SUMMARY

ASTRAZENECA

FINISHED PRODUCT: ACCOLATE™

ACTIVE INGREDIENT: Zafirlukast

Trial title (number): A double-blind, placebo-controlled, parallel-group trial to assess the effects of ACCOLATE™ (20 mg bd) on airway hyperreactivity to inhaled methacholine (9188IL/0037).

Clinical phase: IIIB

First patient recruited: 10 November 1997
Last patient completed: 1 December 1999
AstraZeneca approval date: 23 October 2002

Principal investigator and location (centre number): Professor EH Walters, Department of Respiratory Medicine, The Alfred Healthcare Group and Monash University Medical School, Commercial Road, Prahan, Melbourne, Victoria 3181, Australia (0001).

Publications: None at the time of writing this report.

OBJECTIVES
Primary objective: To determine the effects of zafirlukast (20 mg bd) on bronchial hyperreactivity to methacholine.
Secondary objectives: To determine how nitric oxide release from the airways varies with treatment; to assess how the responsiveness to methacholine changes after cessation of trial medication; to assess how treatment with zafirlukast (20 mg bd) affects the number of eosinophils in induced sputum samples; to assess the safety of zafirlukast.
METHODS
Design: This was a randomised, double-blind, placebo-controlled, parallel-group trial conducted at a single centre in patients (aged 18 to 70) with diagnosed asthma (either mild/moderate [termed steroid-naïve patients], or moderate/severe [termed steroid-maintained patients]).

The total duration of the trial was 14 weeks, comprising a 1-week screening period followed by a 12-week, double-blind, randomised treatment period.
A 7-day washout period immediately followed the completion of the 12 weeks of randomised treatment (patients were assessed at the end of the 7-day washout period to assess if they had a rebound hyperresponsiveness [ie, an increased sensitivity to methacholine challenge following cessation of treatment]).
Prospective patients were observed during the 1-week screening period to assess their suitability for the trial. Eligible patients were then randomised in a stratified way according to asthma severity with a 2:1 allocation bias in favour of zafirlukast across both patient sub-groups to receive 12 weeks of either zafirlukast 20 mg bd or placebo.
Population: A total of 48 patients (24 per treatment group) were required to complete the trial (24 steroid-naïve patients and 24 steroid-maintained patients).
Key inclusion criteria: Male or female aged between 18 and 70 years inclusive; non-smoker or ex-smoker who had stopped smoking at least 6 months before screening; a diagnosed history of asthma; receiving either prn β_2-agonist alone for their asthma (50% of total patients [ie, steroid-naïve patients]) or, ≥1200 µg/day beclomethasone/budesonide or ≥600 µg/day fluticasone along with prn β_2-agonist for their asthma (50% of total patients [ie, steroid-maintained patients]); have a forced expiratory volume in 1 second (FEV_1) >60% predicted, demonstrated at screening; show either a ≥15% improvement in FEV_1 to a dose of up to 400 µg salbutamol metered dose inhaler demonstrated at screening or at any time during the 6 months before entry to the trial or, a ≥15% improvement in morning peak expiratory flow (PEF) following β_2-agonist taken by the patient at home at any time during screening; demonstrate at least 1 of the following in the 7 days before randomisation: a total daytime symptom score of at least 10 (≥10), average daily use of β_2-agonist ≥4 puffs, 2 days with diurnal variation in PEF ≥20%, awakenings due to asthma on ≥2 nights, demonstrate the ability to use the peak flow meter and diary card correctly, have a provocative dose of bronchoconstrictor causing a 20% fall in FEV_1 ($PD_{20\%FEV1}$) <2 mg/ml methacholine at Week 0.
Key exclusion criteria: Overnight hospitalisation for asthma in the 3 months before screening; evidence of respiratory disease other than reversible airways obstruction; lower or upper respiratory tract infection in the 6 weeks before entry or during the screening period; seasonal asthma, as defined by symptoms and/or therapy confined to ≤2 months per year; short courses of oral steroids or regular oral steroids within 3 months of screening, cromones or theophylline within 6 weeks of screening, long-acting β_2-agonists within 1 week of screening, non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief within 12 hours of screening, anticholinergics and oral bronchodilators were stopped on entry to the screening period; any alteration in inhaled corticosteroid therapy in the month before entry into the screening period.
Dosage: Zafirlukast 20 mg bd and placebo bd. Each 20-mg-bd 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 numbers 28124/95); placebo to zafirlukast tablets, F7173 (batch numbers 28062/95).
Key assessments:
Efficacy: The comparisons of interest were zafirlukast versus placebo. The primary endpoint for analysis of efficacy was the doubling dose change in $PD_{20\%FEV1}$ to methacholine challenge from baseline (Week 0) to the end of the randomised period (Week 12). The secondary

