SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: ACCOLATE™

ACTIVE INGREDIENT: zafirlukast (ZD9188)

Trial title (number): A Multicenter, Double-blind Comparison of Zafirlukast (ACCOLATE) with Placebo in Pediatric Subjects with Mild-to-moderate Asthma (9188IL/0150)

Clinical phase: III

First patient recruited: 19 January 1998
Last patient completed: 29 September 1999
Zeneca approval date: 18 May 2000

Publications: None

OBJECTIVES:
Primary: to assess the efficacy of zafirlukast compared with placebo on asthma physiology, daily β_2-agonist usage, and daytime and nighttime asthma symptoms in pediatric patients with mild-to-moderate asthma
Secondary: to assess the safety of zafirlukast compared with placebo; to assess patient and caregiver reported outcomes and asthma quality of life (QOL) and explore health economic consequences of the use of zafirlukast in a pediatric population; to determine plasma concentrations of zafirlukast following twice-daily oral dosing; and to analyze genetic markers that may correlate with efficacy

METHODS:
Design: randomized, double-blind, placebo-controlled, stratified (by background therapy), multicenter trial consisting of 3 periods: a 1-week screening period, 7- to 14-day single-blind placebo run-in, and 10 weeks of double-blind treatment (10 mg zafirlukast bid or placebo bid)

Population: 900 pediatric patients with mild-to-moderate asthma were expected to be exposed to trial procedures to achieve approximately 450 randomized patients

Key inclusion criteria:

During screening: (a) were boys or girls aged 5 through 11 years; (b) had a documented clinical history of mild-to-moderate asthmaand currently treated with only short-acting β_2-agonists or short-acting β_2-agonists and inhaled steroids, and 1 of the following: demonstrated reversible airway disease shown by at least a 12% increase in 1-second forced expiratory volume (FEV_1) after inhaled β_2-agonist or demonstrated (within 6 months of screening) nonspecific bronchial hyperreactivity to methacholine or histamine challenge; (c) demonstrated FEV_1 greater than or equal to 45% and less than or equal to 85% of predicted without medication (ie, 6 hours after inhaled β_2-agonist or 8 hours after oral β_2-agonist, or 48 hours after salmeterol [SEREVENT™, Glaxo Wellcome]); (d) performed 3 acceptable forced expiratory maneuvers, with 1 reproducible FEV_1 within 10% of the largest FEV_1. Patients on a stable dose of inhaled steroid therapy for at least 60 days before screening were eligible if the dose did not exceed maximum allowable doses specified in the protocol.

At randomization: (a) demonstrated FEV_1 greater than or equal to 45% and less than or equal to 85% of predicted without medication (at least 6 hours after inhaled β_2-agonist) on the day of randomization; (b) demonstrated symptomatic asthma, as defined by either the patient's assessment of asthma symptoms that limit activity at least 4 of the last 7 consecutive days of the placebo run-in period or an investigator's assessment of overall asthma condition of 2 or greater (on a scale of 1 to 4) during the placebo run-in period; (c) performed 3 acceptable forced expiratory maneuvers, with 1 reproducible FEV_1 within 10% of the highest FEV_1; (d) had an average morning-to-evening peak flow variability (PFV) greater than or equal to 10% within the last 7 days of the placebo run-in period; (e) had an average daily β_2-agonist usage of at least 2 puffs per day during the last 7 consecutive days of the placebo run-in period.

Key exclusion criteria: (a) were placed at undue risk by a temporary postponement of initiating long-term asthma therapy; (b) had any clinically significant deviation from the reference range laboratory results except for abnormalities related to asthma or allergy; (c) had a history of any illness that might confound the results of the trial or place the patient at undue risk; (d) used any disallowed concomitant medications within a specified time period before screening

Dosage: Zeneca Pharmaceuticals supplied the following trial medications (Formulation number followed by lot numbers): 10 mg zafirlukast tablets (F12064; N83098, N73036) and matching placebo tablets (F7216, N73195). Patients were given 10 mg of zafirlukast or matching placebo twice daily for 10 weeks. All patients were issued albuterol inhalers (VENTOLIN™, Allen and Hansburys, Division of Glaxo Inc; F10000 [lot and batch numbers found in Table 2 of the clinical trial report]) and instructed to use in accordance with package labeling.

Key assessments:

Efficacy: Primary end points were daily measures of morning and evening peak expiratory flow (PEF), spirometry (changes in FEV_1), peak flow variability (PFV), daily inhaled bronchodilator usage, and total number of nights awakened by asthma per week. Secondary end points were school absenteeism for asthma, doctor or hospital contacts for asthma, treatment failures, patient and caregiver asthma quality-of-life questionnaire, health, outcomes questionnaire, asthma interference with activity, and assessment of overall asthma control and treatment response, awakening-free nights, and β_2-agonist free days.

