AstraZeneca

Abbreviated Clinical Study Report	
Drug substance:	Zafirlukast (ZD9188)
Edition No.:	FINAL
Study code:	9188US/0020
Date:	25 October 2005

A double-blind, placebo-controlled trial of zafirlukast (ACCOLATE®) 20 mg bid versus placebo for the treatment of symptoms associated with rhinovirus infection

Abbreviated Report of Safety Data

Study dates: First dose date: 11 May 1999
Last dose date: 27 December 1999

Phase of development: Therapeutic confirmatory (III)

Principal Investigator:

Sponsor's Responsible Medical Officer:

This study was performed in compliance with Good Clinical Practice.

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Principal investigator

Study centers

The study was conducted in the United States (2 centers).

Publications

There were no publications at the time of this report.

Study dates		**Phase of development**
First dose date	11 May 1999	Therapeutic confirmatory (III)
Last dose date	27 December 1999	

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
BID	Twice daily
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CSR	Clinical study report
DAE	Adverse event leading to discontinuation
ECG	Electrocardiogram
FDA	Food and Drug Administration
FEV_1	One-second forced expiratory volume
LTRA	Leukotriene receptor antagonist
N	Number of subjects
OAE	Other significant adverse event
RV16	Rhinovirus 16
SAE	Serious adverse event
SOP	Standard operating procedure
ULN	Upper limit of normal

1. INTRODUCTION

Zafirlukast (AstraZeneca ZD9188, ACCOLATE) is a leukotriene receptor antagonist (LTRA) that was approved as asthma therapy in 1996 (January in Europe and March in the US). This abbreviated clinical study report (CSR) presents safety results from a double-blind study conducted to determine whether zafirlukast could attenuate the symptoms of viral infection. Efficacy results are not reported for 2 reasons. First, the efficacy measured was in patients with a viral infection (an off-label indication); approval for this indication is not being sought. Second, patients with ACCOLATE's primary indication (asthma) were excluded from the study population. The abbreviated format for this report was chosen to focus on comparing the safety results against the known safety profile of zafirlukast in clinical studies and post-marketing use (particularly with respect to known issues such as effects on the liver). This approach is in accordance with AstraZeneca SOPs and Guidelines and Food and Drug Administration (FDA) Guidance (Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications, August 1999).

2. OBJECTIVE

The objective of this study was to assess the efficacy of zafirlukast 20 mg BID at attenuating the symptoms associated with infection with experimental rhinovirus (RV16) in atopic subjects.

This abbreviated report includes only safety results, however, for reasons outlined above.

3. STUDY DESIGN

This was a 2-center, randomized, double-blind, placebo-controlled study. Subjects first completed a screening visit (visit 1), confirmation of negative RV16 antibody titer and nasal lavage and inoculation with RV16 (visit 2, Day 0). On Day 1, subjects underwent nasal lavage and repeat inoculation with RV16 and were randomized to receive either zafirlukast 20 mg BID or matching placebo BID for a maximum of 10 days of drug exposure after inoculation with RV16. Following the 10 day drug exposure period, subjects underwent a washout period of up to 18 days before returning to the study center for Visit 6 (Day 21 to 28).

3.1 Target subject population and sample size

A total of 100 subjects were planned to be enrolled in order to obtain a minimum of 50 evaluable subjects, aged 18 to 50 years, with a positive skin test to at least 2 seasonal allergens.

3.2 Investigational product and comparator: dosage and mode of administration

Zafirlukast, 20 mg BID (40 mg per day), and matching placebo were supplied as tablets for oral use.

3.3 Duration of treatment

The maximum duration of study treatment defined in the protocol was 10 days.

3.4 Criteria for evaluation (main variables)

3.4.1 Efficacy and pharmacokinetics

Efficacy results are not included in this abbreviated report, but during the study the following variables were measured: symptom severity scores, incidence rates of RV16 infection, duration of cold symptoms, cumulative severity scores, one-second forced expiratory volume (FEV_1), and global severity. No pharmacokinetic variables were measured in this study.

