SUMMARY

ASTRAZENECA

FINISHED PRODUCT: ACCOLATE™

ACTIVE INGREDIENT: Zafirlukast

Trial title (number): A randomised, double-blind, placebo-controlled, multicentre trial to demonstrate the efficacy, steroid-sparing effect and safety of oral zafirlukast (ACCOLATE™) 20 mg (morning and bedtime) in symptomatic asthma patients currently being treated with inhaled corticosteroid (9188IL/0147).

Clinical phase: IIIB

First patient recruited: **03 June 1999**

Last patient completed: Trial stopped before completion

AstraZeneca approval date: 14 December 2000

Principal investigator and location (centre number): None appointed.

Publications: None

OBJECTIVES

The primary objectives of this trial were: to assess the add-in effect of zafirlukast 20 mg bd compared with placebo, on lung function and asthma symptom control in patients who have room for improvement in asthma control, despite being treated with inhaled corticosteroid; and to assess the effect of zafirlukast 20 mg bd compared with placebo on lung function and asthma symptom control when the dose of inhaled corticosteroid is halved. The secondary objectives of this trial were: to assess the effect of zafirlukast 20 mg bd compared with placebo (both given in addition to fluticasone) on quality of life over the trial period; and to assess the safety of zafirlukast 20 mg bd compared with placebo (both given in addition to fluticasone) over the trial period.

PURPOSE AND SCOPE OF THIS SYNOPSIS

Due to an unexpectedly high screening failure rate, a decision was taken to stop patient recruitment and terminate the trial. As only 23 patients had been randomised to treatment before trial closure, the data from this trial were clearly insufficient for a meaningful analysis of efficacy; therefore, this synopsis summarises the patient demography and safety results only. A full description of the trial is given in the protocol (presented as Appendix A), whilst the safety results (summary tables and listings) and efficacy results (listings only) are presented in Appendix B.

METHODS

Design: This was a randomised, double-blind, placebo-controlled, parallel-group, multinational, multicentre trial. The trial comprised a 3-week placebo run-in period during which patients were standardised to 1000 μg/day of inhaled fluticasone, followed by 18 weeks of double-blind randomised treatment with either zafirlukast 20 mg bd or placebo. During the first 6 weeks of randomised treatment, patients continued to receive 1000 μg/day fluticasone. For the remaining 12 weeks of randomised treatment, patients either had their fluticasone dose reduced by half (in 2 of the 4 arms of the trial) or continued on fluticasone 1000 μg/day (in the other 2 arms of the trial). The 4 treatment groups are referred to in this synopsis as: zafirlukast 20 mg bd plus fluticasone 500 μg bd; zafirlukast 20 mg bd plus fluticasone 250 μg bd; placebo bd plus fluticasone 500 μg bd; and placebo bd plus fluticasone 250 μg bd, where the dose of fluticasone refers to the dose given in the latter half of the treatment period.

Population: Patients were aged 16 years or over, with symptomatic reversible airways obstruction, currently receiving high-dose inhaled corticosteroid therapy and β_2-agonist for their asthma. Approximately 1600 patients were expected to enter the screening period to ensure that 800 patients were randomised to treatment.

Key inclusion criteria: A diagnosed history of asthma; ≥12% reversibility in forced expiratory volume in 1 second (FEV_1) to inhaled β_2-agonist (up to 400 μg salbutamol/albuterol from a metered dose inhaler); currently receiving ≥1000 μg/day beclomethasone/budesonide, ≥500 μg/day fluticasone, ≥2000 μg/day flunisolide or ≥2000 μg/day triamcinolone, along with β_2-agonist (salbutamol/albuterol or terbutaline) pro re nata only for asthma; a combination of percent predicted FEV_1 and morning-to-evening peak expiratory flow (PEF) variability during the last week of the run-in period of either 50 to 75% FEV_1 and ≥10% PEF variability, or 76 to 85% FEV_1 and a ≥15% PEF variability; a symptom score of ≥2 on at least 4 days, or use of ≥4 actuations of β_2-agonist to control asthma symptoms, or ≥4 disturbed nights with awakening due to asthma in the last week of the placebo run-in period; demonstrate the proper use of a peak flow meter, and daily electronic diary entries.

