AstraZeneca

Drug product:		**SYNOPSIS**	
Drug substance(s):	AZD9056		
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A Randomised, Double-blind Placebo-controlled, Parallel Group Study to Assess the Efficacy, Safety and Tolerability of AZD9056 Administered for 28 Days in Patients with Osteoarthritis of the Knee

Study centres

A total of 404 patients were enrolled into the study (102 in Norway, 302 in UK), of which 108 patients were randomised to treatment (Norway, 41 patients; UK, 67 patients).

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	30 March 2005	

Objectives

Primary objective

To evaluate the efficacy of a single daily dose of AZD9056 compared with placebo in patients with knee osteoarthritis (OA) by assessment of the change from baseline to the end of the 28-day treatment period in WOMAC, VA 3.1 pain subscale score.

Secondary objectives

Secondary objectives of the study were:

1. To evaluate the efficacy of a single daily dose of AZD9056 compared with placebo in patients with knee OA over a 28-day treatment period by assessment of: the change from baseline to 28 days in WOMAC composite score, stiffness subscale score, physical function subscale score, pain on walking score, patient and physician global disease assessments, SF-36, the proportion of responders according to the OMERACT-OARSI criteria, the number of withdrawals due to lack of efficacy and the use of rescue medication.

2. To determine the safety and tolerability of 28 days' treatment with AZD9056 in patients with knee OA.

3. To determine the pharmacokinetics of AZD9056 in patients with knee OA.

4. To investigate the potential relationship between clinical responses to AZD9056 and *ex-vivo* ATP-stimulated IL-1β release.

5. To provide samples for investigation of the potential relationship between clinical responses to AZD9056 and relevant biomarkers. Data will be used to aid project progression, and will be reported separately from the main study.

Study design

This was a randomised, double-blind, placebo-controlled, parallel group, multicentre, international study to assess the efficacy, safety and tolerability of AZD9056 in patients with OA of the knee.

Target patient population and sample size

A total of 112 male and female patients between 40 and 80 years of age with OA of the knee.

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

AZD9056 was administered orally as one tablet (200 mg) once daily for the first 7 days followed by 2 tablets (400 mg) once daily for the remaining 21 days, unless the patient experienced any tolerability issues which in the investigator's opinion meant the dose of study medication should not be increased. During the final 21 days, the study medication could be reduced back at any time to one tablet daily if the patient experienced any tolerability problems.

Matching placebo to AZD9056 was administered in the same manner as the active treatment.

AZD9056 200 mg tablets, batch numbers: A16887, A16899, A16898. Placebo to AZD9056, batch numbers: A16888, A26888.

Duration of treatment

Twenty-eight days.

Criteria for evaluation (main variables)

Efficacy

Primary outcome variable: change from baseline to the end of the 28-day treatment period in Western Ontario and MacMaster Universities Osteoarthritis Index, Visual Analog, Version 3.1, (WOMAC, VA 3.1) pain subscale score.

Secondary outcome variables: change from baseline in WOMAC stiffness subscale, physical function subscale, composite score and pain on walking score; patient and physician global disease assessments; 36-item Short Form Health Survey (SF-36); the proportion of responders according to the Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society (OMERACT-OARSI) criteria (Pham *et al* 2003); the number of withdrawals due to lack of efficacy; and the use of rescue medication.

Pharmacokinetic (PK)

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

One- and 2-compartment models were fitted to the data, and non-linear mixed effects modelling (NONMEM) was used as the analysis tool. The inter-subject variability around the PK parameters was examined, and the residual error modelled.

Pharmacodynamic

Any pharmacodynamic (biomarker) effects discovered as a result of the exploratory analyses are reported separately from the main study.

Safety

Secondary 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 future analysis. The results do not form part of the main study database and are not included in this clinical study report.

Exploratory

Exploratory variables: a panel of biomarkers will be explored to investigate retrospective differentiation of OA patients and to investigate the relationship between biomarker concentrations and clinical response to AZD9056; plasma samples have been archived for possible future exploratory analyses of other biomarkers which may be important to OA and/or its treatment; tuberculosis (TB) status and blood samples for TB testing in a subset of

patients. The results of these analyses 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; data were analysed according to the treatment the patient received. Analysis and reporting of efficacy data used the Intention to treat (ITT) analysis set, comprising all patients in the Safety analysis set who had at least one piece of evaluable data; data were analysed according to the treatment to which the patient was randomised. No Per Protocol analysis was specified for this study; however, to explore the robustness of the results of the primary objective, a Per Protocol analysis was conducted. This analysis set consisted of all patients in the ITT analysis set, except for those who had specified major protocol deviations. The results of the Per Protocol analysis are not presented in this CSR.

The primary outcome variable (WOMAC pain subscale score) was compared between both treatment groups (AZD9056 and placebo) using analysis of covariance (ANCOVA) with treatment as a fixed effect and the baseline value as a covariate. The mean changes from baseline to 28 days in the secondary variables derived from the WOMAC questionnaire were also compared between treatment groups using ANCOVA. All other efficacy assessments were summarised using descriptive statistics. Safety data were summarised by means of descriptive statistics.

