AstraZeneca

Abbreviated Clinical Study Report

Drug substance:	Zafirlukast (ZD9188)
Edition No.:	FINAL
Study code:	9188IL/0088
Date:	25 January 2006

A multicenter, randomized, double-blind, dose escalation trial to compare the effect of oral doses of zafirlukast (ACCOLATE®) in subjects with mild to moderate asthma

Abbreviated report for safety results

Study dates: First dose date: 20 June 1995
Last dose date: 20 November 1998

Phase of development: Therapeutic confirmatory (III)

Principal Co-ordinating Investigator: None

Sponsor's Responsible Medical Officer:

This study was performed in compliance with Good Clinical Practice.

A multicenter, randomized, double-blind, dose escalation trial to compare the effect of oral doses of zafirlukast (ACCOLATEP®P) in subjects with mild to moderate asthma

Abbreviated report for safety results

Principal co-ordinating investigator

None

Study center(s)

The study for 9188IL/0088 was conducted in 30 centers in the US.

Publications

There were no publications at the time of this report.

Study dates		**Phase of development**
First open-label dose date	20 June 1995	Therapeutic confirmatory (III)
Last open-label dose date	20 November 1998	

The objectives of the trial were

- To assess the efficacy of zafirlukast by increasing the dose (an increase of 0 mg, 20 mg, or 60 mg BID, given as doses of 20 mg, 40 mg, or 80 mg BID) in mild to moderate asthmatic subjects not responding to 20 mg BID.

- To assess the safety of zafirlukast treatment and residual efficacy and safety following withdrawal of zafirlukast in subjects with mild to moderate asthma.

- ICI 204,219 plasma concentration data will be used to aid in evaluating unusual responses to treatment, to evaluate the possibility for drug-drug interactions, and to explore the plasma concentration-response relationship.

Study design

The design included a placebo run-in period (7 to 14 days), a 4-week single-blind period with zafirlukast 20 mg BID (40 mg per day), and a 4-week double-blind period with zafirlukast 20, 40, or 80 mg BID. (Patients who responded to 20 mg BID continued at that dose; non-responders were randomized to a double-blind treatment of 20, 40, or 80 mg BID.) The zafirlukast treatment period was followed by a placebo wash-out period (4 weeks).

Target patient population and sample size

Approximately 1500 patients (males and females, age 12 years or older) with mild to moderate asthma were expected to enroll and provide 360 non-responders. Patients who used some concomitant medications were excluded.

Investigational product and comparator(s): dosage and mode of administration

No comparator was used in this study. The investigational product, zafirlukast, was supplied as tablets for oral use. The daily doses were 40 mg, 80 mg, or 160 mg given in divided doses BID.

Duration of treatment

The duration of zafirlukast treatment defined in the protocol was 8 weeks (56 days).

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

Pharmacokinetic and efficacy evaluations were performed, but not analyzed or presented in this report. Because no safety signals of concern or unusual responses were identified, a formal exposure-response analysis using population predicted steady-state exposure to zafirlukast was unwarranted, and a decision was taken not to conduct the population pharmacokinetic analysis in this study. This report focuses on comparing the safety results against the known safety profile of zafirlukast, and efficacy results are not included.

Safety

The primary measures for safety were adverse events (AEs); clinical laboratory measurements; and electrocardiogram (ECG), vital sign, and physical examination results. The safety variables were

- Extent of exposure
- Categories of AEs
- Most common AEs
- Clinical laboratory tests
- Vital signs, ECG, physical examinations

Statistical methods

All patients who received study treatment were included in the safety analyses. Results from this study were analyzed using summary statistics only; no inferential statistical testing was performed.

Patient population

Table 1 summarizes demographic characteristics, 1-second forced expiratory volume (FEV_1) percent predicted at baseline, and disposition for the entire study population.

Table 1 Patient characteristics

			Total patients (N=1147)	
Demographic characteristics				
Sex	Male	n (%)	474	(41.3)
	Female	n (%)	673	(58.7)
Age (years)	Mean (SD)		30.3	(13.1)
	Range		11 to 81	
	11 to 15	n (%)	168	(14.6)

	16 to 64	n (%)	968	(84.4)
	≥65	n (%)	11	(1.0)
Race	Caucasian	n (%)	1010	(88.1)
	Black	n (%)	66	(5.8)
	Asian	n (%)	8	(0.7)
	Hispanic	n (%)	50	(4.4)
	Oriental	n (%)	2	(0.2)
	Other	n (%)	11	(1.0)
Severity of asthma				
FEV1 % predicted at baselinea	Mean (SD)		76.5	(13.1)
Disposition				
	Completed	n (%)	910	(79.3)
	Discontinued	n (%)	237	(20.7)
n (%) analyzed for safetyb			1147	(100.0)

[a] For FEV_1, N=1146.
[b] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing.
FEV_1: 1-second forced expiratory volume; SD: Standard deviation.

