AstraZeneca

Drug product:		**SYNOPSIS**	
Drug substance(s):	AZD9056		
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A Randomised, Double-Blind, Placebo-Controlled, Parallel Group, Ascending Dose Study to Assess the Activity, Safety and Tolerability of 2 Doses of AZD9056 for 4 Weeks in Patients with Active Rheumatoid Arthritis Receiving Methotrexate and/or Sulphasalazine

Study centres

This study was conducted in the UK (10 centres) and Romania (14 centres).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	22 July 2004	Therapeutic exploratory (II)
Last patient completed	26 May 2005	

Objectives

The primary objectives of the study were:

- to investigate the preliminary clinical effects of AZD9056 compared to placebo on signs and symptoms of rheumatoid arthritis (RA), as measured by changes in composite measures of disease activity (ACR scores and DAS 28, and changes in their individual components, including CRP), ESR, patient's assessment of fatigue and duration of morning stiffness
- to investigate the safety and tolerability of 28 days' treatment with AZD9056 in patients with RA.

Secondary objectives of the study were:

- to investigate the pharmacokinetics of AZD9056 in patients with RA
- to provide samples for exploratory analyses to provide additional insight into the role of IL-1β and $P2X_7$ signalling in RA (including samples used to generate data from the *ex vivo* IL-1β assay)
- to provide samples to allow investigation of genetic factors that may influence the Absorption, Distribution, Metabolism and Elimination (ADME), efficacy and tolerability of AZD9056 in patients with RA. Data will form part of a pooled analysis to be reported separately.

Study design

This was a randomised, double-blind, placebo-controlled, parallel group, ascending dose, stratified, multicentre study to assess the activity, safety and tolerability of 2 doses of AZD9056 for 4 weeks in patients with active RA receiving methotrexate and/or sulphasalazine.

Target patient population and sample size

Male and female patients between 18 and 80 years of age with active RA despite current treatment with methotrexate and/or sulphasalazine.

A formal sample size calculation to address all of the endpoints in the primary objective was not perfomed; however, 20 evaluable patients in each treatment group was considered sufficient to investigate the preliminary clinical effects of AZD9056.

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

AZD9056 was administered orally once daily at 2 doses (100 and 400 mg) to 2 separate cohorts of patients. The 400 mg dose was administered following the satisfactory outcome of a formal safety review after approximately 70% of patients in the first cohort had completed treatment. 50 mg tablets batch number: A16882. 200 mg tablets batch numbers: 05-000451AZ, 05-000454AZ.

Matching placebo to AZD9056 was administered orally once daily. Batch numbers: A16888, 05-000449AZ.

Duration of treatment

Twenty-eight days.

Criteria for evaluation (main variables)

Efficacy

The outcome variables were ACR scores and DAS 28 (and their components: CRP; swollen joint count, tender joint count, patient's assessment of pain, patient's global assessment of disease activity, physician's assessment of disease activity and patient's assessment of physical function, as measured by HAQ), ESR, patient's assessment of fatigue and duration of morning stiffness (all markers of treatment efficacy in RA) during and following 28 days' treatment.

Patient reported outcomes (PROs)

Patient reported outcomes were the patient's assessment of pain, fatigue and global disease activity (all measured using separate visual analogue scales), the patient's assessment of physical function as measured by the HAQ, and the duration of morning stiffness.

Pharmacokinetic

Pharmacokinetic parameters of AZD9056 were investigated:CL/F, CL_d/F, V_1/F, V_2/F, $t_{½}$.

Safety

Primary outcome variables: adverse events, safety laboratory analyses, (clinical chemistry, haematology and urinalysis), 12-lead ECG, vital signs (blood pressure and pulse), Amsler test and physical examination.

Genetic

The genetic component of this study provided samples for retrospective analysis. The results do not form part of the main study database and are not included in this clinical study report.

Exploratory

Exploratory variables: gene expression profiling, cytokine screening, matrix metalloproteinase (MMP), proteomics, *ex-vivo* ATP-stimulated IL-1β release, and plasma archive for possible future exploratory analyses of inflammatory or other markers which may be important to RA or its treatment. These results do not form part of the main study database and are not included in this clinical study report.