There were no interim analyses.

Patient population

It was planned to randomise 112 patients into the study in order to ensure that a minimum of 84 patients completed. A total of 404 patients were enrolled into the study with 108 patients randomised to treatment and 87 patients completing the study. Forty one patients were randomised in Norway and 67 in the UK. All 108 patients received at least one 200 mg dose of AZD9056/placebo. One hundred and one patients received at least one 400 mg dose of AZD9056/placebo; of these, only one patient had their dose reduced back down, and this patient was in the placebo group. Twenty-one patients discontinued from the study after the start of treatment. All 108 randomised patients were included in the safety analysis set. There were no exclusions from the ITT analysis set, and hence the Safety and ITT analysis sets were identical. Thirty-six patients (33%) were excluded from the Per Protocol analysis set. Table S1 summarises the patient demographics and Table S2 summarises patient disposition by treatment group.

Of the 108 patients who received treatment, 36 were males and 72 were females. All patients were Caucasian. The mean age was 60 years, (range 44 to 77). Overall, the treatment groups were considered comparable with respect to demographic and baseline characteristics.

Within each treatment group, the most common ACR functional class was Class II. There were more patients with ACR functional Class III in the AZD9056 group; this difference is not considered to have any impact on the efficacy results of the study.

Table S1 Patient demographics and baseline characteristics

Demographic or baseline characteristic	Statistic or Category	Placebo n= 54	AZD9056 n= 54	Total n=108
Sex	Male	20 (37%)	16 (30%)	36 (33%)
	Female	34 (63%)	38 (70%)	72 (67%)
Race	Caucasian	54 (100%)	54 (100%)	108 (100%)
	Black	0	0	0
	Oriental	0	0	0
	Other	0	0	0
Age (years)	Mean	60	60	60
	SD	7.5	7.3	7.4
	Median	60	60	60
	Minimum	46	44	44
	Maximum	75	77	77
Baseline Characteristics				
ACR Functional Class	Class I	14 (26%)	14 (26%)	28 (26%)
	Class II	32 (59%)	27 (50%)	59 (55%)
	Class III	8 (15%)	13 (24%)	21 (19%)

Table S2 Patient disposition (completion or discontinuation)

	Placebo	AZD9056	Total
Enrolled			404
Randomised	54 (100%)	54 (100%)	108 (100%)
Dosed 200 mg	54 (100%)	54 (100%)	108 (100%)
Dosed 400 mg	50 (93%)	51 (94%)	101 (94%)
Dose reduced back to 200 mg	1 (2%)	0 (0%)	1 (1%)
Prematurely discontinued	10 (19%)	11 (20%)	21 (19%)
Completed Study	44 (81%)	43 (80%)	87 (81%)
N Analysed for safety	54 (100%)	54 (100%)	108 (100%)
N Analysed for efficacy (ITT)	54 (100%)	54 (100%)	108 (100%)
N Per Protocol Population	41 (76%)	31 (57%)	72 (67%)

ITT=Intention to treat; N=Number

Of the 21 premature discontinuations, 7 were due to an AE, 6 were due to lack of therapeutic response, 4 were due to the eligibility criteria not having been fulfilled, 2 were because the patients were not willing to continue in the study, one was due to the development of study-

specific discontinuation criteria, and one patient was lost to follow up. The reasons for discontinuation and the rate of discontinuations were similar between treatment groups.

Efficacy and pharmacokinetic results

Efficacy

A summary of the change from baseline in WOMAC subscale scores is provided in Table S3.

Table S3 Summary of the analysis of the WOMAC subscales: change from baseline data comparing AZD9056 and Placebo after 4 weeks

Subscale	AZD9056		Placebo		Difference between AZD9056 and Placebo				
	N	LS Mean	N	LS Mean	N	LS Mean	SEM	95% CI	p-value
Primary variable									
pain	51	-15	50	-20	101	5	4.7	(-4 , 15)	0.249
Secondary variables									
stiffness	50	-18	50	-20	100	1	4.8	(-8 , 11)	0.773
physical	50	-13	50	-16	100	3	4.4	(-6 , 11)	0.562
composite	49	-15	50	-19	99	3	4.5	(-6 , 12)	0.478
walking	51	-22	50	-23	101	2	4.8	(-8 , 11)	0.737

There was no significant difference between AZD9056 and placebo with respect to the change in WOMAC pain subscale score at the end of the 28-day treatment period. Both treatment groups showed an improvement upon dosing compared to baseline, but the improvement was greater in the placebo group. The results of the secondary variables derived from the WOMAC questionnaire reflected those of the primary variable; there was no significant difference between AZD9056 and placebo with respect to the change in the WOMAC composite score or any of subscale scores at the end of the 28-day treatment period. The Per Protocol analysis of the primary variable demonstrated results consistent with the ITT analysis (data not presented).