endpoints for the analysis of efficacy were: the amount of nitric oxide in exhaled air at Week 12, and at Week 13 (7 days after the cessation of treatment); the doubling dose change in $PD_{20\%FEV1}$ to methacholine challenge from baseline (Week 0) to Week 13 (7 days after the cessation of treatment); induced sputum differential eosinophil cell count at Week 11. The primary "per-protocol" analysis included all randomised patients who adhered closely to the protocol and for which follow-up data on at least 1 efficacy endpoint was available. The secondary "intention-to-treat" analysis included all randomised patients for which follow-up data on at least 1 efficacy endpoint was available.

The primary endpoint was analysed by analysis of covariance (ANCOVA) models. The 1st model provided an estimate of treatment effect in each sub-group of patients (steroid-naïve patients and steroid-maintained patients). The 2nd model provided an overall treatment effect for the whole trial population.

The amount of nitric oxide in exhaled air at Week 12 was analysed using an ANCOVA model. The trial was not powered to detect differences within the 2 sub-groups for this endpoint and so estimated treatment effects were made for the whole trial population. The amount of nitric oxide in exhaled air at Week 13; the number of eosinophils in induced sputum samples collected at Week -1 and Week 11; and the doubling dose change in $PD_{20\%FEV1}$ from baseline (Week 0) to Week 13 were analysed using ANCOVA models. No analysis of the 2 sub-groups was performed unless a significant sub-group-by-treatment interaction was found.

Safety: Safety was assessed during each visit by a review of the patient's health, subjective symptomatology and recording of adverse events, routine clinical laboratory tests and review of the diary cards.

RESULTS

Demography: In total, 72 patients entered the initial screening period of the trial. Of these, 45 patients (21 male, 24 female), aged between 20 and 70 years, were eligible for, and chose to enter the 12-week randomised treatment period and received 1 of the 2 treatments: 30 received zafirlukast 20 mg bd; and 15 received placebo. Their mean (SD) percentage predicted FEV_1 at baseline was 80.8 (13.06). Twice as many female patients received placebo than male patients (10 and 5, respectively). The number of male and female patients receiving zafirlukast 20 mg bd was comparable (16 male and 14 female). Both treatment groups were comparable with respect to age and baseline predicted FEV_1. In the steroid-naïve group, 14 patients received zafirlukast 20 mg bd and 7 received placebo; in the steroid-maintained sub-group, 16 patients received zafirlukast 20 mg bd and 8 received placebo.

Twelve patients withdrew from the zafirlukast 20 mg bd group: 5 due to adverse events, 2 due to worsening asthma, 2 due to withdrawal of consent and 3 for other reasons. Four patients withdrew from the placebo group: 1 due to an adverse event, 1 due to worsening asthma, and 2 for other reasons.

Efficacy:

Primary endpoint: Results of the per-protocol analysis (whole trial population) of the doubling dose change in $PD_{\mathbf{20}\%FEV1}$ to methacholine challenge from baseline (Week 0) to the end of the randomised period (Week 12), are summarised in Table I.

Table I Analysis of doubling dose change in $PD_{20\%FEV1}$ for the whole trial population

Treatment	n	lsmean	Comparison	Treatment effect[a]	95% CI	p-value
Zafirlukast 20 mg bd	18	0.71	Zafirlukast 20 mg bd - placebo	0.63	(-0.50, 1.75)	0.2584
Placebo	6	0.08	NA			

[a] Difference in lsmeans; CI Confidence intervals; lsmean Least squares mean; NA Not applicable; n Number of patients
$PD_{20\%FEV1}$ provocative dose causing a 20% fall in FEV_1.