Statistical methods

Data for randomised patients who received at least one dose of study medication were included in the Safety analysis set for reporting of safety data. Analysis and reporting of efficacy data used the Per Protocol analysis set, comprising all patients in the Safety analysis set who had at least one piece of evaluable data, but excluding patients with major detected protocol deviations. Data were analysed according to the treatment the patient received. A Full analysis set was also defined, comprising all patients in the Safety analysis set who had at least one piece of evaluable data.

The median percentage change in CRP and ESR from baseline to the end of the 4-week treatment period were compared between treatment groups using non parametric methods as the data were right-skewed. Confidence intervals were based on Wilcoxon Rank Sum test and p-values were calculated using Mack-Skillings test. Safety data were analysed by means of descriptive statistics.

There was an interim blinded safety review after approximately 70% of patients in Cohort 1 had completed the study; this confirmed that it was safe to proceed to the 400 mg dose.

An independent interim efficacy analysis of ACR scores and DAS 28 (and their components), ESR, patient's assessment of fatigue and duration of morning stiffness was performed once all patients from Cohort 1 had completed treatment. The purpose of this was to determine whether the primary objective of the study, as defined by pre-specified stopping rules, had been achieved, enabling the study to stop early. The analysis showed that AZD9056 did not meet the pre-specified efficacy criteria at 100 mg and the study continued as planned at the 400 mg dose. AstraZeneca remained blinded to the actual results.

Patient population

It was planned to recruit 72 patients into the study. A total of 210 patients were enrolled into the study with 75 patients randomised to treatment. All 75 patients received at least one dose of AZD9056/placebo. Nine patients discontinued from the study after the start of treatment; 66 patients completed the study. The reasons for discontinuation and the rate of discontinuations were similar between treatment groups: 5 were due to an AE, 3 were due to the eligibility criteria not having been fulfilled, and one was because the patient was not willing to continue in the study. Sixty-two patients were included in the Per Protocol analysis set.

Of the 75 patients who received treatment 14 were males and 61 were females. All patients were Caucasian. Overall, the treatment groups were considered comparable with respect to disease and demographic characteristics.

Table S1 summarises the patient demographics and Table S2 summarises the patient population and disposition.

Table S1 Patient demographics and baseline characteristics

Demographic or baseline characteristic	Statistic or Category	Placebo (n=26)	AZD9056 100 mg (n=24)	AZD9056 400 mg (n=25)	Total (n=75)
Sex	Male	6 (23%)	4 (17%)	4 (16%)	14 (19%)
	Female	20 (77%)	20 (83%)	21 (84%)	61 (81%)
Race	Caucasian	26 (100%)	24 (100%)	25 (100%)	75 (100%)
Age (years)	Mean (SD)	61 (9.1)	56 (7.3)	56 (10.6)	58 (9.4)
	Median	64	57	55	58
	Range	46-73	44-73	20-73	20-73
Baseline Characteristics					
Current Functional Capacity Class	Class I	2 (8%)	1 (4%)	5 (20%)	
	Class II	21 (81%)	17 (71%)	17 (68%)	
	Class III	3 (12%)	6 (25%)	3 (12%)	
CRP[a]	Median (range)	14 (4-82)	21 (4-52)	13 (4-115)	
Swollen joint count[a]	Mean (SD)	13.6 (5.0)	12.3 (4.9)	12.0 (4.6)	
Tender joint count[a]	Mean (SD)	20.9 (5.1)	18.1 (6.4)	21.3 (5.7)	
Background therapy	Not known[b]	1 (4%)	0 (0%)	0 (0%)	1 (1%)
	Methotrexate	19 (73%)	15 (63%)	21 (84%)	55 (73%)
	Sulphasalazine	4 (15%)	5 (21%)	3 (12%)	12 (16%)
	Methotrexate and Sulphasalazine	2 (8%)	4 (17%)	1 (4%)	7 (9%)
Patient currently taking steroids	No	20 (77%)	17 (71%)	12 (48%)	49 (65%)
	Yes	6 (23%)	7 (29%)	13 (52%)	26 (35%)

All data are based upon the safety population unless otherwise stated.

a Baseline values based on the Per Protocol analysis set.

b This patient (Patient 51) received a single dose of study drug and was then withdrawn from the study; some of the baseline information for this patient, including background therapy, was not recorded.

