SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: ACCOLATE™

ACTIVE INGREDIENT: zafirlukast (ZD9188)

Trial title (number): A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Trial to Determine the Efficacy of Oral Zafirlukast (ACCOLATE™) When Administered According to Current Labeling Instructions or Simplified Dosing Instructions in Subjects With Asthma Receiving Inhaled β_2–agonist Alone or Inhaled β_2–agonist in Combination With Inhaled Corticosteroids (ICS) (9188IL0155)

Clinical phase: III

First subject recruited: 11 April 1999
Last subject completed: 27 September 2000
AstraZeneca approval date: 13 February 2003

Principal investigator(s) and location (center number): None

Publications: None

OBJECTIVE:
The objective of this trial was to determine the effect of zafirlukast on lung function, asthma symptoms, inhaled β_2-agonist use, and safety when patients using inhaled β_2-agonist alone or inhaled β_2-agonist in combination with ICS received instructions to take the trial medication in the morning and at bedtime or take the trial medication twice daily at least 1 hour before or 2 hours after meals.

METHODS

Design: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial involving approximately 750 evaluable patients with asthma. The trial consisted of a 3-week run-in period and a 6-week double-blind period. Following the run-in period, eligible patients were randomized for a 6-week double-blind period to 1 of 4 treatment groups in a 2:1:2:1 ratio: 20-mg oral zafirlukast or placebo taken in the morning and at bedtime or 20-mg oral zafirlukast or placebo taken twice daily at least 1 hour before or 2 hours after meals.

Population: 1500 patients were expected to be exposed to trial procedures to achieve approximately 750 evaluable patients.

Key inclusion criteria: During run-in period: (a) were males or females aged 12 years or older; (b) if sexually active or of child-bearing potential, females were required to practice a reliable method of contraception during the trial unless they were incapable of becoming pregnant; (c) was a non-smoker for 6 months before screening and had a 10 pack-year history of smoking or less; (d) had a documented clinical history of asthma and demonstrated reversible airway disease by at least a 12% increase in forced expiratory volume in 1 second (FEV_1) after inhaled β_2-agonist during screening; (e) had an acceptable FEV_1 no greater than 85% of predicted during the screening visit; (f) was able to perform 3 acceptable forced expiratory maneuvers with 1 reproducible FEV_1 within 10% of the highest FEV_1.

At randomization: (a) demonstrated a FEV_1 no greater than 85% of predicted on the day of randomization, (Visit 3); (b) performed at least 3 acceptable forced expiratory maneuvers with 1 reproducible FEV_1 within 10% of the highest FEV_1; (c) demonstrated clinically symptomatic asthma defined by meeting 1 of the following criteria during the last week of the 3-week run-in period: (symptom score of 2 or more on at least 4 days in the last week of the 3-week run-in period, 4 puffs per day or more of inhaled rescue β_2-agonist use on at least 4 days in the last week of the 3-week run-in period, or 4 nights or more with awakening due to asthma in the last week of the 3-week run-in period); (d) had a morning-to-evening peak flow variability (PFV) greater than or equal to 10%, calculated as the mean (arithmetic average) of the daily PFV values from the last 7 consecutive days of the 3-week run-in period.

Key exclusion criteria: (a) acute illness within 1 week of screening; (b) upper or lower respiratory tract infection within 4 weeks of screening; (c) clinically significant deviation from the reference range in laboratory results except for abnormalities related to asthma or allergy; (d) evidence of chronic lung disease other than asthma, including cystic fibrosis or bronchopulmonary dysplasia, chronic obstructive pulmonary disease (COPD), or chronic bronchitis; (e) evidence of hepatic disease other than isolated hyperbilirubinemia associated with a diagnosis of Gilbert's syndrome; (f) evidence of any disease that affects gastrointestinal absorption; (g) any significant unstable medical condition.

