SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: ACCOLATE™

ACTIVE INGREDIENT: Zafirlukast

Trial title (number): A Study to Compare the Effects of ACCOLATE (80 mg bd), Loratadine (10 mg bd), Placebo, and a Combination of the 2 Treatments on the Response to Exercise Challenge in Asthmatic Patients (9188IL/0112)

Clinical phase: IIIB

First patient recruited: 1 October 1997
Last patient completed: 31 December 1998
Zeneca approval date: 17 May 2000

Publications: None at the time of writing this report.

OBJECTIVES

The objectives of this trial were:

- to compare the effects of zafirlukast (80 mg bd), loratadine (10 mg bd), placebo, and a combination of the 2 treatments on the airway response to exercise challenge and to determine whether a combination of the 2 active drugs produced any increase in efficacy on the airway response to exercise challenge than was observed with either drug alone
- to assess the safety of zafirlukast, loratadine, and the combination in comparison to placebo

METHODS

Design: This was a randomised, double-blind, double-dummy, placebo-controlled, 4-period cross-over, single-centre trial conducted in patients with diagnosed asthma. The trial involved 4 treatments: zafirlukast 80 mg bd; loratadine 10 mg bd; zafirlukast 80 mg bd plus loratadine 10 mg bd; and placebo. For each patient the total duration of the trial was 12 weeks, comprising a 2-week screening period followed by four 7-day, double-blind, double-dummy, randomised treatment periods, each period being separated by a 2-week washout period. All patients were to receive each of the 4 treatments. Prospective patients were observed during the 2-week screening period to assess their suitability for the trial; those who failed the entry criteria were not permitted to re-enter the trial. Patients were assessed at entry to the trial (Visit 1), at the beginning of the randomised period (Visit 2), and after each of the 4 randomised treatment periods: Visits 3, 4, 5, and 6, respectively.

Population: A total of 16 patients were required to complete the trial. This was based on the number of patients required to detect the effects of the active treatments on exercise-induced bronchoconstriction and not on the number required to detect an interaction between zafirlukast and loratadine.

Key inclusion criteria: Male or female, aged between 18 and 45 years inclusive; a diagnosed history of asthma; no change in therapy in the previous 4 weeks; non-smokers, or ex-smokers who had stopped smoking at least 6 months before screening; a maximal exercise test recorded anytime prior to screening and a sub-maximal test recorded 18 months prior to screening (ie, a fall in forced expiratory volume in 1 second [FEV_1] of ≥15%); able to demonstrate a positive response to sub-maximal exercise challenge (ie, a fall in FEV_1 of ≥15%); written informed consent.

Key exclusion criteria: Overnight hospitalisation for asthma in the 3 months before screening; evidence of any disease that affected gastrointestinal absorption; respiratory disease other than reversible airways obstruction; upper or lower respiratory tract infection in the 6 weeks before screening or during the screening period; currently experiencing seasonal asthma or expected to experience seasonal asthma during the trial; use of oral steroids or regular oral steroids in the 3 months before entry; use of cromones, theophylline, combination products, astemizole, long-acting or oral β_2-agonists, or anticholinergic bronchodilators in the 2 weeks before entry; use of other anti-histamines 1 week before screening; use of non-steroidal anti-inflammatory drugs (NSAIDs) within 24 hours before the exercise challenge; vaccination with live attenuated influenza virus within 6 weeks before screening; clinically important electrocardiogram (ECG) abnormalities; changes in asthma therapy during the screening period.

Dosage: Four oral treatments were administered during the course of the trial: zafirlukast 80 mg bd; loratadine 10 mg bd; zafirlukast 80 mg bd plus loratadine 10 mg bd; and placebo. Each zafirlukast 80 mg bd dose was composed of 2 zafirlukast 40 mg tablets. Each loratadine 10 mg bd dose was composed of 1 loratadine 10 mg tablet. Formulation and batch numbers were: zafirlukast 40 mg tablets, F11401 (batch number 37509K96); placebo to zafirlukast tablets, F7173 (batch number 36271G96); loratadine 10 mg tablets, F12339 (batch number 38593G97); placebo to loratadine, F12340 (batch number 38594D97).

Key assessments:

Efficacy: The primary endpoint for the analysis of efficacy was the area under the percentage change from baseline in FEV_1 time curve recorded 0 to 60 minutes after the exercise challenge

(FEV_1AUC_{0-60}). Secondary endpoints for the analysis of efficacy were: maximum percentage fall in FEV_1, AUC 0 to 30 minutes after the exercise challenge (FEV_1AUC_{0-30}), AUC 30 to 60 minutes after the exercise challenge (FEV_1AUC_{30-60}), and time to recovery of FEV_1. FEV_1AUC_{0-60}, maximum percentage change in FEV_1, FEV_1AUC_{0-30}, and FEV_1AUC_{30-60} endpoints were analysed using an analysis of variance (ANOVA) model to compare the treatment groups in a "per-protocol" population. Results of the analysis were presented in terms of least squares means (lsmeans) for each treatment period, the differences between the lsmeans (estimate of treatment effect) with associated 95% confidence limits and p-values, and the percentage protection of active treatment over placebo. For time to recovery, the proportions of patients recovering after 30 and 60 minutes were analysed as binary response variables using a generalised linear mixed model with a pseudo-likelihood approach. For the comparisons specified, the odds ratio, the 95% confidence limits, and the associated p-values were presented.
Safety: Safety was assessed by the recording of adverse events, physical examinations, ECGs, and routine clinical laboratory tests.