Table S2 Patient disposition (completion or discontinuation)

	Placebo	AZD9056 100 mg	AZD9056 400 mg	Total
Enrolled				210
Randomised	26 (100 %)	24 (100 %)	25 (100 %)	75 (100 %)
Treated (AZD9056 or placebo)	26 (100 %)	24 (100 %)	25 (100 %)	75 (100 %)
Completed	22 (85 %)	21 (88 %)	23 (92 %)	66 (88 %)
Safety analysis set	26	24	25	75
Full analysis set	23	23	24	70
Per Protocol analysis set	22	20	20	62

Efficacy and pharmacokinetic results

Efficacy

The CRP data after 4 weeks' treatment, and the corresponding statistical analyses, are summarised in Table S3.

Table S3 Summary and statistical analysis of CRP (mg/L) after 4 weeks of treatment (per protocol analysis set)

Statistic or Comparison	Placebo (n=22)	AZD9056 100 mg (n=20)	AZD9056 400 mg (n=20)
Median CRP at baseline [a] (range)	14 (4-82)	21 (4-52)	13 (4-115)
Median CRP at 4 weeks (range)	10 (4-55)	14 (4-48)	11 (3-104)
Median change from baseline after 4 weeks (range)	-3 (-63-11)	-2 (-20-28)	-1 (-52-53)
Median % change from baseline at 4 weeks (range)	-21 (-86-131)	-6 (-70-147)	-3 (-76-400)
Analysis of placebo versus AZD9056			
N of patients analysed	22	20	20
Median difference	NA	19.2	19.1
95% confidence interval	NA	(-5,52)	(-4,57)
p-value	NA	[b]	0.533

[a] Baseline was the Visit 2 reading.
[b] Not tested because no statistically significant difference obtained between 400 mg dose and placebo.

The median baseline CRP results were similar for the placebo and 400 mg AZD9056 treatment groups, and slightly higher in the 100 mg AZD9056 treatment group. The median percentage change in CRP after 4 weeks' treatment was –21% in the placebo group, -6% in the 100 mg AZD9056 group, and –3% in the 400 mg AZD9056 group. There was no statistically significant difference in the median percentage change in CRP from baseline to 4 weeks between 400 mg AZD9056 and placebo (p=0.533).

The ESR data after 4 weeks' treatment, and the corresponding statistical analyses, are summarised in Table S4.

Table S4 Summary and statistical analysis of ESR (mm/h) after 4 weeks of treatment (per protocol analysis set)

Statistic or Comparison	Placebo (n=22)	AZD9056 100 mg (n=20)	AZD9056 400 mg (n=20)
Median ESR at baseline [a] (range)	35 (22-84)	32 (8-80)	41 (25-80)
Median ESR at 4 weeks (range)	32 (10-80)	31 (8-93)	40 (16-90)
Median change from baseline after 4 weeks (range)	-3 (-33-22)	-6 (-31-40)	-4 (-38-18)
Median % change from baseline at 4 weeks (range)	-7 (-65-79)	-15 (-71-133)	-9 (-69-56)
Analysis of placebo versus AZD9056			
N of patients analysed	22	20	20
Median difference	NA	-3.8	-3.0
95% confidence interval	NA	(-27,22)	(-22,22)
p-value	NA	[b]	0.166

[a] Baseline was the Visit 2 reading.
[b] Not tested because no statistically significant difference obtained between 400 mg dose and placebo.

The median baseline ESR results were similar for all treatment groups. The median percentage change in ESR after 4 weeks' treatment was –7% in the placebo group, -15% in the 100 mg AZD9056 group, and –9% in the 400 mg AZD9056 group. There was no statistically significant difference in the median percentage change in ESR from baseline to 4 weeks between 400 mg AZD9056 and placebo (p=0.166).

The ACR data after 4 weeks' treatment are summarised in Table S5.

Table S5 Summary of proportion of patients achieving ACR at Week 4 (per protocol analysis set)

Proportion of patients achieving	Statistic	Placebo (n=22)	AZD9056 100 mg (n=20)	AZD9056 400 mg (n=20)
ACR20	N (%)	6 (27%)	8 (40%)	13 (65%)
ACR50	N (%)	0 (0%)	3 (15%)	0 (0%)
ACRN	Mean (SD)	12 (15.0)	19 (22.9)	23 (12.9)

The results showed an overall improvement in ACR in patients treated with AZD9056, with the greatest response in ACR20 at the 400 mg dose. No patient achieved ACR70 during the study.

The DAS 28 data after 4 weeks' treatment are summarised in Table S6.