Dosage: AstraZeneca supplied the following trial medications (formulation and lot numbers): zafirlukast 20 mg (F7157, 983157A) and matching placebo (F7173, N53204F). Patients were given 20-mg oral zafirlukast or placebo taken in the morning and at bedtime or 20-mg oral zafirlukast or placebo taken twice daily at least 1 hour before or 2 hours after meals. All patients were issued albuterol inhalers VENTOLIN™ (Allen and Hansburys, Division of Glaxo Inc) (F10000 and ZP1433A and ZP1741A) and instructed to use in accordance with package labeling.

Key assessments:

Efficacy: Clinic FEV_1 was the primary efficacy variable. Secondary end points were AM peak expiratory flow (PEF), clinic visit PEF, β_2-agonist use (puffs per day), exacerbations of asthma, daytime asthma symptoms score, PM PEF, number of nighttime awakenings because of asthma, doctor visits, emergency room visits or hospitalization for asthma, PFV, and peripheral blood eosinophils (absolute counts).
Safety: Safety was assessed on the basis of results of adverse event monitoring, subjective symptomatology, clinical laboratory measurements, vital signs measurements, and physical examinations.
Statistical analyses: It was estimated that 250 patients per group would provide 92% power to detect (α=0.05, 2-sided) a mean difference between treatment groups of 7 percentage points in FEV_1 (percentage change from baseline) with α=23% for the planned primary contrast of zafirlukast administered with simplified dosing instructions (SDI) (taken once in the morning and once at bedtime) minus placebo (pooled across both dosing instructions). Thus, it was planned to include approximately 750 patients (250 for each zafirlukast treatment group and 125 in each of the placebo groups) in the efficacy analyses to achieve sufficient power for all comparisons of interest. The number of patients expected to be exposed to trial procedures to achieve approximately 750 evaluable patients (ie, randomized patients with both baseline and post-randomization data) was 1500.

A repeated-measures analysis of covariance was the primary method for determining efficacy. A baseline covariate was included in the model, as well as terms for stratum, visit, and treatment. The primary contrast to determine the efficacy of zafirlukast when administered with the simplified dosing instructions was the following 1 degree of freedom contrast of treatment: zafirlukast SDI minus placebo (pooled). Several sensitivity analyses were conducted to ensure the stability and robustness of the results of the primary analysis. Using the primary analysis model, a contrast of secondary importance was constructed: zafirlukast LDI minus zafirlukast SDI. A 2-sided 90% confidence interval (ie, 5% in each tail) was calculated for this contrast to determine if the simplified dosing instructions resulted in a clinically significant loss of efficacy compared to the labeled dosing instructions. Another contrast of secondary importance was also constructed: zafirlukast LDI minus placebo. This contrast served as a benchmark for the efficacy of zafirlukast, to verify that the results of this trial are similar to results of past trials that used the labeled dosing instructions.

Adherence to dosing instructions was assessed via a food questionnaire collected at the end of the trial. A second frequency distribution included only those patients randomized to the labeled dosing instructions because the simplified dosing instructions provided no control over timing of dose in relation to meals. This summary focused on adherence or non-adherence with this regimen based on the responses to the food questionnaire. Subset analyses of primary and secondary efficacy data were performed according to these categorizations of adherence to dosing instructions.

RESULTS

Demography: A total of 3521 patients from 104 centers were screened for the trial; 2739 (78%) failed the trial eligibility criteria either at screening. A total of 782 patients met the screening criteria and were entered in the trial. Of these, 466 patients were randomized to zafirlukast (257 to zafirlukast current labeling dosing instructions [Z-LDI] and 259 to zafirlukast simplified dosing instructions [Z-SDI]) and 266 patients were randomized to placebo (135 to placebo current labeling dosing instructions [P-LDI] and 135 patients to placebo simplified dosing instructions [P-SDI]). Of the 782 patients randomized, 432 (23%) were receiving a β_2-agonist alone as background asthma therapy and 350 (24%) were receiving inhaled corticosteroid therapy in addition to a β_2-agonist. Of the 782 patients randomized, 716 (92%) completed the trial and 66 were withdrawn from the trial (16 [6.2%] Z-LDI group, 24 [9.3%] Z-SDI group, and 26 [9.8%] placebo group. All available data for these 66 patients were included in the efficacy analysis.