Pharmacokinetics: Plasma zafirlukast concentrations were determined at Visits 1 (screening) and 7 (after 10 weeks of double-blind treatment).
Safety: Safety was assessed based on results of adverse event monitoring, subjective symptomatology, clinical laboratory measurements, vital signs measurements, and physical examinations.
Statistical analyses: Sample size calculations were based on variability observed in a dose-ranging clinical trial (Trial 9188IL/0079) conducted in mild-to moderate asthmatic children. Two hundred twenty-five patients per treatment group (450 patients total) were considered to provide sufficient power to detect statistically significant treatment differences between zafirlukast and placebo at a significance level of 0.05 (2-sided) for the primary efficacy parameters.
For all primary efficacy assessments (morning PEF, office-visit FEV_1, β_2-agonist use, PFV, nights awakened by asthma, and evening PEF), a repeated measures analysis was the primary method to assess treatment differences. The model included terms for center, background therapy (design stratification, patients treated with β_2-agonist alone compared with those treated with β_2-agonist and inhaled corticosteroids), time, and treatment, in addition to the baseline covariate. The repeated measures analysis of morning PEF, expressed as a percent change from baseline, was prospectively designated as the primary efficacy analysis in this trial.
End point and week-by-week analyses were the secondary foci of efficacy and were assessed for treatment differences with analysis of covariance (ANCOVA). The ANCOVA model included the same model terms (excluding time) used in the repeated measures analysis. Nonparametric analyses were performed to confirm the ANCOVA results where underlying assumptions of the ANCOVA model were not met. Nights awakened due to asthma were also analyzed with a Cochran-Mantel-Haenszel test, stratified by presence or absence of nights awakened by asthma at baseline.
Intention-to-treat (ITT) and per-protocol (PP) analyses were performed for each primary efficacy assessment.

RESULTS
Demography: A total of 479 pediatric patients from 59 centers were randomized (250 to zafirlukast and 229 to placebo) and entered the trial. Of the 479 randomized patients, 380 (79%) were receiving a short-acting β_2-agonist alone as background asthma therapy and 99 (21%) received inhaled corticosteroid therapy in addition to a short-acting β_2-agonist. Of the 479 randomized patients, 391 (82%) completed the trial and 88 (18%) were withdrawn from the trial (43 zafirlukast-treated and 45 placebo-treated). All available data from the 479 randomized patients were included in the ITT analysis of efficacy and analysis of safety, and data from 416 patients were included in the PP analysis of efficacy.
Efficacy: This trial succeeded in its primary objective by demonstrating that, over the course of 10 weeks, treatment with 10-mg zafirlukast bid significantly improved morning PEF when compared with placebo treatment. The repeated measures analysis of the percent change from baseline in AM PEF in the ITT population, the pre-specified primary analysis, is presented in Table I.

Table I ITT and PP analyses of percent change from baseline in morning PEF

Analysis/ Treatment	N	Mean percent change from baseline across double-blind treatment	LS mean % change from baseline[a] (%)	Difference from placebo		
				Difference in LS means[b] (%)	95% CI (LL, UL) (%)	Repeated measures p-value
ITT analysis						
Placebo	222	6.5	7.50			
Zafirlukast 10 mg bid	243	9.8	10.92	–3.4	–6.2, –0.7	0.015

Data derived from Table T5.1.2.

[a] From repeated measures analysis.

[b] Difference between treatments (placebo minus zafirlukast) in least squares means from repeated measures contrast.

PEF Peak expiratory flow.

LS Least squares.

CI Confidence interval (LL Lower limit, UL Upper limit).

ITT Intention-to-treat.

These changes in the percent change in AM PEF correspond to an estimated mean difference between zafirlukast and placebo, averaged over the course of the trial, of 8.2 L/min (p=0.001), in favor of the zafirlukast-treated group. For other measures of pulmonary function (ie, FEV_1 and evening PEF), treatment with zafirlukast resulted in statistically significant mean improvements when compared with placebo. Statistical superiority was not established for FEV_1 percent of predicted normal; however, mean values for the zafirlukast-treated group were higher than for the placebo-treated group at all timepoints across the trial.

For 2 measures of asthma control, mean total daily β_2-agonist use and nights awakened because of asthma, statistically significant differences in favor of the zafirlukast-treated group were demonstrated when comparisons were made with the placebo-treated group. The percentage of trial days that were free of β_2-agonist use was 27% for zafirlukast-treated patients compared with 20% for placebo-treated patients ($p<0.05$). Additionally, patients did not awaken because of asthma during an average of 90% of the trial days with zafirlukast treatment compared with 85% of trial days with placebo treatment ($p<0.05$). Further protocol-specified analyses of nights awakened revealed that 82.5% of zafirlukast-treated patients who had reported nights awakened at baseline had a decrease at end point in the number of nights awakened when compared with placebo-treated patients (69.2%) and fewer zafirlukast-treated patients (16.5%) reported an increase in the number of nights awakened compared with placebo-treated patients (25.3%) (p=0.030). In addition, 58.8% of zafirlukast-treated patients who reported awakenings at baseline were awakening-free at end point compared with 48.4% of placebo-treated patients; for zafirlukast-treated patients who reported no awakenings at baseline, 86.2% remained awakening-free at end point compared with 77.8% of placebo-treated patients (p=0.029). For

most measures, the onset of action of zafirlukast was evident within the 1st day of treatment and was sustained over the 10-week trial period.