Table S6 Summary of DAS 28 by EULAR response after 4 weeks of treatment (per protocol analysis set)

Baseline disease activity	Statistic	Placebo	AZD9056 100 mg	AZD9056 400 mg
3.2 - 5.1 (medium disease activity)	N	1	2	1
	No Response	1 (100%)	2 (100%)	0 (0%)
	Moderate Response	0 (0%)	0 (0%)	1 (100%)
>5.1 (high disease activity)	N	21	18	19
	No Response	17 (81%)	14 (78%)	11 (58%)
	Moderate Response	4 (19%)	4 (22%)	8 (42%)

The majority of patients (58 patients; 94%) had high disease activity at baseline. Of these, there were more patients in the 400 mg AZD9056 treatment group than in the 100 mg AZD9056 and placebo groups with a moderate response (improvement in DAS 28 score of >1.2).

The data for other efficacy variables after 4 weeks' treatment are summarised in Table S7.

Table S7 Summary of other efficacy variables after 4 weeks of treatment (per protocol analysis set)

Variable	Placebo (n = 22)		AZD9056 100 mg (n = 20)		AZD9056 400 mg (n = 20)	
	Mean baseline score (SD)	% Δ from baseline (SD)	Mean baseline score (SD)	% Δ from baseline (SD)	Mean baseline score (SD)	% Δ from baseline (SD)
HAQ	1.79 (0.70)	-6 (12.4)	1.90 (0.63)	-16 (26.6)	1.74 (0.52)	-21 (21.0)
Patient's GDA (mm)	67 (17.7)	-24 (19.0)	65 (20.2)	-26 (28.8)	61 (13.5)	-22 (17.1)
Pain (mm)	64 (17.9)	-27 (26.0)	67 (20.8)	-32 (41.0)	62 (13.2)	-29 (16.3)
Swollen joint count	13.6 (5.0)	-37 (35.0)	12.3 (4.9)	-42 (48.4)	12.0 (4.6)	-65 (28.4)
Tender joint count	20.9 (5.1)	-17 (27.2)	18.1 (6.4)	-27 (39.9)	21.3 (5.7)	-45 (25.6)
Physician's GDA (mm)	58 (19.0)	-21 (20.9)	56 (15.7)	-23 (28.2)	57 (15.1)	-32 (20.3)
DAS 28	6.5 (0.7)	-13.6 (10.7)	6.2 (0.8)	-16.3 (16.3)	6.3 (0.7)	-21.9 (10.7)
Fatigue (mm)	69 (14.8)	-19 (26.4)	67 (20.3)	-27 (35.4)	63 (20.9)	-15 (23.6)

Δ change; DAS 28 disease activity score (based on 28 joint count);
GDA global assessment of disease activity; HAQ health assessment questionnaire

The mean baseline scores for each of the variables presented in Table S7 were similar for all treatment groups. There was an improvement in all groups, but no difference between treatments in the mean percentage change from baseline for patient assessment of disease activity and patient assessment of pain. There was also an improvement in all groups in the patient assessment of physical function (HAQ), swollen and tender joint counts, physician's assessment of disease activity and DAS 28, with a greater improvement observed in the 400 mg AZD9056 group. For the patient assessment of fatigue, there was an improvement in

all groups, with the greatest improvement in the 100 mg AZD9056 group, but no improvement in the 400 mg AZD9056 group over placebo.

Patients' assessment of morning stiffness was very variable both within and between treatment groups (data not shown).

Pharmacokinetics

A 2- compartment linear model was found to best fit the plasma concentration time data. The mean population parameters associated with this model are given in Table S8.

Steady state appeared to be reached following 3 days dosing with minimal accumulation (1.3-fold) and the effective $t_{½}$ was estimated at approximately 15 hours.

The apparent volume of distribution at steady state was 458 L.

CL/F was estimated at 25.1 L/hour with inter-patient variability at approximately 28%. This variability was examined with respect to common demographic variables, but no significant influential covariates could be found.

Table S8 Mean population PK parameter estimates and associated inter-patient variability

Parameter	Population estimate	RSE%	Interindividual variability
CL/F (L/hr)	25.1	10.5%	28%
V_1/F (L)	259	17.1%	NC
V_2/F (L)	199	14.1%	NC
CL_d/F (L/hr)	7.68	24.0%	NC
Proportional Residual Error	38.5%		

NC Not calculable
RSE Relative standard error
The PK data did not support the estimation of inter-patient variability on V_1/F and V_2/F.