Safety results

No meaningful deviations from the known safety profile of zafirlukast were found.

Extent of exposure

The maximum duration of zafirlukast treatment defined in the protocol was 8 weeks (56 days). Exposure data indicate the median exposure was 85 days, a mean of 76.7 days (SD 23.1), and a range of 1 to 113 days.

Adverse events

Table 2 presents the number of patients who had an AE in any category after first zafirlukast dose.

Table 2 Number (%) of patients who had an adverse event in any category after first zafirlukast dose (safety analysis set)

Category of adverse event	Patients who had an adverse event in each category[a] (N=1147)	
	n	**(%)**
Any adverse events	699	(60.9)
Serious adverse events (SAEs)[b]	14	(1.2)
Serious adverse events leading to death	1	(0.1)
Serious adverse events not leading to death[b]	13	(1.1)
Discontinuations due to adverse events (DAEs)[c]	101	(8.8)
Other significant adverse events (OAEs)[d]	0	(0.0)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] Three patients whose SAEs began before their first zafirlukast dose are not included in the count for this table.

[c] Three patients whose only DAEs began before their first zafirlukast dose are not included in the count for this table. Included in this table is 1 patient, who had a DAE before the first zafirlukast dose and another DAE in the double blind phase.

[d] Clinically significant results (ie, alanine aminotransferase level ≥5 x ULN or bilirubin level ≥3 mg/dL [≥51 μmol/L]) were counted as OAEs only if they were reported as adverse events by the investigator.

Approximately 60% (699/1147) of patients experienced 1 or more AEs in this study. Of these patients, 14 (1.2%) experienced an SAE, and 1 (0.1%) of these patients died. One hundred and one (8.8%) patients experienced DAEs, and no patients experienced an OAE.

Table 3 presents the most commonly reported adverse events after first zafirlukast dose.

Table 3 Number (%) of patients with the most commonly reported adverse events (≥2.0% of patients) after first zafirlukast dose sorted by decreasing order of frequency

	Patients who had an adverse event (N=1147)	
Adverse event preferred term	**n**	**(%)**
Pharyngitis	239	(20.8)
Headache	102	(8.9)
Aggravation reaction	74	(6.5)
Sinusitis	68	(5.9)
Flu syndrome	45	(3.9)
Accidental injury	36	(3.1)
Gastroenteritis	28	(2.4)
Cough increased	26	(2.3)
Rash	25	(2.2)
Nausea	25	(2.2)
Pain	23	(2.0)

The frequency and nature of fatal AEs, non-fatal SAEs, DAEs, and OAEs did not raise any new safety concerns. The results are summarized below

- There was 1 death. It occurred 16 days after the completion of the study and was due to glioblastoma multiforme.

- Including 3 patients whose SAEs began before the first zafirlukast dose, 1.4% of patients (16/1147) experienced 1 or more non-fatal SAEs. None of these SAEs were assessed by the investigator as related to study drug.

- Including 3 patients whose only DAEs began before the first zafirlukast dose, 9.1% of patients (104/1147) discontinued due to AEs. The investigators assessed 28 DAEs experienced by 20 patients as definitely or probably related to study drug. These related AEs (and the number of patients experiencing each) were SGPT (ALT) increased (6); aggravation reaction (4); headache, nausea, and rash (2 each); and abdomen enlarged, abdominal pain, acne, alopecia, insomnia, migraine, nervousness, paresthesia, SGOT (AST) increased, urticaria, vasodilatation, and weight gain (1 each).

- No patients had AEs that met the criteria for an OAE (ALT level ≥5 x ULN or bilirubin level ≥3 mg/dL or both).

Clinical laboratory results

No meaningful deviations from the known safety profile of zafirlukast were identified from the clinical laboratory results, even though higher-than-recommended doses were included in the study.

Laboratory results were retrospectively examined to identify patients with marked abnormalities indicative of abnormal liver function, specifically ALT levels ≥5 x ULN and/or bilirubin levels ≥3 mg/dL. No patients with abnormal liver function met these criteria.

Vital signs, ECG, physical findings, and other observations related to safety

No meaningful deviations from the known safety profile of zafirlukast were identified from these results, even though higher-than-recommended doses were included in the study.