SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: ACCOLATE™

ACTIVE INGREDIENT: zafirlukast (ZD9188)

Trial title (number): A Dose-ranging, Safety, and Efficacy Trial with Zafirlukast (ACCOLATE™) in the Treatment of Pediatric Subjects with Mild-to-moderate Asthma; up to a 52-week Open-label Safety Extension (9188IL/0139). Report for the Open-label Extension only.

Clinical phase:	III	**Double-blind period began:**	28 February 1997
		Open-label extension began:	15 July 1997
		Zeneca approval date:	18 May 2000

Publications: None

OBJECTIVE

To assess the safety of zafirlukast 20 mg bid in pediatric patients with mild-to-moderate asthma during a 52-week open-label period.

This summary presents the methods, results, and conclusions from the open-label extension (OLE) period. Data from the 6-week double-blind (DB) period are summarized in a separate report.

METHODS

Design: open-label, multicenter trial of pediatric patients, aged 5 through 11 years, with mild-to-moderate asthma (Patients entered directly into the OLE period or entered the OLE after completion of the 6-week DB period. Patients were to receive treatment with zafirlukast [20 mg bid] during the OLE for up to 52 weeks. Trial 0139 included 4 periods: a 1-week observation and screening, 7- to 14-day single-blind placebo run-in, 6-week DB efficacy and safety, and an optional 52-week OLE. This report summarizes the OLE period only).

Population: 321 pediatric patients aged 5 through 11 years with mild-to-moderate asthma

Key inclusion criteria: patients who completed the DB period; or patients who entered the OLE period directly after meeting the following screening criteria: (a) were boys or girls aged 5 through 11 years; (b) had a documented clinical history of mild-to-moderate asthma treated with only β_2-agonist and 1 of the following: demonstrated reversible airway disease shown by at least a 12% increase in 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 50% 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 highest FEV_1

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): 20 mg (F7211; N63128, T63129, T63132, T63138, and T73046) zafirlukast tablets. Patients were given 20 mg of zafirlukast twice daily for 52 weeks. All patients were issued albuterol inhalers (VENTOLIN™, Allen & Hanburys, Division of Glaxo Inc; F10000; ZPAO24, ZPO318, and ZPO527) and instructed to use in accordance with package labeling.

Key assessments:

Efficacy: Efficacy measures included clinic spirometry (changes in FEV_1), daily measures of morning and evening PEF, asthma episode scores, total number of nights awakened by asthma, and daily inhaled bronchodilator usage. Additional efficacy measures were school absenteeism for asthma, doctor or hospital contacts for asthma, treatment failures, and quality-of-life assessments.

Safety: Safety was assessed based on results of adverse event monitoring, which included clinically significant findings in subjective symptomatology or physical examinations reported as adverse events; clinical laboratory measurements; vital signs measurements; and electrocardiography.

Statistical analyses: The primary focus of efficacy for this trial was OLE end point measurements with the last observation carried forward (LOCF) for all patients who entered the OLE. For comparison, changes from baseline were assessed for all patients who completed the 52-week period. Additionally, in order to evaluate changes in efficacy measures when the group assigned to placebo treatment in the DB period entered the OLE period, patients were stratified according to their original DB treatment groups (zafirlukast [10, 20, and 40 mg bid combined] or placebo received during the DB period of the trial, or no DB treatment) for OLE Weeks 0 through 52. Each of the 3 DB treatment groups were evaluated for changes from baseline at OLE Week 4. Descriptive summary statistics are presented for each efficacy measure. Paired t-tests were used to detect differences from baseline to each OLE time point for each efficacy measure.

RESULTS

Demography: A total of 321 pediatric patients with mild-to-moderate asthma from 35 research centers in the United States entered into the OLE period of this trial; 87 of these 321 patients did not participate in the DB period and entered directly into the OLE period. Patients who entered the OLE period from the DB period included 55 placebo-treated and 179 zafirlukast-treated. For 34% of these patients, there was at least a 2-week delay between completion of the DB period and entry into the OLE period. For all patients who entered the OLE period from the DB period, the mean and median delay were 23.4 and 1 day, respectively (range of delay from less than 1 day to 214 days). During this time between the DB and OLE periods, patients did not receive zafirlukast. A total of 208 (64.8%) of 321 patients completed the trial. The mean age of all patients was 8.7 years (range 5 through 12 years). There were 203 boys (63%) and 118 girls (37%), and 68% of all patients were white.