Pharmacokinetics

AZD9056 plasma concentration data were available from all 54 patients who received AZD9056. Data were only analysed when both plasma concentration values and associated elapsed time post-dose data were available. The maximum observed plasma concentration was 3720 nM, seen at 3.2 hours after the 400 mg dose on Study Day 15.

A 2-compartment model was found to best fit the plasma concentration time data. The mean population parameters associated with this model are given in Table S4. The mean population half-life ($t_{½}$) was 14.8 hours. The inter-patient variability around CL/F was 16.4%. This variability was examined graphically with respect to common demographic variables, but no significant influential covariates could be found.

Table S4 Final model parameters

Parameter (units)	Parameter estimates	RSE (%)	Inter-individual variability (%)	(RSE) (%)
t_{max} (h)	3.66	3.5		
CL/F (L/h)	12.6	3.7	16.4	24.4
CL_d/F (L/h)	29.4	24.3		
V_1/F (L)	17.8	6.8		
V_2/F (L)	252	7.3		

RSE Residual standard error
The PK data did not support the estimation of inter-subject variability on t_{max}, CL_d/F, V_1/F and V_2/F.

The apparent volume of distribution at steady state was 269.8 L.

Ex vivo ATP-stimulated IL-1β release

Pre-treatment blood samples for the assay of *ex-vivo* ATP-stimulated IL-1β release were taken at Visit 2 from UK centres. Data were only available from 25 patients (17 placebo, 8 active). A visual inspection of the *ex vivo* ATP-stimulated IL-1 β release versus ATP concentration curves suggests that the pattern of pre-treatment IL-1β release was similar in both placebo and AZD9056 treated patients. There were insufficient data to draw conclusions regarding the relationship between IL-1β release phenotype and clinical response.

Safety results

There were no deaths during the study. One patient receiving 400 mg AZD9056 experienced a serious adverse event (SAE) and was discontinued from the study. Seven patients in total discontinued study treatment due to AEs (3 placebo, 1 AZD9056 200 mg, and 3 AZD9056 400 mg). There were no other significant AEs. There was a total of 191 AEs occurring after the start of treatment during the study (89 in the placebo group, 31 in the 200 mg AZD9056 group, and 71 in the 400 mg AZD9056 group). A further 38 AEs were reported at baseline (22 in the placebo group, 16 in the AZD9056 group). Adverse events were reported by 69% of patients in the placebo group and 72% of patients in the AZD9056 group after the start of treatment.

An overall summary of the AEs is provided in Table S5, and the most commonly reported AEs are summarised in Table S6.

The SAE was a viral infection in a 56-year-old woman. It started on Day 27 of treatment with AZD9056. The patient complained of severe throat and chest pain on Day 29; she was hospitalised that day and study drug administration was stopped. The event was considered to be severe in intensity and the Investigator considered that there was a reasonable possibility that the event was caused by study drug.

Adverse events were most commonly reported in the GI disorders system organ class (SOC) (20% of patients receiving placebo, 33% of patients receiving AZD9056). Diarrhoea,

vomiting and nausea were reported most frequently following dosing with 400 mg AZD9056, and with a greater incidence in the 200 mg AZD9056 group than placebo.

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

Table S5 Number (%) of patients who had at least 1 adverse event in any category and total numbers of adverse events after the start of treatment (safety analysis set)

Category of adverse event	Placebo (n=54)	AZD9056 200mg (n=54)	AZD9056 400mg (n=51)	AZD9056 Total (n=54)
Number of patients:				
SAE	0 (0%)	0 (0%)	1 (2%)	1 (2%)
Deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinued study drug due to AE	3 (6%)	1 (2%)	3 (6%)	4 (7%)
Other significant AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any AE	37 (69%)	19 (35%)	34 (67%)	39 (72%)
Total number of AEs	89	31	71	102

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.

Table S6 Number (%) of patients with the most commonly reported adverse events occurring after the start of treatment, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Preferred Term	Placebo (n=54)	AZD9056 200mg (n=54)	AZD9056 400mg (n=51)	AZD9056 Total (n=54)
Headache	11 (20%)	9 (17%)	8 (16%)	12 (22%)
Diarrhoea	2 (4%)	4 (7%)	4 (8%)	7 (13%)
Nasopharyngitis	5 (9%)	0 (0%)	5 (10%)	5 (9%)
Vomiting	0 (0%)	1 (2%)	4 (8%)	5 (9%)
Nausea	2 (4%)	1 (2%)	3 (6%)	4 (7%)
Arthralgia	5 (9%)	0 (0%)	3 (6%)	3 (6%)
Fatigue	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Osteoarthritis	4 (7%)	1 (2%)	2 (4%)	3 (6%)
Dizziness	4 (7%)	0 (0%)	1 (2%)	1 (2%)
Upper respiratory tract infection	3 (6%)	1 (2%)	0 (0%)	1 (2%)

This table uses a cut-off of 5%