# SUMMARY

**ZENECA PHARMACEUTICALS**

**FINISHED PRODUCT:** ACCOLATE™

**ACTIVE INGREDIENT:** zafirlukast (ZD9188)

**Trial title (number):** A Randomized, Double-blind, Placebo-controlled, Dose-ranging, Parallel-group, Multicenter, Safety and Efficacy Trial of Zafirlukast (ACCOLATE) in the Treatment of Pediatric Patients with Mild-to-moderate Asthma; up to a 52-week Open-label Safety Extension (9188IL/0079). Report for the Open-label Extension only.

**Clinical phase:** III

**Double-blind period began:** 17 October 1995
**Open-label extension began:** 6 June 1997
**Zeneca approval date:** 2 August 1999

**Publications:** None at the time of this report.

**OBJECTIVES:** The primary objective was to assess the safety of zafirlukast during a 52-week open-label extension period.

This summary presents the methods, results, and conclusions from the open-label extension (OLE) period. Data from the 4-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 4-week DB period. Patients were to receive treatment with zafirlukast [10 mg bid] during the OLE for up to 52 weeks. Trial 0079 included 4 periods: a 1-week screening, 7- to 14-day single-blind placebo run-in, 4-week DB efficacy and safety, and an optional 52-week OLE. This report summarizes the OLE period only).

**Population:** 179 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 $\beta_2$-agonist and 1 of the following: demonstrated reversible airway disease shown by at least a 12% increase in $FEV_1$ after inhaled $\beta_2$-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 $\beta_2$-agonist or 8 hours after oral $\beta_2$-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 $FEV_1$
**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 (F7212; T63122A, N63123A, T63137A, and T63137B) zafirlukast tablets. Patients were given 10 mg of zafirlukast twice daily for 52 weeks. All patients were issued albuterol inhalers (VENTOLIN™, Allen & Hanburys, Division of Glaxo Inc; F10000; Z1045, Z1045A, ZPA177, ZPO177, ZPO261, ZPO612, and ZPO755) 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, and treatment failures.
**Pharmacokinetics:** Plasma zafirlukast concentrations were determined at every visit during the OLE. For analysis purposes, plasma samples drawn 10 to 12 hours after dosing were considered to be the trough plasma concentrations.
**Safety:** Safety was assessed based on results of adverse event monitoring, subjective symptomatology, clinical laboratory measurements, vital signs measurements, electrocardiography, and physical examinations.
**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 5 or 10 mg bid, or placebo) for OLE Weeks 0 through 52. Each of the 3 DB treatment groups were evaluated for changes from baseline at the last DB visit (DB Week 4) and OLE Week 4. Descriptive summary statistics are presented for each efficacy measure. Paired t-tests were used to detect differences from baseline to the end of DB Week 4 and to each OLE time point for each efficacy measure.

**RESULTS**

**Demography:** A total of 179 pediatric patients with mild-to-moderate asthma from 30 research centers in the United States entered the trial; 69 of these 179 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 38 treated with placebo, 39 with 5 mg of zafirlukast, and 33 with 10 mg of zafirlukast; for approximately 66% of these patients, there was at least a 2-week delay between completion of the DB period and entry into the OLE period (mean and median delay of 106.2 and 72.5 days, respectively; range of delay from 0 to 497 days). During this time between the DB and OLE periods, patients did not receive zafirlukast. A total of 118 (65.9%) of 179 patients completed the trial. The mean age of all patients was 8.8 years (range 5 through 12 years). There were 99 boys (55%) and 80 girls (45%), and 71% 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.

**Pharmacokinetic:** Trough plasma zafirlukast concentrations were similar to those seen for zafirlukast-treated patients in the DB period of the trial and to those seen in Trial 0029 (20 mg bid), an OLE trial conducted in patients aged 12 years or older.

**Safety:** One hundred two (56.9%) of 179 patients received zafirlukast treatment (DB plus OLE) for longer than 52 weeks; the mean and median total days of zafirlukast treatment was 309.4 and 367.0 days (range 5 to 447 total days). No patients died during the trial. In general, long-term administration of 10-mg bid dosages of zafirlukast was well tolerated. Patients were defined as treatment failures and withdrawn from the trial if they had asthma exacerbation that required chronic treatment with medications that were not permitted; the treatment failure rate for the entire OLE period was 2.8% (5 of 179 patients). There were no unexpected adverse events identified with long-term treatment with zafirlukast. Of the 179 patients enrolled in the OLE period, 150 (83.8%) reported at least 1 adverse event and 10 (5.7%) reported at least 1 serious adverse event. The overall incidence rate of common adverse events per 3-month period generally remained the same or decreased. There were 7 events of liver function abnormalities in 4 (2.2%) of 179 patients. One patient was withdrawn because of a nonserious adverse event associated with an elevated ALT value of 1.8 times the upper limit of normal (ULN). As was the case during the DB period, the most frequently occurring adverse events during the OLE were pharyngitis (COSTART term that includes cold, cold symptoms, and upper respiratory tract infections) in 81 (45.3%) patients, aggravation reaction (COSTART term that includes asthma exacerbation or acute asthma exacerbation) in 43 (24.0%) patients, and sinusitis in 30 (16.8%) patients. During the OLE, the most frequently reported serious adverse event was aggravation reaction, which occurred in 5 (2.8%) of 179 patients. The next most frequently reported serious adverse event was pneumonia, reported in 2 (1.1%) of 179 patients. Eleven patients were withdrawn from the trial during the OLE period because of adverse events; 4 had events due to asthma exacerbation and 7 had events other than asthma exacerbation, including nonserious adverse events of hyperkinesia (hyperactivity), pneumonia, alopecia, ALT elevations, pharyngitis and serious adverse events of hemoptysis and grand mal convulsion. Assessment of compliance, by means of tablet counts, demonstrated that patients were, on average, 91% compliant with their treatment regimen throughout the 52-week OLE period.