SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: **ACCOLATE™**

ACTIVE INGREDIENT: **zafirlukast (ICI 204,219)**

Trial title (number): A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Zafirlukast (ACCOLATE™) in Subjects Who Present to the Emergency Department with Asthma Exacerbations (9188IL/0093)

Clinical phase: III

First patient recruited: 17 September 1997
Last patient completed: 04 February 1999
AstraZeneca approval date: 29 May 2002

Publications: Silverman RA, Chen Y, Bonuccelli CM, Simonson SG. Zafirlukast improves emergency department outcomes after an acute asthma episode. Ann Emerg Med 1999;116(suppl 2):296S. Silverman RA, Miller CJ, Chen Y, Bonuccelli CM, Simonson SG. Zafirlukast reduces relapses and treatment failures after an acute asthma episode. Chest 1999;116(suppl 2):296S. Korenblat PE, Silverman RA, Nowak RM, Chen Y, Bonuccelli CM, Miller CJ, Simonson SG. Zafirlukast improves outpatient outcomes after acute asthma treatment. Ann Allergy Asthma Immunol 2000;84:118.

OBJECTIVES: The primary objectives of this trial were: to assess the efficacy of oral zafirlukast (one 20-mg or 160-mg dose, followed by a 20-mg bid dose for 4 weeks after discharge from the emergency department [ED]) in conjunction with a standard ED treatment regimen on patients who presented to the ED with asthma exacerbation; to evaluate the need for medical intervention for asthma exacerbations after discharge from the ED and during the 4 weeks of outpatient (OP) treatment.

METHODS

Design: This was a multicenter, randomized, double-blind, placebo-controlled trial of zafirlukast, involving patients who presented to the ED with asthma exacerbations. At randomization, patients were given a loading dose of zafirlukast (20 mg or 160 mg) or placebo in addition to standard ED treatment for asthma exacerbation including a 60-mg dose of

prednisone. Patients who were discharged from the ED within 4 hours continued randomized treatment (20-mg zafirlukast or placebo bid for 4 weeks). Patients were also given 20 mg of prednisone bid for the first 7 days after discharge from the ED and continued their regular therapeutic regimen without change for the 4-week outpatient period. Trial treatment was discontinued for patients who were unable to be discharged from the ED at the end of 4 hours of ED treatment period or at the time of relapse.

Population: 641 patients presenting to the ED with asthma exacerbation; 546 patients continuing on to the outpatient period.

Key inclusion criteria: Males or females aged 12 to 65 years presenting to the ED with asthma exacerbation and an FEV_1 of less than or equal to 70% of predicted, which remained less than or equal to 70% of predicted after treatment with nebulized albuterol; and patients having a documented history of asthma, were eligible for inclusion in the trial.

Key exclusion criteria: Excluded patients were those diagnosed with pneumonia on admission to ED or patients who had hemodynamic instability, were treated with zafirlukast, zileuton, montelukast or who received oral corticosteroids for 5 or more days within 2 weeks of presentation to the ED; or, patients who had a history of any disease, which contraindicated inclusion in the trial (ie, cancer, sarcoidosis, hyperbilirubinemia).

Dosage: AstraZeneca Pharmaceuticals supplied all trial medication; formulation, lot, and batch numbers are found in the full clinical trial report Table 3. Trial treatment for the ED period was a single oral dose of 20-mg or 160-mg zafirlukast or placebo given within 30 minutes after ED admission in conjunction with standard ED treatment for asthma exacerbation. (Note: The standard ED treatment was predefined and included prednisone 60 mg given orally at the time of randomization, 3 nebulized albuterol treatments within the 1^{st} hour of ED admission, and scheduled doses thereafter.) Trial treatment for the outpatient (OP) period was: 20-mg zafirlukast bid or placebo bid for 4 weeks and 20-mg prednisone bid for the first 7 days of the OP period. (Note: Patients also resumed their pre-ED asthma treatment regimen.).

Key assessments:

Efficacy: time to asthma relapse, need for extended care, time to treatment failure, spirometry (ie, FEV_1, FEV_1 as a % of predicted, FVC), PEF (morning and evening), daytime asthma symptom scores, nighttime awakenings, β_2-agonist use, Borg scale measurements, asthma diary, Juniper quality of life, resource utilization, and global rating of change.

