: in the park on Trial Day 1 for runny nose scores (ITT and PP analyses) and in the park on Trial Day 2 for total nasal symptoms scores (PP analysis).

The loratadine 10-mg treatment group showed statistically significantly greater improvement than the placebo treatment group in stuffy nose scores, runny nose scores, sneezing scores, itchy, watery eyes scores, total symptoms scores, and total nasal symptoms scores for numerous time points during the trial. There was no statistically significant difference between the loratadine and placebo treatment groups in itchy nose, throat, and palate scores.

The loratadine 10-mg treatment group also showed sporadic occurrences of statistically significantly greater improvement than the zafirlukast treatment groups for all parameters evaluated in this trial except for stuffy nose, for which there were no statistically significant differences.

Survival analysis on time until onset of action showed no statistically significant differences across the four treatment groups. The global evaluation of effectiveness yielded statistically

significant results when comparing the zafirlukast 20-mg and placebo treatment groups; results approached statistical significance when the zafirlukast 80-mg treatment group was compared with the placebo treatment group. The zafirlukast-treated groups had more than double the proportion of patients describe their treatment as providing good or substantial control than the placebo group but also a higher proportion of patients compared to placebo who indicated that trial treatment provided no control of symptoms. Aggravation of symptoms occurred only in the placebo treatment group.

Safety: No deaths or serious adverse events occurred. No severe adverse events occurred in either zafirlukast treatment group. Accidental injury (bee sting or bug bite) was the most commonly reported adverse event and occurred in all treatment groups. Headache was the next most commonly reported adverse event; occurrences were evenly distributed among the placebo group and the zafirlukast treatment groups. A total of three patients withdrew. Only one patient (loratadine-treated) withdrew from the trial because of adverse events excluding allergy exacerbation; the patient reported severe dizziness and nausea. Two patients (both placebo-treated) withdrew from the trial because of allergy exacerbation. A summary of patients with adverse events is presented in Table A.

TABLE A Summary of adverse events

Category	Placebo	Zafirlukast 20 mg BID	Zafirlukast 80 mg BID	Loratadine 10 mg QD
All patients at risk	45	47	43	48
Patients with adverse events (%)	9 (20%)	7 (15%)	4 (9%)	6 (13%)
Total number of adverse events	11	10	4	8

CONCLUSIONS

The pollen counts during the time of the trial were relatively high (600-700 grains/m^3) and were adequate to allow the demonstration of efficacy.

In the analysis of daily diary scores, the zafirlukast 80-mg treatment group showed improvements versus the placebo treatment group in stuffy nose scores, which approached statistical significance for the in-the-park assessments on Trial Day 2 (average of assessments made from 830 through 1630) as well as for Trial Day 2 overall (average of assessments made from 830 through 2230). The assessment of linear dose response with respect to improvement in stuffy nose scores also approached statistical significance at these time points. During the evening of Trial Day 2, the mean stuffy nose scores in the zafirlukast 80-mg treatment group continued to show approximately the same level of improvement from baseline as was seen in the park on Trial Day 2; however, the placebo effect increased slightly and statistical significance was not achieved.

The zafirlukast 20-mg treatment group did not show any statistically significant improvements versus the placebo treatment group in the analysis of daily diary scores.

The loratadine 10-mg treatment group showed statistically significant improvements over the placebo treatment group on the evening (average of assessments made at 1830, 2030, and 2230, after subjects left the park) of Trial Day 1 for stuffy nose, runny nose, sneezing, total symptoms, and total nasal-symptoms scores. Loratadine did not show consistent, statistically

significant improvements over placebo for the in-the-park assessments on either trial day or for the evening assessments on Trial Day 2.

With respect to the global evaluation of effectiveness, the zafirlukast 20-mg treatment group was statistically different from the placebo treatment group. Twenty-three percent of zafirlukast 20-mg-treated patients versus 12% of placebo-treated patients rated their treatment as providing good or substantial control. However, 21% of zafirlukast 20-mg-treated patients versus 9% of placebo-treated patients rated their treatment as providing no control. This pattern of responses was similar for patients treated with zafirlukast 80 mg. These patterns of responses do not suggest a clear benefit over placebo with either dose of zafirlukast.

All active treatments were well tolerated and not clinically different from placebo treatment with respect to their safety profiles.