Efficacy: Efficacy was maintained over the 52-week OLE period for all pulmonary and diary card assessments. In general, pulmonary function measures and diary card assessments showed significant improvement from baseline at every time point during the OLE period of the trial, regardless of DB exposure. Because of the infrequency of days absent from school for asthma and days with a medical contact for asthma during the OLE period, it was difficult to determine the effect of zafirlukast over time. For the analysis of days of limited activity, days missed by the caregiver, and days with a childminder, no formal comparisons were offered because of limitations in the trial design and in the method of capturing these data. For all OLE patients, a consistent increase or improvement in the mean Pediatric Asthma Quality-of-life Questionnaire and Child Health Questionnaire scores occurred throughout the OLE period when compared with baseline scores. Without a concurrent comparator group, it is difficult to determine what degree of improvement in asthma symptoms and pulmonary function seen in this trial can be attributed to zafirlukast treatment. However, these data are reassuring in that the mean improvements over placebo seen during the initial 6-week DB period appear to be maintained over the course of a year, even after adjusting pulmonary function data for growth, without apparent diminution of effect or tolerance developing with time.

Safety: One hundred seventy-four (54.2%) of 321 patients received zafirlukast treatment in the OLE period for longer than 52 weeks; the mean and median total days of zafirlukast treatment were 294.1 and 365.0 days (range 1 to 459 total days). No patients died during the trial. Long-term administration of 20-mg bid dosages of zafirlukast was generally safe and well tolerated. Patients were defined as treatment failures and withdrawn from the trial if they had asthma exacerbation that required exceeded dosages of oral inhaled and/or oral corticosteroids; the treatment failure rate for the entire OLE period was 3.4% (11 of 321 patients) . There were no unexpected adverse events identified with long-term treatment with zafirlukast and no increase in incidence of adverse events with increased extent of exposure. Of the 321 patients enrolled in the OLE period, 260 (81.0%) reported at least 1 adverse event and 8 (2.5%) reported at least 1 serious adverse event. The overall incidence rate of the most common adverse events (ie, pharyngitis, aggravation reaction, headache, and sinusitis) per 3-month period generally remained the same or decreased. Two patients had liver function abnormalities (ie, elevations in AST and ALT concentrations) that the investigator reported as nonserious adverse events. One of these patients was withdrawn from trial treatment because of elevations in AST and ALT values of 2.6 and 3.2 times the upper limit of normal (ULN), respectively. Approximately 1

week after this patient was withdrawn, both AST and ALT values had returned to normal. As was the case during the DB period and in previous clinical trials in adolescent and adult patients, the most frequently occurring adverse events during the OLE were pharyngitis (COSTART term that includes cold, cold symptoms, and upper respiratory tract infections, but not strep throat, which is mapped to bacterial infection) in 119 (37.1%) patients, aggravation reaction (COSTART term that includes asthma exacerbation or acute asthma exacerbation) in 66 (20.6%), headache in 46 (14.3%), and sinusitis in 43 (13.4%). During the OLE, the most frequently reported serious adverse event was aggravation reaction, which occurred in 6 (1.9%) of 321 patients. Sixteen patients were withdrawn from the trial during the OLE period because of adverse events; 11 had events due to asthma exacerbation (2 of which were serious) and 5 had events other than asthma exacerbation, including nonserious adverse events of headache, myalgia, abdominal pain, eosinophilia, SGOT and SGPT elevations, agitation, and hyperkinesia (hyperactivity). One of the 2 patients who had a serious asthma exacerbation also had serious bronchitis that led to withdrawal of trial treatment. Assessment of mean compliance, by tablet counts, demonstrated that patients were greater than 90% compliant with their treatment regimen at OLE Visits 6 through 9.