Safety: adverse event monitoring, clinical laboratory measurements, subjective symptomatology, and vital signs measurements.

Statistical analyses:

All statistical tests were 2-sided with a statistical significance level of 0.05. Intention-to-treat and per-protocol analyses were performed on each efficacy assessment (modified ITT and PP analyses were performed for the time to relapse and the time to treatment failure). Analysis of covariance (ANCOVA) was used to assess treatment differences for continuous variables. Nonparametric analyses replaced ANCOVA as the primary method of analysis for assessments where underlying normality assumptions were not met. The primary efficacy variable (the time to relapse) was analyzed using a Cox's proportional hazard regression model; secondary measures for duration of extended care were analyzed by the Wilcoxon rank sum test and were used to summarize the type of care and proportion of patients requiring mechanical ventilation. The Cochran-Mantel-Haenszel test was the primary tool for analysis of the Juniper QOL and

global rating of change. Analysis of variance (ANOVA) was used to assess treatment effects for urine LTE_4, resource utilization, and global rating of change. Stepwise linear, logistic, and Cox's proportional hazard regression were done for exploratory and subgroup analyses.
Clinical laboratory test results were summarized by treatment group using descriptive statistics; clinically significant results occurring after randomization were tested for treatment differences using Fishers exact test.

RESULTS

Demography: A total of 641 patients (162 zafirlukast 160-mg, 158 zafirlukast 20-mg, and 321 placebo) from 21 centers in the United States were randomized into the ED phase of the trial (94.5% completed this phase). The mean age of all patients was 32.5 years with a range of 11 to 67 years; females were 57.1% of the population. There were slightly more females in all treatment groups except the 160-mg zafirlukast-treated group where there was a slight predominance of males. The predominant race of all patients was black (64.1%); 22.3% of patients were white, 11.1% were Hispanic, and the remaining patients were Oriental or of other origin. Of the 546 patients who entered the 4-week outpatient period of the trial, 457 (83.7%) were completely evaluated; 323 (59.2%) patients completed this period of the trial (98 [35.5%] were withdrawn from the 20-mg zafirlukast-treated group and 125 [46.3%] were withdrawn from the placebo-treated group). A total of 546 of patients entered the double-blind, outpatient period of the trial; 59.2% completed this phase including those patients that relapsed. Demographic characteristics were similar among groups in both trial phases.

Efficacy: The addition of treatment with zafirlukast to the standard ED regimens for the immediate treatment of acute asthma episodes and the standard ED discharge regimen produced many clinically beneficial outcomes. These improvements were demonstrated both during the ED period and the month following discharge from the ED. Notably, treatment failures were decreased by the addition of treatment with zafirlukast to standard ED asthma therapy.
During the ED period of this trial, the most striking benefits of the addition of zafirlukast to the standard ED treatment regimen were seen in the 160-mg zafirlukast-treated group. This group had a 39% improvement in FEV_1 and a 31% reduction in dyspnea (as measured by the reduction in mean Borg Scale scores). Most notably this group had a 34% reduction in the need for extended care (9.9% for the 160-mg zafirlukast-treated group compared with 15.0% for the placebo-treated group, p=0.052). The 20-mg zafirlukast-treated group demonstrated numerical superiority over the placebo-treated group for some efficacy variables but did not achieve statistical significance and did not reduce the need for extended care in the ED. It should be noted however, that when data from the post-ED period were analyzed, the 20-mg zafirlukast-treated group showed some benefit from having received treatment with zafirlukast. For example, nocturnal awakenings were significantly reduced in the 20-mg zafirlukast-treated group on the first night following ED discharge.
The primary efficacy assessment for this trial was the number of asthma relapses in the 28 days following discharge from the ED (Table I). Zafirlukast, given at a dose of 20 mg bid for the 4-week outpatient period of the trial, clinically and statistically reduced asthma relapses by 23.5% (p=0.021). When compared with the placebo-treated group 23.6% of patients relapsed in the zafirlukast-treated group compared with 28.9% of patients in the placebo-treated group.

