SUMMARY

ASTRAZENECA

FINISHED PRODUCT: ACCOLATE™

ACTIVE INGREDIENT: Zafirlukast

Trial title (number): A randomized, double-blind, placebo-controlled, crossover trial to assess the effects of zafirlukast (ACCOLATE™) 20 mg twice daily when administered with food on exercise-induced bronchoconstriction induced in subjects with asthma (9188US/0025).

Clinical phase: IV

First patient recruited: 17 February 1999
Last patient completed: 10 July 1999
AstraZeneca approval date: 17 March 2003

Publications: Ostrom NK, Larsen JS, Miller CJ, Mezzanotte WS. Sustained attenuation of exercise-induced bronchoconstriction by zafirlukast when administered with food. J Allergy Clin Immunol 2001; Part 2(Vol 107);2: Abstract 371.

OBJECTIVES: (1) To determine the antagonism of exercise-induced bronchoconstriction by zafirlukast (20 mg bid) when taken with food for 5 to 7 days compared to the antagonism of exercise-induced bronchoconstriction by placebo when taken with food for 5 to 7 days;
(2) to determine the antagonism of exercise-induced bronchoconstriction 20 to 24 hours after the last dose of zafirlukast compared to the antagonism of exercise-induced bronchoconstriction 20 to 24 hours after the last dose of placebo.

METHODS

Design: This was a randomized, double-blind, placebo-controlled, multicenter, crossover trial conducted in patients with mild asthma (aged 12 to 45 years). The total duration for each patient was 14 to 18 days, comprising screenings, followed by two, 5- to 7-day randomized treatment periods, each separated by a 2-day washout period.

Prospective patients were assessed during the 2 days of screening to determine their suitability for the trial. Eligible patients were then randomized to receive either zafirlukast 20 mg bid or placebo taken with food for 5 to 7 days (minimum 5 daily doses) followed by a 2-day washout period. In the 2nd treatment period, patients received whichever treatment (zafirlukast 20 mg bid or placebo) they had not received in the 1st period.

Population: It was planned to screen up to 116 patients in an attempt to obtain 48 evaluable patients.

Key inclusion criteria: Male or female, aged 12 to 45 years; no history of smoking within 6 months of screening and ≤5-pack-year history of smoking; a forced expiratory volume in 1 second (FEV_1**)** of at least 70% of predicted [Crapo for adults, Polgar for subjects <18 years of age (at least 12 hours after short-acting inhaled β_2-agonist and at least 48-hours after antihistamines at both Visit 1 and Visit 2)]; a documented clinical history of asthma and either reversible airway disease demonstrated by at least a 15% increase in FEV_1 after inhaled β_2-agonist within 6 months of screening, or non-specific bronchial hyperreactivity to histamine or methacholine challenge (where the provocative concentration of methacholine that produced a 20% decrement in FEV_1 [PC_{20} FEV_1] was at least 0.25 mg/ml but not >8.0 mg/ml or the PC_{20} FEV_1 of histamine was ≤8.0 mg/ml) within 12 months of screening or, documentation of at least a 25% reduction in FEV_1 during standard exercise challenge within the last year. The screening exercise challenge test (see section 4.3.2) at Visit 1 could be utilized to fulfill this criteria; asthma currently treated by short-acting β_2-agonist alone; on each of the 2 occasions, each patient was to have demonstrated at least a 20% reduction in FEV_1 after standard exercise challenge tests (see section 2.6.3.2). The maximum post exercise FEV_1 percent decrement was recorded for each challenge. The variability between the 2 observations was not to be >10 percentage points. For example, if a 27% reduction in FEV_1 after exercise were observed at Visit 1 and a 37% reduction in FEV_1 were observed at Visit 2, the patient qualified for randomization. Patients with a >50% reduction in FEV_1 during either screening challenge were not eligible for trial entry.

