Drug Product	<< >>	**SYNOPSIS**	
Drug Substance	AZD9056		
Study Code	D8830C00002		
Edition Number	1		
Date	28 March 2008		

Efficacy and safety of AZD9056 200 mg once daily versus placebo in adult patients with active Crohn´s disease – A randomized, pilot, double-blind, four week, parallel-group, multicentre, phase II study

Study centre(s)

A total of 10 centres in 5 countries: Belgium, France, Germany, Austria and Hungary participated in the study.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First subject enrolled	24 January 2006	*Therapeutic exploratory (II)*
Last subject completed	18 April 2007	

Objectives

Primary objective

The primary objective of this study was to study the efficacy of a single daily dose of 200 mg AZD9056 in patients with active Crohn's disease (CD) affecting the ileum and/or colon by assessment of the change in Crohn's Disease Activity Index (CDAI) score from baseline after 28 days of treatment.

Secondary objectives

1. To study efficacy by assessment of

   a) proportion of patients in clinical remission after 28 days, where clinical remission is

defined as CDAI ≤ 150
b) proportion of patients with clinical response after 28 days, where clinical response is defined as reduction in CDAI of at least 70 points from baseline
c) time to remission
d) time in study
e) patient reported outcomes

2. To study safety by assessment of AEs, safety laboratory analyses, ECG, vital signs, fundoscopy and physical examination

3. To study pharmacokinetics of AZD9056 in plasma

Study design

This was a randomized, double blind, placebo-controlled, parallel-group, multicentre study to estimate the efficacy and safety of AZD9056 in adult patients with active Crohn´s disease.

Target subject population and sample size

The study was planned to enroll approximately 40 patients to be able to randomize a total number of 30 patients (≥ 18 years of age) with a moderate to severe (CDAI ≥ 220) Crohn's disease affecting ileum and/or colon. Twenty patients were to be randomized to active treatment and 10 patients to placebo.

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

AZD9056 was administered orally as one tablet of 200 mg once daily. A matching placebo to AZD9056 was administered in the same manner as the active treatment.

AZD9056 batch numbers: 05-003020AZ, 06-008574AZ, 06-006506AZ. Placebo batch numbers: 05-003021AZ, 06-008576AZ, 06-006507AZ.

Duration of treatment

28 days.

Criteria for evaluation (main variables)

Efficacy

Primary variable: The change in CDAI from baseline after 28 days of treatment.

Secondary variables:

- Clinical remission defined as CDAI ≤ 150 and measured after 28 days of treatment.

- Clinical response is defined as a reduction in CDAI of at least 70 points from baseline and measured after 28 days of treatment.
- Time to remission
- Time in study
- Short-Form-36 (SF-36) and Inflammatory Bowel Disease Questionnaire (IBDQ)

Pharmacokinetics

Secondary outcome variable: Plasma concentrations of AZD9056.

Safety

Secondary outcome variables: AEs, safety laboratory analyses, ECG, vital signs, fundoscopy, and physical examination.

Statistical methods

Data for patients who received at least one dose of study treatment were included in the Safety analysis set for reporting of safety data. Analysis and reporting of efficacy data used the full analysis set, comprising all patients in the Safety analysis set who had at least one piece of evaluable data. No per protocol analysis was specified for this study.

All hypothesis testing was done using two-sided alternative hypotheses. P-values less than 5% were considered statistically significant.

The changes in CDAI within the active group were analysed by paired t-tests. For a formal comparison with placebo an analysis of covariance was made. Remission and reduction of CDAI by at least 70 points was analysed by chi-square tests. Time to remission and time in study was analysed by Kaplan-Meier curves. Other continuous variables were analysed by paired t-tests.

Subject population

In total, 44 patients were enrolled and 34 patients were randomised. Overall the treatment groups were comparable for demographic characteristics. However, although both treatment groups consisted of patients with moderate to severe Crohn´s disease (CDAI≥220), the mean baseline CDAI of the placebo group was 48 units less than the baseline CDAI of the AZD9056 treatment group. In the AZD9056 treatment group 3 of 24 randomised patients discontinued (due to Adverse events). In the placebo treatment group 1 of 10 randomised patients discontinued (due to incorrect randomisation). The subject population and disposition are shown in Table S 1.