The investigator's assessments of therapeutic response and overall patient condition were statistically significant favoring the zafirlukast-treated group.

Mean differences between treatments in PFV were not statistically significant, but the model indicated a strong treatment-by-stratum interaction. Further investigation revealed a marked difference between the zafirlukast- and placebo-treated groups for the inhaled corticosteroid plus β_2-agonist stratum compared with the difference for the β_2-agonist only stratum. When the repeated-measures model was applied separately to the inhaled corticosteroid plus β_2-agonist stratum, the treatment group difference was statistically significant in favor of zafirlukast ($p=0.033$; estimated mean treatment difference = 3.04%).

Examination of the data within each of the subgroups of baseline background asthma therapy demonstrated that mean treatment effects (ie, zafirlukast compared with placebo) were generally greater for the inhaled corticosteroid and β_2-agonist stratum than for the β_2-agonist alone stratum. For the inhaled corticosteroid plus β_2-agonist stratum, zafirlukast was demonstrated to be statistically superior to placebo for PFV, total β_2-agonist use, and β_2-agonist use before exercise. Statistical significance was approached for AM PEF ($p=0.054$; estimated mean treatment difference [-12 L/minute]). For nights awakened by asthma and for FEV_1, treatment differences were greater for the inhaled corticosteroid plus β_2-agonist stratum but were not statistically significant. However, this trial was not powered to detect treatment group differnces within these subgroups. These findings demonstrate the efficacy of zafirlukast for the treatment of patients on inhaled corticosteroids and β_2-agonists and suggest there may be additional benefit when given to patients already on inhaled corticosteroid therapy.

The results of PP analyses of the primary efficacy variables were consistent with those for the ITT analyses. This suggests that the relatively small number of protocol violators and deviators in this trial had little effect on the ability to differentiate zafirlukast from placebo. Therefore, the results presented here and the conclusions inferred are robust to minor departures from the protocol-defined population and methodology.

The analyses of the secondary efficacy variables were performed only for the ITT population. School absenteeism and doctor or hospital contacts for asthma were rare and were not clinically or statistically different between treatment groups. No statistically significant differences were found for the number of days asthma interfered with activities, the Juniper quality-of-life questionnaires, or the results of the health outcomes questionnaires. Although quality of life and health outcomes are expected to improve with zafirlukast therapy, this trial was not powered for these parameters. The young mean age (8.6 years) of patients enrolled in this trial may also have impacted the results and made treatment differentiation difficult. Treatment failures were relatively uncommon in both treatment groups (8.0% for zafirlukast and 10.9% for placebo; $p=0.347$).

Blood was drawn for plasma zafirlukast assays at the beginning of the trial and after 10 weeks of double-blind therapy. Because the protocol did not specify the time of blood collection relative to the most recent dose of trial medication, no attempt was made to correlate plasma zafirlukast concentrations with efficacy measures. Analysis of asthma-related genetic markers and their correlation with efficacy has not yet been done; this analysis will be reported at a later date. The exercise-challenge subprotocol will also be completed, analyzed, and reported at a later date.

Safety: The overall adverse event profile for 10-mg of zafirlukast bid given over a 10-week period was similar to that of placebo in this pediatric population. No patient deaths occurred during the trial and there were no new or unexpected adverse events. The most common adverse events during the trial were pharyngitis in 46 (18.4%) and 46 (20.1%), aggravation reaction in 22 (8.8%) and 29 (12.7%), and headache in 24 (9.6%) and 21 (9.2%) of zafirlukast- and placebo-treated patients, respectively.

No clinically significant differences between treatment groups were detected in the incidence of any adverse events or laboratory variables assessed. The incidence of accidental injury and of pain was statistically significantly higher in the zafirlukast-treated group (5.2% and 3.2%, respectively) compared with the placebo-treated group (1.3% and 0.4%, respectively). Epistaxis reported as an adverse event for 5 (2.0%) zafirlukast-treated patients and 1 (0.4%) placebo-treated patient [odds ratio (95% CI) = 4.65 (0.65 to 33.13)] was, for all patients, mild in intensity, considered by the investigators as unrelated to trial treatment, and required no additional medical treatment. The analysis of peripheral blood eosinophil counts showed no significant treatment group differences. Findings for all other safety parameters assessed were similar between treatment groups. The incidence of liver function abnormalities, as assessed by ALT and AST elevations, was low for both treatment groups; increases in ALT did not exceed 1.8 times the ULN for placebo-treated patients or 1.6 times the ULN upper limit of normal for zafirlukast-treated patients.

No vital signs measurements were reported as adverse events and intermittent variability in vital signs measurements during the trial was not clinically significant.