Efficacy: The primary efficacy analysis was a repeated-measured analysis of covariance on the change from baseline in FEV_1, expressed in liters, in the ITT patient population (Table 1). The primary comparison was Z-SDI minus placebo.

Table I ITT repeated-measures analysis of change from baseline in FEV_1

Treatment or comparison	N	Mean at baseline (SD) (L)	Mean change from baseline to DB period (SD) (L)	Difference between treatments[a]		
				LS mean difference (L)	CL[b] (LL,UL) (L)	p-value
Z-LDI	254	2.14 (0.65)	0.20 (0.35)			
Z-SDI	257	2.13 (0.66)	0.16 (0.33)			
Placebo	261	2.13 (0.67)	0.08 (0.33)			
Z-SDI minus placebo				0.09	(0.05 , 0.13)	<0.001
Z-LDI minus placebo				0.12	(0.08 , 0.16)	<0.001
Z-SDI minus Z-LDI				-0.03	(-0.07 , 0.00)	0.100

a Estimates of mean differences between treatments are from a repeated-measures analysis of covariance adjusting for factors of baseline, strata, visit, and treatment.
b For the comparison of Z-SDI to Z-LDI, a 2-sided 90% confidence interval is presented. For all other comparisons, a 2-sided 95% confidence interval is presented.
SD Standard deviation.
DB Double-blind.
CL Confidence limits (LL Lower limit, UL, upper limit).
FEV_1 Forced expiratory volume in 1 second.
ITT Intention to treat.
LS Least squares.

For the primary analysis, treatment with Z-SDI resulted in a statistically significantly greater mean improvement in FEV_1 than did placebo ($p<0.001$), demonstrating that treatment with zafirlukast when administered with simplified dosing instructions is efficacious.

The active control group, Z-LDI, also experienced a mean improvement in FEV_1 that was statistically significantly greater than that of placebo ($p<0.001$) and similar to results seen in previous studies with zafirlukast, thus validating this study. The mean improvement with Z-LDI was numerically greater than that with Z-SDI ($p=0.100$); the lower bound of the 2-sided 90% CI for the mean difference between these treatments was –0.07 L.

The results of the analysis of FEV_1, when expressed as a % change from baseline, are consistent with those of the primary analysis: both zafirlukast treatment groups had mean improvements from baseline that were statistically significantly greater than that seen in the placebo group. The lower bound of the 2-sided 90% CI for the mean difference between Z-SDI and Z-LDI in percentage change in FEV_1 was –2.86%. This was greater than –5.00%, the pre-specified non-inferiority bound from the protocol.

The effect of Z-SDI on FEV_1 (versus placebo) was consistent across the strata of baseline asthma medications and baseline lung function (as measured by FEV_1) in this study. However, treatment with Z-LDI produced a greater mean effect than did Z-SDI in patients treated with as needed β_2-agonist alone at baseline and in patients with less-impaired lung function at baseline.

At the request of the Food and Drug Administration, additional analyses were conducted to explore the potential effects of dosing instructions on patient behavior (with regards adherence to dosing instructions) and then to relate patient behavior to the efficacy of zafirlukast. These analyses revealed that the effect of zafirlukast (compared with placebo) on FEV_1 was markedly smaller in the group of patients who usually took these medication near meal times than in those who did not, regardless of what dosing instructions the patients were given. Upon further exploration, it was revealed that this small treatment effect in the subgroup of patients who took their medication near meal times was predominantly driven by patients assigned to the simplified dosing instructions.