Steroid-naïve patients randomised to zafirlukast 20 mg bd had a higher $PD_{20\%FEV1}$ than those patients randomised to placebo at the baseline methacholine challenge (40.184 µg and 9.401 µg, respectively). This trend was reversed in the steroid-maintained patients, though to a lesser degree (20.783 µg and 26.195 µg, respectively). After 12 weeks treatment, the mean doubling dose change in both groups was higher in steroid-maintained patients than in steroid-naive patients. In the per-protocol analysis, all of the patients in the placebo group were steroid-maintained patients. Although Week 12 methacholine challenge data was available for 3 steroid-naive patients on placebo, they were judged to have significantly deviated from the protocol. The mean doubling dose change in the zafirlukast 20 mg bd group was therefore a combination of both sub-groups, whereas the placebo mean was based only on the steroid-maintained patients who seemed to have responded well during the randomised phase. Hence, although there was no evidence of a significant difference between the 2 groups (p=0.2584), the above analysis should be interpreted with caution. The results of the per-protocol analysis was supported by the intention-to-treat analysis (p=0.1961).

A per-protocol analysis of the steroid-naive patients was not possible as no patients completed the trial from the placebo group without a significant protocol deviation (as described above). Since only 3 patients were recruited to the placebo arm of this sub-group rather than the protocolled 6, analysis of this endpoint using an intention-to-treat population, was considered under-powered. There was a positive treatment effect for zafirlukast 20 mg bd over placebo, but there was no evidence that this effect was statistically significant (p=0.2173).

A per-protocol analysis of the steroid-maintained patients showed a greater mean doubling dose change in $PD_{20\%FEV1}$ for the zafirlukast 20 mg bd group (0.92), than for the placebo group (0.60), but this was not statistically significant (p=0.5999). This result was supported by the intention-to-treat analysis (p=0.8777). The greater mean doubling dose change for the zafirlukast 20 mg bd group could have been due to random variation in the response measurement. This could have been due to random variation in the response measurement, but the fact that this increase was in both treatment groups and differences at endpoint between treatment groups were smaller in this population, could indicate an improved use of concomitant steroids in this population.

Secondary endpoints:

Mean NO concentrations at Week 12 were lower in the zafirlukast 20 mg bd group (16.21 parts per billion [PPB]) than in the placebo group (19.61 PPB). The difference was not statistically significant (p=0.2420). After the post-treatment 1-week washout period, the mean NO concentrations in the 2 groups were similar (20.86 and 20.39 PPB for the zafirlukast 20 mg bd and placebo groups, respectively).

After washout (Week 13), similar effects on dose-doubling change in $PD_{20\%FEV1}$ to methacholine challenge were seen to those at the end of the treatment period (Week 12), with a

greater mean improvement in the zafirlukast 20 mg bd group (0.76) than for the placebo group (0.06), but with no statistical significance (p=0.1098).
After 11 weeks of treatment, the mean induced sputum eosinophil counts were similar for both groups (3.40 cells/mm and 3.16 cells/mm, for the zafirlukast 20 mg bd and placebo groups, respectively).
Results of the above per-protocol analyses were broadly supported by the corresponding intention-to-treat analyses.
Safety: Adverse events in each treatment group are summarised in Table II.

Table II Overview of adverse events

Category[a]	Zafirlukast 20 mg bd		Placebo	
	Number of adverse events	Number of patients (%)	Number of adverse events	Number of patients (%)
Patients at risk	-	30 (100)	-	15 (100)
All adverse events	69	23 (76.7)	33	14 (93.3)
Adverse events associated with death	0	0 (0)	0	0 (0)
Adverse events reported as serious[b]	0	0 (0)	0	0 (0)
Adverse events leading to withdrawal	7	7 (23.3)	2	2 (13.3)
Other adverse events leading to withdrawal:				
not asthma exacerbation	5	5 (16.7)	1	1 (6.7)
asthma exacerbation	2	2 (6.7)	1	1 (6.7)
Other adverse events	62	23 (76.7)	31	14 (93.3)

[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 hospitalisation, 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 during this trial. There were 12 withdrawals from the zafirlukast 20 mg bd group: 5 due to adverse events, 2 due to worsening asthma, 2 due to withdrawal of consent, and 3 for other reasons. There were 4 withdrawals from the placebo group: 1 due to an adverse event, 1 due to worsening asthma, and 2 for other reasons.
Both treatments were well tolerated, with no clinically meaningful changes in individual or mean haematology or clinical biochemistry parameters, and no new or unexpected adverse events.