RESULTS

Demography: Twenty-five patients entered the initial screening period of the trial. Nineteen Caucasian patients with asthma (5 male, 14 female) entered the randomised treatment period of the trial. Their mean age was 27.2 years (range 21 to 36 years). Mean baseline FEV_1 was 89% of predicted normal. Baseline demographic characteristics were comparable across the treatment periods.

Three patients withdrew from the trial due to adverse events (1 whilst receiving zafirlukast 80 mg bd and 2 whilst receiving placebo).

Efficacy:

Primary endpoint: The results for the analysis of FEV_1AUC_{0-60} are summarised in Table I.

Table I Analysis of change in FEV_1AUC_{0-60} (%.min)

Treatment	n	FEV_1AUC_{0-60} (%.min) lsmean	Estimate of treatment effect	LCL	UCL	p-value	% protection
Zafirlukast 80 mg bd	17	-279.30	400.04	245.55	554.52	<0.0001	55.64
Loratadine 10 mg bd	16	-684.05	-4.71	-160.30	150.89	0.9516	-8.66
Placebo	16	-629.56	NA	NA	NA	NA	NA
Zafirlukast 80 mg bd plus loratadine 10 mg bd	16	-234.23	49.78 [a]	-104.28 [a]	203.84 [a]	0.5177 [a]	62.79

[a] Interaction between zafirlukast and loratadine (analysis of the effect of the combination treatment over and above the sum of the effects of the 2 single treatments).
LCL Lower 95% confidence limit; lsmean Least squares mean; n Number of patients;
NA Not applicable; UCL Upper 95% confidence limit.

Zafirlukast significantly reduced the effect of exercise challenge on FEV_1AUC_{0-60} ($p<0.0001$), whereas loratadine on its own had no statistically significant effect. The combination treatment

produced a greater inhibition of the effects of challenge than either treatment alone, but the increase in effect over the sum of the individual treatments was small and not clinically relevant.
Secondary endpoints: The secondary endpoints of maximum percentage fall in FEV_1, FEV_1AUC_{0-30}, and FEV_1AUC_{30-60} showed a similar pattern in that the zafirlukast group reduced the effect of exercise challenge to a highly significant level whereas the loratadine group did not show a positive treatment effect. The combination treatment produced a greater inhibition of the effects of challenge than either individual treatment alone, but the increase in effect over the sum of the individual treatments was small and not clinically relevant. For the secondary endpoints of time to recovery of FEV_1 to within 5% of baseline, in the first 30 minutes after exercise challenge, zafirlukast exhibited a positive treatment effect to a highly statistically significant level and the zafirlukast plus loratadine interaction produced a greater inhibition of the effects of challenge than the sum of the individual treatments, which approached statistical significance. For the odds of a patient recovering within the first 60 minutes after exercise challenge, zafirlukast again showed a positive treatment effect to a highly statistically significant level but the effect of the zafirlukast plus loratadine interaction did not approach significance.
Safety: Adverse events in each treatment group are summarised in Table II.

Table II Overview of adverse events

Category [a]	Zafirlukast 80 mg bd		Loratadine 10 mg bd		Zafirlukast 80 mg bd plus loratadine 10 mg bd		Placebo	
	AEs	n (%)	AEs	n (%)	AEs	n (%)	AEs	n (%)
Patients at risk	NA	17 (100)	NA	16 (100)	NA	17 (100)	NA	18 (100)
All adverse events	7	4 (24)	2	2 (13)	4	3 (18)	8	4 (22)
Adverse events associated with death	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Adverse events reported as serious [b]								
not leading to withdrawal	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
leading to withdrawal	1	1 (6)	0	0 (0)	0	0 (0)	0	0 (0)
Other adverse events leading to withdrawal								
not asthma exacerbation	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
asthma exacerbation	0	0 (0)	0	0 (0)	0	0 (0)	2	2 (11)
Other adverse events	6	4 (24)	2	2 (13)	4	3 (18)	6	3 (17)

[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; caused or prolonged hospitalisation; caused disability or incapacity; required medical intervention to prevent permanent impairment or damage; was a congenital abnormality.
AEs Adverse events; n Number of patients; NA Not applicable.

All treatments were well tolerated and the combination of zafirlukast and loratadine did not produce any clinically significant safety issues. A total of 21 adverse events were reported by 12 patients. Three patients experienced adverse events leading to withdrawal; 1 of which was considered to be serious (psychosis) in nature and 2 non-serious (exacerbation of asthma). None of these 3 events was considered to be related to trial treatment. No other serious adverse event was reported and there were no deaths during this trial.
There was no clinically meaningful effect on any of the clinical laboratory or ECG parameters during this trial.