3.4.2 Safety

Safety was evaluated using the following criteria (as detailed in the study protocol which is Appendix B):

- **Adverse events**
  Adverse events (AEs) were recorded during the study. AEs leading to death, other serious AEs (SAEs), AEs leading to discontinuation (DAEs), and other significant AEs (OAEs) were identified. All adverse events throughout the study, including those for subjects with no zafirlukast exposure and for events whose onset preceded zafirlukast exposure (prior to Visit 2, Day 1), were recorded and are included in the study G listings (Appendix G, Tables G3.1.1 through G3.3.4). However, to focus on the safety profile of zafirlukast, the study T tables (Section 7, Tables T3.1 through T3.3) and this report include only AEs that began on or after the first day of double-blind exposure (Visit 2, Day 1). For each AE, the relationship to the study treatment was assessed by the investigator, and the investigator's description of the event was mapped to a standardized set of preferred terms using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) dictionary.

- **Clinical laboratory measures**
  Laboratory assessments were performed before and after the study treatment period (ie, at screening and on Day 11). Clinically significant results were identified using thresholds similar to those used in other contemporary zafirlukast studies (see Table T4 in Section 7). Because zafirlukast is known to affect markers of liver function, this report pays special attention was given to subjects with clinically significant elevations in ALT (≥5 x ULN), bilirubin (≥3 mg/dL which is ≥51 µmole/L), or both. These abnormalities were retrospectively categorized as considered OAEs if they were reported as AEs by the investigator.

- **Physical examinations**
  Physical exams were conducted before and after the study treatment period (ie, at screening and on Day 11).

- **Vital signs and subjective symptoms**
  Vital signs were assessed at screening; on Days 0, 1, 2, 4, and 11; and at termination (Day 28 or sooner).

3.5 Statistical methods

The results in this report were analyzed using summary statistics only; no inferential statistical testing was performed. All subjects that received study treatment were included in the safety analysis.

4. SUBJECT POPULATION

Table 1 summarizes the characteristics of the subject population for each treatment group and for the total population.

Table 1 Subject characteristics

			Zafirlukast 20 mg (N=27)		**Placebo (N=28)**		**Total (N=55)**	
Population								
Number of subjects			27		28		55	
Demographic characteristics								
Sex	Male	n (%)	14	(51.9)	13	(46.4)	27	(49.1)
	Female	n (%)	13	(48.1)	15	(53.6)	28	(50.9)
Age (years)	Mean (SD)		29.6	(7.9)	26.4	(7.3)	28.0	(7.7)
	Range		20 to 44		18 to 43		18 to 44	
Race	Caucasian	n (%)	24	(88.9)	26	(92.9)	50	(90.9)
	Black	n (%)	1	(3.7)	0		1	(1.8)
	Asian	n (%)	0		1	(3.6)	1	(1.8)
	Hispanic	n (%)	2	(7.4)	1	(3.6)	3	(5.5)
Severity of asthma								
FEV_1% predicted at baseline	Mean (SD)		95.1	(13.0)	99.2	(12.6)	97.2	(12.8)

Disposition

	Completed	n (%)	27	(100.0)	27	(96.4)	54	(98.2)
	Discontinued	n (%)	0		1	(3.6)	1	(1.8)
n (%) analysed for safety[a]		n (%)	27	(100.0)	28	(100.0)	55	(100.0)

Data from Tables T1.2, T1.3, and T2.1 (Section 7)

Of the 55 subjects included in this study, 27 were treated with zafirlukast and 28 were treated with matching placebo. The treatment groups had similar characteristics and were suitable for providing additional support for the established safety profile of zafirlukast.

The study population included only adult subjects. There was a similar gender distribution in both treatment groups with approximately 50% males in each. Both populations were predominately Caucasians (88.9% and 92.9% for zafirlukast and placebo groups, respectively).

During the study 1 subject (1.8%) discontinued treatment. This subject experienced an AE (sinusitis) while taking study treatment (placebo). All other subjects completed the study.