Efficacy/pharmacokinetic relationship

Exposure and effect variables (ACR20, DAS 28, CRP and ESR) were explored graphically and formally modelled. Concentration in this range did not appear to be a driver of effect on any of the variables; however, cumulative AUC was found to be a statistically significant predictor of ACR score at the 95% significance level, and the modelled relationship suggested that a typical patient receiving 400 mg daily had a 59% chance (95% CI 35% to 80%) of achieving ACR20 by the end of the study.

Safety results

There were no deaths during the study. One patient was hospitalised due to SAEs of nausea and vomiting starting 30 minutes after administration of 400 mg AZD9056 on Study Day 3.

However, no action was taken with the study drug and the patient completed the study without reporting any further AEs after Day 3. Five patients discontinued study treatment due to AEs (2 following placebo, 1 following 100 mg AZD9056, and 2 following 400 mg AZD9056 administration). There were no other significant AEs. There was a total of 58 AEs occurring after the start of treatment during the study (11 following placebo, 14 following 100 mg AZD9056, and 33 following 400 mg AZD9056 administration). Adverse events were reported by 23% of patients in the placebo group, 33% of patients in the 100 mg AZD9056 group, and 48% of patients in the 400 mg AZD9056 group.

An overall summary of the AEs is provided in Table S9, and the most commonly reported AEs are summarised in Table S10.

Table S9 Number (%) of patients who had at least one adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	Placebo (n=26)	AZD9056 100 mg (n=24)	AZD9056 400 mg (n=25)
Number of patients:			
SAE	0 (0%)	0 (0%)	1 (4%)
Deaths	0 (0%)	0 (0%)	0 (0%)
Discontinued study drug due to AE	2 (8%)	1 (4%)	2 (8%)
Other significant AE	0 (0%)	0 (0%)	0 (0%)
Any AE	6 (23%)	8 (33%)	12 (48%)
Total number of AEs	11	14	33

Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

Table S10 Number (%) of patients with the most commonly reported adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Preferred Term	Placebo (n=26)	AZD9056 100 mg (n=24)	AZD9056 400 mg (n=25)
Dizziness	2 (8%)	2 (8%)	5 (20%)
Nausea	0 (0%)	0 (0%)	7 (28%)
Headache	2 (8%)	3 (13%)	2 (8%)
Vomiting	0 (0%)	1 (4%)	2 (8%)
Anxiety	0 (0%)	0 (0%)	2 (8%)
Diarrhoea	0 (0%)	0 (0%)	2 (8%)
Hypertension	0 (0%)	2 (8%)	0 (0%)

Events with a frequency of ≥5% one or more treatment groups are included in this table.

Within any one treatment group, adverse events were most commonly reported in the GI disorders system organ class (SOC). Nausea was the most commonly reported AE in any treatment group during the study. Nausea, vomiting and diarrhoea were reported more frequently following dosing with 400 mg AZD9056 than with 100 mg; there were no reports following placebo. One patient in the 400 mg group had study drug permanently stopped because of nausea and upper abdominal pain; both events were moderate in intensity and not considered serious.

Adverse events were also commonly reported in the nervous system disorders SOC, primarily due to dizziness. Dizziness was the second most commonly reported AE in any treatment group during the study.

Eight patients (3 placebo, 2 in the 100 mg AZD9056 group, and 3 in the 400 mg AZD9056 group) had raised ALT values and/or changes from baseline of potential clinical relevance. Of these, 2 patients receiving AZD9056 had study treatment discontinued due to ALT increases; one was >3xULN (134 U/L). None of the 5 patients in the AZD9056 treatment groups with ALT changes had bilirubin values outside of either the normal or extended reference ranges or AST >3xULN. Two patients in the placebo group had ALT values >3xULN (110 U/L and 179 U/L); one of these also had bilirubin values outside of the normal reference range, and the other also had AST >3xULN (117 U/L). These values were recorded after the end of study treatment.

The ECG results indicate a small AZD9056-related, not clinically significant, prolongation of the heart rate-corrected QT interval. There were no other treatment-related ECG findings. However, due to the methodology employed, the ECG results in this study should be interpreted with caution.

There were no clinically significant differences between the treatment groups regarding changes from baseline in vital signs and physical examination parameters.