Key exclusion criteria: Hospitalisation for asthma within the last 3 months prior to entry; significant respiratory disease, other than reversible airways obstruction; new use or changing regimen of cromolyn sodium, nedocromil sodium, theophylline, cromolyn sodium nasal solution or nasal corticosteroids within 4 weeks of entry; use of oral steroids in the 4 weeks before entry, long acting β_2-agonists in the week before entry and zafirlukast, montelukast, or zileuton within 1 week prior to entry; use on entry of anticholinergics or oral salbutamol; upper or lower respiratory tract infection in the 6 weeks before entry or during the run-in period; asthma

exacerbations requiring change to the existing asthma treatment or the introduction of new asthma therapy during the run-in period.

Dosage: Zafirlukast 20 mg bd (one 20-mg tablet in the morning and one at bedtime) or matching placebo tablets bd, plus 1000 μg/day fluticasone propionate (250 μg MDI, 2 puffs twice daily) or 500 μg/day fluticasone propionate (125 μg MDI, 2 puffs twice daily). Formulation and batch numbers were: zafirlukast 20-mg tablets, F7157 (batch numbers N82042E, 60978E99 and 62595A99); placebo tablets, F7173 (batch numbers N53204E and 60979B99); fluticasone 250 μg MDI (Flovent 220 μg MDI), F12538 (batch numbers ZP1610A, ZP1452A and 61294D99); fluticasone 125 μg MDI (Flovent 110 μg MDI), F12537 (batch numbers ZP1609A, ZP1269A, ZP1651A and 61285E99).

Key assessments

Efficacy: The primary efficacy endpoint was morning PEF. Secondary endpoints were clinic visit FEV_1; number of asthma exacerbations; number of emergency room visits; number and duration of hospital admissions; peripheral eosinophil count; electronic diary recordings of evening PEF, daytime asthma symptom score, β_2-agonist use, night-time awakenings, quality of life (Juniper Asthma Quality of Life Questionnaire) and peak flow variability.

Safety: Safety was assessed by the recording of adverse events, routine clinical laboratory tests, medical history and physical examinations. The safety results were not subjected to formal statistical analysis.

RESULTS

Demography: A total of 255 patients were screened of which 23 (12 male, 11 female) were randomised to receive 1 of 4 treatment combinations: zafirlukast 20 mg bd plus fluticasone 500 μg bd (9 patients; 4 male and 5 female), zafirlukast 20 mg bd plus fluticasone 250 μg bd (2 patients; 1 male and 1 female), placebo bd plus fluticasone 500 μg bd (6 patients; 5 male and 1 female) or placebo bd plus fluticasone 250 μg bd (6 patients; 2 male and 4 female). The mean age of patients in each of these treatment groups was 43.78, 55.50, 44.33 and 44.00 years, respectively (range, 21 to 72 years inclusive). Twenty-one patients were Caucasian, 1 was of Indian subcontinent origin (zafirlukast 20 mg bd plus fluticasone 500 μg bd group) and 1 was black (placebo bd plus fluticasone 250 μg bd group).

Of the 23 patients who were randomised to treatment, 4 completed the trial, 2 withdrew because their asthma became worse, 1 withdrew consent, and 1 was lost to follow-up; the remaining 15 patients were not able to complete the trial as a direct consequence of its closure. The last patient was withdrawn from the trial on 15 November 1999.

Efficacy: Due to the premature termination of the trial, insufficient data were available to conduct a meaningful analysis of the efficacy endpoints; the individual patient data listings for the efficacy assessments (G7 to G15) are presented in Appendix B.

Safety: Individual patient data listings (G16 to G25) and summary tables (T18.1 to T18.5) for the safety assessments are presented in Appendix B.

There were no deaths, serious adverse events, or adverse events leading to withdrawals during the trial. Four patients (44.4%) reported 9 adverse events in the zafirlukast 20 mg bd plus fluticasone 500 μg bd group, and 3 patients (50.0%) reported 4 adverse events in each of the placebo groups (placebo bd plus fluticasone 500 μg bd and placebo bd plus fluticasone

250 μg bd); there were no adverse events in the zafirlukast 20 mg bd plus fluticasone 250 μg bd group.
The most common adverse events were: headache, affecting 3 patients (1 in the zafirlukast plus fluticasone 500 μg bd group and 1 in each of the placebo groups); pharyngitis, affecting 3 patients (2 in the placebo bd plus fluticasone 500 μg group and 1 in the placebo bd plus fluticasone 250 μg bd group); and rhinitis, affecting 2 patients in the zafirlukast plus fluticasone 500 μg group. Other adverse events were experienced by 1 patient only.
A small number of patients in each treatment group had clinical laboratory test variables which fell outside of the normal range; however, in all cases changes across the trial were not clinically significant.