Key exclusion criteria: History of convulsive disorders or any significant central nervous system (CNS) disorder, except stable, mild depression; use of barbiturate use, theophylline, cromolyn sodium (INTAL®, Fisons), nedocromil sodium (TILADE®, Fisons), ipratropium bromide (ATROVENT®, Boehringer Ingelheim), salmeterol (SEREVENT®, Allen and Hanburys), zafirlukast (ACCOLATE®, AstraZeneca), montelukast (SINGULAIR®, Merck) zileuton (ZYFLO®, Abbot) oral, inhaled or intravenous corticosteroids (patients were not to be removed from these treatments for the purposes of trial participation) within 4 weeks of screening; treatment with oral β_2-agonists within 2 weeks of screening; treatment with astemizole (HISMANAL®, Janssen) within 3 months of screening; upper or lower respiratory tract infection within 4 weeks of randomization; vaccination with hepatitis A or B surface antigen within 6 weeks of screening; discontinuation from chronic treatment of any leukotriene

modifying agent due to adverse experiences, ie zafirlukast (ACCOLATE®, AstraZeneca), montelukast (SINGULAIR®, Merck) or zileuton (ZYFLO®, Abbott); a change in nasal corticosteroid or antidepressant treatment regimen within 4 weeks of screening (patients whose dosage did not change during the 4 weeks prior to screening were eligible, provided their regimen did not change during the trial); treatment with cisipride (Propulsid®, Janssen) 4 weeks prior to screening; treatment with warfarin at any time during the trial.

Dosage: Zafirlukast 20 mg bid and placebo bid. Each 20-mg bid dose was comprised of 1 zafirlukast 20 mg tablet and each placebo dose was comprised of 1 placebo tablet. Formulation and batch numbers were: zafirlukast 20 mg tablets, F7157 (batch number N83042E A/O, NA); placebo to zafirlukast tablets, F7173 (batch number N53204E); albuterol inhalers (VENTOLIN®, Allen and Hanburys), F1000 (batch number ZP1541A) was supplied as rescue medication.

Key assessments:

Efficacy: The primary endpoint for analysis of efficacy was the maximum percent fall in FEV_1 assessed at 3 hours post dose. The secondary endpoints for the analysis of efficacy were the maximum percent fall in FEV_1 assessed at 24 hours post dose and the area above the FEV_1-time curve and time to recovery at both 3 and 24 hours post-dose. Additionally, the time to recovery, defined as the time (post challenge) for a patient's FEV_1 to return to within 5% of baseline, was assessed at both 3 hours and 24 hours post dose.

The primary analysis was the full analysis set including all evaluable data from all randomized patients in the analysis. Because of the crossover design, this meant that patients who missed a 24-hour challenge were not included in the analysis of 24-hour challenges since the difference in treatment effect at 24 hours was non-evaluable, but their data was included in the analysis of 3 hour challenges if both 3-hour challenges had been carried out. Likewise any patients who missed a 3-hour challenge was not included in the analysis of 3-hour challenges, but could be included in the analysis of 24-hour challenges if both 24-hour challenges had been carried out. Data from the 3-hour challenge was presented and analyzed separately to data from the 20- to 24-hour challenge data.

Protocol violations and deviations were reviewed for severity. If it was felt that they could substantially affect the outcome of the trial, a secondary analysis of the data was conducted by dropping the patients in question for comparison with the primary analysis of all evaluable data. This secondary analysis was designated the per-protocol analysis.

The pulmonary function data was evaluated in the framework of an analysis of covariance (ANCOVA) for a two-period crossover design. Baseline pulmonary function data was used as a covariate in the ANCOVA.

Safety: Safety was assessed by adverse events, routine clinical laboratory tests and the review of the concomitant medications. The safety analysis was conducted on an intention-to-treat population which included all patients who had received at least 1 dose of trial treatment.

RESULTS

Demography: In total, 123 patients entered the initial screening period of the trial; 54 patients were randomized into the double-blind trial period. Of these, 52 (26 male, 26 female) completed both crossover periods and were evaluable for efficacy. Their mean (SD) age at entry was 25.7 years (9.5 years). Their mean (SD) percentage predicted FEV_1 at baseline was 92.52% (14.02%).

Of the 54 patients who were randomized, 3 patients withdrew: 1 due to an adverse event, and 2 due to other reasons.

Efficacy:

Primary endpoint: Results for the primary endpoint, the maximum percent fall in FEV_1 at 3 hours post dose, are summarized in Table I.

