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 Patients with Mild-to-moderate Asthma: 3 Weeks Efficacy and up to 104 Weeks Open-label Safety Extension (9188IL/0095)

Clinical phase: III	**First patient recruited:**	13 September 1995
	Last patient completed:	16 October 1998
	Zeneca approval date:	15 September 2000

OBJECTIVES: The objective of this open-label safety extension was to assess the safety of zafirlukast during long-term use.

METHODS

Design: This report summarizes the data of the 2-year open-label extension (OLE) of a multicenter trial consisting of 4 parts: a 1-week observation and screening period; a 14- to 21-day single-blind placebo run-in period to determine eligibility; a 3-week double-blind efficacy and safety period; and a 2-year open-label safety extension with zafirlukast 40 mg bid. Efficacy was not analyzed in this open-label report. Patients were allowed to enter the OLE directly after screening Visit 3. Data from Center 0024 has been removed from the summary tables because of uncertainty about its reliability.

Population: Approximately five hundred male or female patients with mild-to-moderate asthma aged 12 years or older.

Key inclusion criteria: Patients were eligible for entrance in the trial if the following key inclusion criteria were met: During screening: demonstrated 1-second forced expiratory volume (FEV_1) of at least 45% and no greater than 80% of predicted; demonstrated reversible airway disease shown by at least a 15% increase in FEV_1 after inhaled β_2-agonist or demonstrated nonspecific bronchial hyperreactivity to methacholine or histamine challenge; currently treated with inhaled β_2-agonist, only. During randomization: had mild-to-moderate asthma demonstrated by a total weekly symptom score of greater than or equal to 8 out of 21 (on a scale of 0 to 3) during the last 7 consecutive days of the 14 to 21-day placebo run-in period and an FEV_1 of at least 45% and no greater than 80% of predicted at least 6 hours after β_2-agonist use. (NB: Patients could enter the OLE period either directly after screening [Visit 3] or after completing the double-blind period of the trial.)

Key exclusion criteria: Patients were excluded from entrance into the trial if the following key exclusion criteria were met: History of any condition that might confound the results of the trial

or place the patient at additional or unknown risk. Seasonal asthma as defined by symptoms or therapy confined to 2 months or less per year.

Dosage: 40 mg of commercial zafirlukast (formulation number F7156 IPR-3, lot numbers N53044A, N53205D, N53014A, N53014B, N53047A, N63105A and N63173A) was to be taken bid. Albuterol inhalers (VENTOLIN™, Allen and Hansburys; formulation number F10000, lot numbers ZBA256, Z1045A, ZPA177, ZP0851, and ZP0259) were provided as rescue medication for the duration of the trial.

Key assessments: Safety was assessed based on results of clinical laboratory tests, physical examinations, vital signs measurements, electrocardiography, adverse event monitoring, and subjective symptomatology. For purposes of this report, only adverse events are summarized with a brief description of laboratory results. Efficacy was not analyzed or reported in this open-label report.

RESULTS

Demography: A total of 498 patients (266 [53.4%] females and 232 [46.6%] males, with a mean age of 36.2 years [range 12 through 79 years]) with mild-to-moderate asthma entered into the OLE of this trial; 301 patients (60.4%) patients completed the open-label period of the trial.

Safety: A total of 191 patients (38.4%) withdrew from treatment. Forty-two patients [22.0% of all withdrawals] withdrew because of adverse events or asthma became worse. The most common reason for withdrawal was patient refused to continue or failed to return (38.7%). No patients died during this trial. During the open-label period, 397 (79.7%) patients reported a total of 2270 adverse events; 212 events from 70 (14.1%) patients were assessed by the investigators as being possibly drug-related. Of these 397 patients, 19 reported a total of 31 serious adverse events. Five of the 31 serious events led to the withdrawal of 4 patients. One of these 4 patients withdrew due to 1 drug-related serious adverse event. The most common adverse events reported by patients during the OLE were pharyngitis (42.2%), headache (20.5%), and sinusitis (14.3%). Most adverse events were first reported in the initial 8 weeks of the open-label period and no trends were found in the frequency of the first occurrence of adverse events in relation to duration of treatment. Drug-related adverse events, as assessed by the investigators, were a small proportion of the total. No serious adverse events associated with laboratory abnormalities (in particular abnormalities associated with liver function) led to withdrawal. No clinically significant liver function abnormalities were reported during this trial.