Table I Summary of patient relapses by treatment group

Cut-off date/Treatment[a]				Comparison versus placebo		
	Number of patients	Number of relapses	Percent of patients relapsed	Hazard ratio	95% CI	p-value
ITT population						
Day 21						
Zafirlukast 20 mg bid	276	42	15.2	0.777	0.512 to 1.179	0.235
160 mg/20 mg bid	145	24	16.6	0.851	0.521 to 1.389	0.518
20 mg/20 mg bid	131	18	13.7	0.695	0.402 to 1.200	0.192
Placebo bid	270	48	17.8			
Day 28						
Zafirlukast 20 mg bid	276	65	23.6	0.714	0.512 to 0.996	0.047
160 mg/20 mg bid	145	33	22.8	0.713	0.474 to 1.073	0.104
20 mg/20 mg bid	131	32	24.4	0.715	0.471 to 1.087	0.116
Placebo bid	270	78	28.9			
14 days after treatment						
Zafirlukast 20 mg bid	276	74	26.8	0.729	0.533 to 0.997	0.048
160 mg/20 mg bid	145	40	27.6	0.750	0.515 to 1.092	0.134
20 mg/20 mg bid	131	34	26.0	0.704	0.471 to 1.052	0.087
Placebo	270	86	31.9			
Modified ITT population						
Day 28						
Zafirlukast 20 mg bid	276	61	22.1	0.671	0.478 to 0.941	0.021
160 mg/20 mg bid	145	33	22.8	0.710	0.472 to 1.067	0.099
20 mg/20 mg bid	131	28	21.4	0.628	0.405 to 0.975	0.038
Placebo bid	270	78	28.9			

[a] The number of zafirlukast patients in the 20-mg bid group is broken down by ED treatment received.
CI Confidence interval.

In addition, 20-mg zafirlukast-treated patients demonstrated improvement in most other efficacy assessments for the outpatient period. These included the assessment of daytime asthma symptoms scores, nighttime awakenings, number of nights awakened by asthma, and β_2-agonist use; all were improved by the addition of zafirlukast to the patients' asthma treatment regimen. The number of problem-free days improved significantly for zafirlukast-treated patients during the outpatient period. Additionally, airway function as measured by FEV_1 was significantly improved on Days 10 and 28 for zafirlukast-treated patients (49% greater improvement when compared with placebo-treated patients). The strength of the results and the ability to generalize the results were substantiated by the positive treatment effect seen across both objective and subjective end points for this trial and included subjective symptoms, airway physiology, and clinical outcomes measures. The broad applicability of the results was further strengthened by

the subgroup analyses, which overwhelmingly demonstrated a positive treatment effect favoring the zafirlukast-treated groups. Specifically, the benefits of zafirlukast treatment were demonstrated across patients of both sexes and all ages groups regardless of whether or not the patients were taking inhaled corticosteroids.

Quality of life was improved in both groups during this trial. Nominally greater scores were achieved by the zafirlukast-treated group but were not statistically significant and not comparable to the greater improvement in QOL demonstrated in other trials by zafirlukast-treated patients. The lack of statistical significance was possibly because the QOL instrument used for this trial was of insufficient sensitivity to detect differences in patients with this acuity of asthma exacerbation in a trial of only 28 days.

The conclusions for the results of efficacy variables examined during this trial are listed under conclusions in this summary.

Safety: The overall adverse event profile for zafirlukast was similar to that of placebo. During the ED portion of the trial, the adverse event profiles of 20-mg and 160-mg zafirlukast were similar to each other and to placebo with a nominally lower incidence of adverse events for both zafirlukast groups compared with placebo. No new or unexpected adverse events occurred during the trial. Headache was the most common adverse event during the ED period occurring in 1.3% and 1.6% of pooled zafirlukast-treated and placebo-treated patients, respectively. Headache, pharyngitis, and increased cough were the most common adverse events during the outpatient period and occurred in 40 (14.5.%), 29 (10.5%), 13 (4.7%) of 20-mg zafirlukast-treated patients and 23 (12.2%), 27 (10.0%), 15 (5.6%) of placebo-treated patients, respectively. One placebo-treated patient died during the trial for events considered by the investigator as unrelated to trial treatment.

No clinically significant shifts or differences between groups in the mean change from baseline occurred for any hematology or chemistry parameter, or for vital signs measurements.

Both doses of zafirlukast (160 and 20 mg) in the ED and 20-mg zafirlukast bid during the outpatient period were safe and had a comparable safety profile to placebo.