Table 1 Analysis of the maximum % fall in FEV_1 at 3 hours post dose: evaluable patients

Treatment	n	Mean (%) (SD)	lsmean (%)	Comparison	Treatment effect[a] (%) (SE)	95% CI	p-value
Zafirlukast 20 mg bid	52	-17.03 (12.98)	-17.077	Zafirlukast 20 mg bid minus placebo	9.13 (1.88)	5.348 to 12.920	0.0001
Placebo	52	-26.26 (16.61)	-26.211	NA			

[a] Difference in lsmeans.

CI Confidence intervals; lsmean Least squares mean; NA Not applicable; n Number of patients**; SD Standard deviation; SE Standard error.**

Following exercise challenges performed at 3 hours post dose, zafirlukast 20 mg bid (in the presence of food) significantly reduced exercise-induced bronchoconstriction, compared with placebo, as demonstrated by a significantly lower lsmean % maximum fall in FEV_1 (p=0.0001). At 24 hours post dose, the lsmean % fall in FEV_1 for zafirlukast 20 mg bid was -18.465, compared with -22.958 for placebo (p=0.0141).

Additionally, treatment with zafirlukast resulted in a significantly smaller lsmean area under the % change FEV_1-time curve at 3 hours post dose (-334.562), compared with placebo (-874.592); (p=0.0001). This was also true for at the 24-hour time point although to a lesser degree (zafirlukast = -468.797; placebo = -638.968; p=0.0242). Percent protection in the maximum fall in FEV_1 was 35% at 3 hours and 20% at 24 hours. (In the adult multi-dose trial of Dessanges et al, 1999, percent protection was 35% at 2 hours and 23% at 8 hours, with a lessened placebo effect at 8 hours).

The time to recovery at 3 hours post dose after treatment with zafirlukast was shorter (20.608 minutes), compared with placebo (36.247 minutes); (p=0.0001). The time to recovery at 24 hours post dose after zafirlukast treatment was shorter (22.41 minutes), compared with placebo (30.48 minutes); (p=0.0001). However, since placebo patients had a smaller drop in FEV_1 at 24 hours, a observation seen before on repeat exercise challenge, their time to recovery was shorter.

The effect of zafirlukast (in the presence of food) on exercise-induced bronchoconstriction was similar at the 2 challenge timepoints; however, the placebo group showed attenuated exercise-induced bronchoconstriction more at 24 hours than at 3 hours, leading to a smaller difference between treatments at 24 hours than at 3 hours.

Overall, the secondary per-protocol analyses were supportive of the primary analyses. Although there were some instances (area above the FEV_1 time curve at 24 hours post dose and time to recovery at 24 hours post dose) in which the secondary analyses did not result in a statistically significant p-value, these instances were largely due to effect of reduced samples sizes.

Safety: Adverse events for each treatment are summarized in Table II.

Table 2 Overview of adverse events

Category[a]	Zafirlukast 20 mg bid		Placebo	
	Number of adverse events	Number of patients (%)	Number of adverse events	Number of patients (%)
Patients at risk		53		53
All adverse events	26	11	19	10
Deaths	0	0	0	0
Serious	0	0	0	0
Withdrawals due to adverse events	0	0	3	1
All other adverse events	26	11	16	9

[a] Adverse event categories are mutually exclusive: events are counted in 1 category only. Patient categories are not mutually exclusive; patients may have adverse events in more than 1 category.
[b] A serious adverse event was defined as an adverse event that was fatal, was life-threatening, required or prolonged hospitalization, resulted in disability or incapacity, was a congenital abnormality, required medical intervention to prevent permanent impairment or damage.

There were no deaths or serious adverse events in this trial and the 2 treatments were comparable for all adverse event categories, except headache which had a slightly higher incidence during zafirlukast 20 mg bid treatment (5.88%), compared with placebo (1.89%). Events of asthenia only occurred during treatment with zafirlukast (5.66%), whilst pharyngitis only occurred in the placebo group (7.55%).

Only 1 patient (Patient 0002/0035) was withdrawn during placebo treatment due to an elevated AST/SGOT, creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) values. All values subsequently returned to within normal range.

Both treatments were well tolerated, with no clinically meaningful changes in other individual or mean hematology or clinical biochemistry parameters, and no new or unexpected adverse events.