SUMMARY

ZENECA Limited **FINISHED PRODUCT:** ACCOLATE ™ **ACTIVE INGREDIENT(S):** ICI 204,219	**INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF THE DOSSIER**	**(FOR NATIONAL AUTHORITY USE ONLY)**

Trial title (Trial Number): The Effectiveness and Safety of Oral ICI 204,219 in the Treatment of Acute Seasonal Allergic Rhinitis: A Dose-Ranging Study (9188US/0011:0001)

Principal investigator (Center) and location: PPD PPD, University of Iowa Hospitals, PPD Iowa City, Iowa 52242, USA

Publications: Donnelly A, Glass M, Muller B, Smart S, Hutson J, Minkwitz M, Casale T (1993) Leukotriene D_4 (LTD_4) antagonist, ICI 204,219, relieves ragweed allergic rhinitis symptoms. J Allergy Clin Immunol 91(1) Part 2: 259

KEY OBJECTIVES: To determine (1) the efficacy, safety, and tolerability of oral ICI 204,219 therapy in patients with acute seasonal allergic rhinitis and (2) the minimum effective dose and onset of action of oral ICI 204,219.

METHODS

Design: Randomized, double-blind, placebo-controlled, parallel trial conducted for 2 days in the Iowa City Park in Iowa City, Iowa, USA during the ragweed season (24 and 25 August 1991).

Population: Women or men, aged 16 through 60 years, with acute seasonal allergic rhinitis. Women were also required to be non-fertile or to use oral or double-barrier contraceptives during the trial.

Key inclusion criteria: (1) Documented history of seasonal allergic rhinitis and verification of ragweed allergy and (2) requisite severity of allergic rhinitis and/or conjunctivitis symptoms during 3-hour qualification period on Day 1.

Key exclusion criteria: (1) Upper or lower respiratory infection within 1 week of screening or vaccination with live, attenuated influenza within 6 weeks of screening; (2) dependency on oral or inhaled (including nasal) corticosteroid therapy for allergies; and (3) dependency on cromolyn sodium or corticosteroid therapy for asthma.

Dosage: Single, daily doses of 10, 20, 40, or 100 mg of oral ICI 204,219 [low relative bioavailability (LRB) formulation] or matching placebo. The sponsor supplied the clinical research center with the following trial medications (lot numbers): 5-mg ICI 204,219 tablets (CCI [redacted]); 10-mg ICI 204,219 tablets (CCI [redacted]); 20-mg ICI 204,219 tablets (CCI [redacted]); 50-mg ICI 204,219 tablets (CCI [redacted]); and placebo tablets (CCI [redacted]).

Key assessments:

Efficacy assessments: (1) Patients recorded allergy symptoms (ie, sneezing, stuffy nose, rhinorrhea, itchy nose or throat, and allergic eye symptoms) on symptom score cards while in the park or at home on Days 1 and 2 and (2) each patient provided an overall (global) efficacy evaluation of the trial medication before leaving the park on Day 2. Safety assessments: (1) Adverse events were assessed throughout the trial and (2) results of clinical laboratory tests performed on Day 2.

Statistical considerations: (1) Allergy-symptom data were analyzed using analysis of covariance (ANCOVA) in the framework of a parallel-group design with the baseline mean (ie, mean allergy-symptom screen on Day 1) used as a covariate, and including a linear dose-response contrast of ICI 204,219 versus placebo and pair-wise comparisons of each dose of ICI 204,219 with placebo; (2) analyses were performed on the following end points after dosing on Days 1 and 2: (a) mean allergy-symptom scores while in the park; (b) mean allergy-symptom scores while at home; and (c) mean allergy-symptom scores for the entire day (ie, End points 1 and 2 combined); (3) patients' global evaluations of the trial medication were analyzed using a chi-square test of association; (4) adverse events were tabulated by treatment group and body system using COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) terminology; and (5) repeated-measures ANCOVA were used to evaluate the clinical laboratory test results.

RESULTS

Demographic details: One hundred sixty-four rhinitic patients (86 women and 78 men) were enrolled in the trial, with 160 patients completing the trial. Of the 86 women enrolled, 10 women were either at least 1 year postmenopausal or surgically sterilized; the remaining 76 women used either oral or double-barrier contraception during the trial to prevent pregnancy.

One patient each from the 10-mg and 100-mg ICI 204,219-treated groups and the placebo-treated group were withdrawn from the trial before dosing on Day 2 because of rhinitis or asthma symptoms (an expected outcome with or without reported adverse events). Also, one patient from the placebo-treated group failed to return after Day 1 because of a PPD [redacted] PPD and was withdrawn. The data from these four patients were included in the efficacy analyses for Day 1. In addition, three patients with insufficient allergy symptoms were randomized and received double-blind treatment (a protocol violation); however, the data from these patients were included in the efficacy analyses.

Efficacy results: Mean allergy-symptom scores for the principal symptoms of allergic rhinitis (ie, stuffy nose, sneezing, and rhinorrhea) showed significant improvement ($p \leq 0.05$ in all cases beginning on the evening Day 1 through Day 2) in the ICI 204,219-treated groups over the placebo-treated group. Also, a linear dose response was seen for stuffy nose.

Minimum effective dose of oral ICI 204,219 may not be possible to define, but it appeared to be 20 mg, based on statistically significant improvements in the mean allergy-symptom scores for the principal allergic symptoms. The onset of action was shown to be within the first 2 hours after dosing on Day 1 for all treatment groups including the placebo-treated group.

A statistically significant, treatment-related, linear trend was noted in the patients' global efficacy evaluations.

Safety results: No deaths or serious adverse events were reported. The overall incidences of adverse events noted in the ICI 204,219- and placebo-treated groups were 17% and 18%, respectively. Headache was the most common adverse event, reported for 10 (8%) ICI 204,219-treated patients and 2 (6%) placebo-treated patients. Following analysis of the adverse events data, no treatment- or dose-related effects were noted in the reported incidence of any adverse events.

Clinically significant decreases in serum CO_2 levels were noted in a total of seven patients (all ICI 204,219- and placebo-treated groups, except 40-mg ICI 204,219 group). The investigator reported that the cause of this abnormal result was unclear, but the cause could possibly be related to the trial medication. However, the abnormal values for serum CO_2 (and also decreases in glucose levels noted in a number of patients but not considered clinically significant) may have been the result of blood samples that were unsuitable for the determination of these clinical laboratory parameters because of sample degradation. Analysis of the clinical laboratory data showed no statistically significant treatment effects for serum CO_2 and glucose; although, statistically significant decreases (from screening) of 13% for serum CO_2 and 14% for glucose across all ICI 204,219- and placebo-treated groups were noted. No statistically significant differences between ICI 204,219 and placebo were observed in any additional clinical laboratory test results.

CONCLUSIONS: The data suggest that oral administration of ICI 204,219 for 2 days was effective in relieving the principal allergic symptoms associated with acute seasonal allergic rhinitis. The data also suggest that 20 mg of oral ICI 204,219 is the apparent minimum effective dose in the treatment of acute seasonal allergic rhinitis; however, this may need to be confirmed because of the lack of a treatment effect at the 100-mg dose. The time of onset of relief in allergic symptoms, which was noted within 2 hours of administration, was not statistically different for ICI 204,219 and placebo.

Administration of total daily doses of up to 100 mg of oral ICI 204,219 was well tolerated by all patients. The safety profile of ICI 204,219 was not clinically different from that of placebo.