Table S 1 Subject population and disposition

		AZD9056	Placebo	Total
Population				
Randomized		24	10	34
Demographic characteristics				
Sex	Male	11	6	17
	Female	13	4	17
Age (years)	Mean	35.3	37.2	35.9
	Range	20-51	25-53	20-53
Race	Caucasian	24	10	34
Baseline characteristics				
CDAI	Mean	310.5	262.2	296.3
	Range	231-502	202-376	202-502
Disposition				
N of subjects who	completed	21	9	30
	discontinued	3	1	4

Efficacy and pharmacokinetic results

A statistically significant decrease in Crohn`s Disease Activity Index (CDAI) from baseline compared to the pre-specified value of 30 units was observed within the AZD9056 group after 28 days of treatment, see Table S 2. In contrast, the mean decrease in CDAI in the placebo group was not statistically significant. The improvement in CDAI was significantly better (P=0.0497) in patients treated with AZD9056 than in patients treated with placebo. The proportion of patients in remission and with clinical response was greater in the AZD9056 treatment group as compared to placebo. Furthermore, a statistically significant improvement in the IBDQ score was demonstrated in the AZD9056 group but not in the placebo group. The plasma concentration of AZD9056 in CD patients at steady state were similar to those found in healthy individuals given the same dose once daily.

Table S 2 Descriptive statistics for the changes in CDAI (LVCF)

Visit	Treatment	Mean change	Standard error	95% confidence interval
6	AZD9056	-71.57	14.97	(-102.09, -41.04)
	placebo	-23.40	22.70	(-69.69, 22.89)

Safety results

Overall, AZD9056 was well tolerated, and this study did not identify any issues for continued development of this compound. No serious adverse event (SAE) was reported after randomisation and no liver function test changes or unacceptable gastrointestinal side effects were reported. No deaths were reported in the study. The number of patients who had an adverse event in any category, and the number of adverse events by category is presented in Table S 3.

There were two serious adverse events in the study, both occurring before randomization. In total 4 of the randomized patients discontinued the study. Three patients discontinued study treatment due to adverse events (DAEs) in the AZD9056 treatment group. There was a total of 61 AEs during the study and AEs were reported by 83% of the patients in the AZD9056 group and by 60% of the patients in the placebo group.

Abdominal pain was the most commonly reported AE in both treatment groups. However, gastrointestinal disorders including diarrhea were more common following treatment with AZD9056 (13 patients (54%)) as compared to placebo (3 patients (30%)).

There were no clinically significant changes from baseline in the mean or individual values of any vital signs or laboratory parameter during the study, and no notable difference between treatment groups.

Table S 3 Number (%) of patients after randomisation who had an adverse event in any category, and number of adverse events by category

	AZD9056 **n=24**	**placebo** **n=10**	**All** **n=34**
Number (%) of patients who had an adverse event in each category[a]			
Any adverse events	20 (83%)	6 (60%)	**26** (76%)
Serious adverse events (SAEs)			
SAEs leading to death	0	0	**0**
SAEs other than death	0	0	**0**
DAEs[b]	3 (13%)	0	**3** (9%)
Other significant adverse events	0	0	**0**
Total number of adverse events[c]			
Any adverse events	44	17	**61**
Causally related AEs[d]	16	2	**18**

	AZD9056 **n=24**	**placebo** **n=10**	**All** **n=34**
SAEs (fatal and non-fatal)	0	0	**0**
DAEs	5	0	**5**
Other significant adverse events	0	0	**0**

[a]Patients with multiple events in the same category are counted once in each category [b]Discontinuation of inv. prod./study due to AEs. [c]Multiple events with the same preferred term are counted once for each patient and category. [d]As assessed by the investigator.
Data derived from Appendix 12.2.7.