5. SAFETY RESULTS

The safety evaluation reviewed the results for any meaningful deviations from the known safety profile of zafirlukast. This approach is consistent with AstraZeneca standard operating procedures (SOPs) and with FDA Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications (August 1999). Safety evaluations are presented in the following order:

- Extent of exposure
- Categories of AEs
- Most common AEs
- Deaths, serious adverse events (SAEs) other than death, adverse events leading to discontinuation (DAEs), and other significant adverse events (OAEs)
- Clinical laboratory results
- Vital signs, physical findings, and other observations related to safety

5.1 Extent of exposure

Table 2 presents an overview of the exposure during the double-blind treatment period only. The mean duration of treatment was 11.3 and 13.1 days for zafirlukast and placebo treatment groups, respectively, at a dose of 20 mg twice daily.

Table 2 Exposure to study medication

		Zafirlukast 20 mg bid (N=27)	Placebo (N=28)
Duration of double-blind treatment (days)	Mean (SD)	11.3 (3.0)	13.1 (4.4)
	Range	4.0 to 24.0	10.0 to 25.0
Total exposure to double-blind treatment (mg)	Mean (SD)	453.3 (120.5)	525.7 (174.8)
	Range	160.0 to 960.0	400.0 to 1000.0

Data from Table T2.2 (Section 7).

5.2 Categories of adverse events

Table 3 presents the number of subjects who had an AE in any category.

Table 3 Number (%) of subjects who had an adverse event in any category (safety analysis set)

Category of adverse event	Zafirlukast[a] 20 mg bid (N=27)		Placebo[a] (N=28)	
	n	(%)	n	(%)
Any adverse events	8	(29.6)	13	(46.4)
Serious adverse events (SAEs)	0		0	
SAEs leading to death	0		0	
SAEs not leading to death	0		0	
Discontinuations of study treatment due to adverse events (DAEs)	0		1	(3.6)
Other significant adverse events[b] (OAEs)	0		0	

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories. This report includes only AEs that began on or after the day of first double-blind exposure (Visit 2, Day 1).

[b] Marked laboratory abnormalities (alanine aminotransferase [ALT] levels ≥5 x the upper limit of normal [ULN] and bilirubin levels ≥3 mg/dL [≥51 μmol/L]) were counted as OAEs only if they were reported as adverse events by the investigator.

Data from Tables T3.1 and T3.2 (Section 7).

A larger percentage (46.4 versus 29.6) of subjects in the placebo group experienced an AE. There were no deaths, SAEs, or OAEs in either treatment group. The placebo group had 1 DAE (sinusitis), and the zafirlukast group had none.

5.3 Most common adverse events

The adverse events reported by 2 or more subjects in the zafirlukast group were dry mouth (2/27, 7.4%) and insomnia (2/27, 7.4%). The adverse events reported by 2 or more subjects in the placebo group were insomnia (4/28, 14.3%), nausea (3/28, 10.7%), pain (2/28, 7.1%), and sinusitis (2/28, 7.1%). See Table T3.3 in Section 7 for more information.

5.4 Deaths, serious adverse events, discontinuation due to adverse events, and other significant adverse events

The frequency and nature of these events did not raise any new safety concerns. There were no deaths, no SAEs, and no OAEs in this study. One DAE occurred after 4 days of treatment with placebo. The subject experienced sinusitis and treatment (placebo) was discontinued (see Appendix I for narrative). Overall, these results did not suggest any significant deviations from the known safety profile of zafirlukast.

5.5 Clinical laboratory results

No meaningful deviations from the known safety profile of zafirlukast were identified from the clinical laboratory results.

Laboratory normal ranges are presented in Appendix G Tables G4.1.1, G5.1.1, and G6.1.1. The limits defined for abnormal results and the numbers of subjects with abnormal results are presented in Section 7 Table T4.

Approximately 30% of subjects in the zafirlukast treatment group and 18% of subjects in the placebo group had an abnormally elevated laboratory result at some point during the study, but no overall pattern was apparent for any variable. During the study treatment period, no subjects experienced an AE that resulted from abnormal lab results. The most frequent abnormalities were elevated creatine kinase (4 subjects, 14.8%) in the zafirlukast group and elevated eosinophils (2 subjects, 7.1%) in the placebo group.

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

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

Observations of vital signs are summarized in Table G8, and physical findings are provided in Table G10 (Appendix G).

No meaningful deviations from the known safety profile of zafirlukast were identified from these results.

Date of report

25 October 2005