The results of the analyses of the secondary efficacy variables support the conclusions drawn from the primary analysis. Treatment with Z-SDI and Z-LDI both resulted in a statistically significantly greater mean improvement than did placebo for most variables. Among the secondary variables, Z-SDI resulted in a greater improvement than did treatment with Z-LDI for most diary card measures. This finding is in contrast to the primary analysis and the analysis of clinic-visit PEF, in which Z-LDI slightly outperformed Z-SDI. The analysis of peripheral blood eosinophil counts showed that both the Z-LDI and Z-SDI groups demonstrated a statistically significantly greater mean change from baseline in total eosinophil count compared with the placebo group. Moreover, there was no statistically significant difference between the Z-LDI and Z-SDI group.

Safety: The overall adverse event profile for 20 mg zafirlukast over the 6-week period was similar to that of placebo when these treatments were taken in the morning and at bedtime or at least 1 hour before or 2 hours after meals. No patient deaths occurred during double-blind treatment; however, 1 patient who did not receive double-blind treatment died of status asthmaticus, considered severe in intensity, during the screening run-in period. The most common adverse events during the trial were pharyngitis (reported for 22 [8.6%] Z-LDI-treated patients, 27 [10.4%] Z-SDI-treated patients, and 26 [9.8%] placebo-treated patients), headache (reported for 9 [6.7%] Z-LDI-treated patients, 14 [5.4%] Z-SDI-treated patients, and 17 [6.4%] placebo-treated patients) and sinusitis (reported for 11 [4.3%] Z-LDI-treated patients, 8 [3.1%] Z-SDI-treated patients, and 15 [5.6%] placebo-treated patients).

Six zafirlukast-treated patients, all in the Z-SDI group, and 5 placebo treated patients, 3 P-LDI and 2 P-SDI, were withdrawn from the study for adverse events. Of these, 2 Z-SDI-treated patients and 1 P-LDI-treated patient were withdrawn for adverse events considered by the investigator as serious. Asthma exacerbations, unless they were out of proportion to the patient's expected course or were possibly related to drug, were not considered adverse events but rather a lack of efficacy. One placebo-treated patient was withdrawn for a serious adverse event of asthma exacerbation that the investigator felt was not related to drug but was out of proportion to the expected course for this patient. In addition, one P-LDI-treated patient (0032/1167) had a serious adverse event not leading to withdrawal. With respect to nonserious adverse events, 4 Z-SDI-treated patients and 4 placebo-treated patients (1 P-SDI and 3 P-LDI) were withdrawn from the study.

No clinically significant differences were observed between groups in the results of clinical laboratory tests. Two zafirlukast-treated patients had nonserious adverse events of leukopenia reported and 1 placebo-treated patient had a nonserious adverse event of leukocytosis reported. Among zafirlukast-treated patients, 3 were reported to have hematocrit decreased, 3 were reported to have hemoglobin decreased, and 1 was reported to have platelet count decreased below the protocol specified acceptability criteria for trial entry after the first dose of double-blind treatment. There were no patients in either treatment group with leukocyte counts either increased or decreased or elevated platelet counts outside the protocol specified acceptability criteria for trial entry after the first dose of double-blind treatment.

Findings for all other safety parameters were similar between groups. No adverse events were reported for any zafirlukast-treated patient for clinical chemistry. Three placebo-treated patients were reported to have nonserious adverse events of alanine transaminase (ALT/SGPT) increased and 2 placebo-treated patients were reported to have nonserious adverse events of aspartate transaminase (AST/SGOT) increased. There were no zafirlukast-treated patients who had clinical chemistry results outside the protocol specified acceptability criteria for trial entry after the first dose, and there was one placebo-treated patient each with elevated ALT/SGPT and AST/SGOT. For all chemistry variables, the change from baseline to Week 6 was generally

similar between treatment groups and not clinically significant. Chemistry variables that fell outside of the normal range after randomization were minor. There was no pattern detected relative to chemistry variables that were outside of normal range.

Mean vital sign (pulse, respiration, systolic and diastolic blood pressure and oral temperature) results at baseline and throughout the trial were similar between treatment groups. No vital sign measurements were reported as adverse events, and intermittent variability in vital sign measurements throughout the trial were not clinically significant.