SUMMARY

ZENECA INC

FINISHED PRODUCT: ACCOLATE™

ACTIVE INGREDIENT(S): Zafirlukast (ICI 204,219)

Trial title (number): Randomized, Double-blind, Parallel-group Trial to Compare the Safety and Effectiveness of Zafirlukast (ACCOLATE™) With That of Pseudoephedrine and Placebo in Subjects With Seasonal Allergic Rhinitis: A Day-in-the-park Trial (9188IL/0125)

Clinical phase: III

First patient entered: 1 August 1995 **Last patient completed:** 30 August 1995

Principal investigator (center) and location: PPD, International Medical Technical Consultants, Inc, PPD, Lenexa, KS 66219

Publications: none at the time of this publication

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

METHODS

Design: double-blind, single-center, randomized, placebo-controlled, parallel comparison of safety and efficacy of zafirlukast, pseudoephedrine, and placebo conducted for 2 days on the clinic grounds in Lenexa, Kansas during the ragweed season (26 and 27 August 1995)

Population: women or men, aged 12 through 70 years

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: dependency on oral or inhaled (including nasal) corticosteroid therapy for allergies; dependency on cromolyn sodium or corticosteroid therapy for asthma; clinically significant laboratory or electrocardiogram (ECG) abnormalities or significant history of other illness

Dosage: doses of 20 or 80 mg BID of oral zafirlukast, 30 mg TID of pseudoephedrine, or matching placebo administered for 2 days

Batch numbers:

20-mg zafirlukast tablets (formulation number CCI , batch number CCI , lot number CCI)

zafirlukast-matching placebo tablets (formulation number CCI , batch number CCI , lot number CCI)

30-mg pseudoephedrine capsules (formulation number CCI , batch number CCI , lot number CCI)

pseudoephedrine-matching placebo capsules (formulation number CCI , batch number CCI , lot number CCI)

Key assessments:

Efficacy assessments: Pollen data were collected during the trial. 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 nonnasal symptoms - itchy, teary, red eyes. Additionally, patients completed a global efficacy assessment at the end of the trial.

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

Statistical considerations: The symptom-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 treatment groups and the pseudoephedrine group were performed within the ANCOVA framework, as well as a contrast analysis testing linear trend with dose among the zafirlukast treatment groups and the placebo group. Primary analyses were performed on the following end points: (1) mean allergy-symptom scores while in the park; (2) mean allergy-symptom scores while at home; and (3) mean allergy-symptom scores for the entire day (ie, end points [1] and [2] combined).

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.

Adverse events were tabulated by treatment group and body system using the Food and Drug Administration's (FDA) Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) terminology.

RESULTS:

Demographic details: One hundred eighty-nine patients (122 women and 67 men; 160 white, 18 black, 6 Hispanic, 2 Asian, and 3 other) aged PPD to PPD years were enrolled in this trial; 186 patients completed the trial.

Efficacy results: Ragweed counts were 122 and 187 grains/m^3 during the trial, and mold spore counts were 644 spores/m^3 and 1512 spores/m^3 during the trial. There were no statistically significant differences (in the direction of improved symptoms with active treatment) between either zafirlukast treatment group and the placebo group, or between the pseudoephedrine treatment group and the placebo group, for any diary-card assessment of allergic symptoms.

Runny-nose scores for 80-mg zafirlukast patients were significantly better than scores for 30-mg pseudoephedrine patients for the average of the in-the-park assessments on Trial Day 1. Runny-nose scores for both zafirlukast treatment groups were significantly better than those for the pseudoephedrine treatment group on Trial Day 2 (average of the in-the-park assessments, average of the evening assessments, and average of all assessments).

Survival analysis on time until onset of action showed no statistically significant differences across the four treatment groups.

With respect to the global evaluation of effectiveness, no active treatment group (zafirlukast or pseudoephedrine) was statistically significantly different from the placebo treatment group using the chi-square test of independence. The assessment of linear dose response was not statistically significant.

Safety results: No serious adverse events occurred for any patient. Forty-two patients reported a total of 56 adverse events during double-blind treatment in this trial. Four adverse events were described as severe: one (headache) in the placebo group, and three (itching, diarrhea, and headache) in the 80-mg zafirlukast group. All other events were either mild or moderate. All adverse events had resolved by the end of the trial. The most commonly reported event during the trial was headache, reported by 11 placebo-treated patients, 12 zafirlukast-treated patients, and 6 pseudoephedrine-treated patients. One patient from the placebo group withdrew from the trial because of hives on the left arm, right leg, and stomach. Table A summarizes the number of patients by reported outcome.

TABLE A Number of patients by reported outcome

Patient outcomes	Treatment			
	Placebo	Zafirlukast 20 mg BID	Zafirlukast 80 mg BID	Pseudoephedrine 30 mg TID
	n	n	n	n
Patients at risk analyzed for safety	48	47	47	47
Patients completing the trial	47	45	47	47
Patients withdrawn for reasons other than adverse events	0	2	0	0
Patients withdrawn for adverse events	1	0	0	0
Patients withdrawn for allergy exacerbation	0	0	0	0
Patient deaths	0	0	0	0

CONCLUSIONS:

The pollen counts during the time of the trial were relatively low. However, mold spore counts were moderate to high and adequate to allow the demonstration of efficacy.

Zafirlukast failed to show efficacy in the relief of the symptoms of allergic rhinitis over placebo or a dose-response relationship indicative of greater improvement with higher doses of zafirlukast on either day of the trial. Pseudoephedrine also failed to show efficacy in the relief of the symptoms of allergic rhinitis.

Survival analysis on time until onset of action showed no statistically significant differences across the four treatment groups. The global evaluation of effectiveness yielded no statistically significant results when comparing any active treatment group (zafirlukast or pseudoephedrine) with placebo.

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