AstraZeneca

Drug product	AZD9056 tablet 5 to 3000 mg	**SYNOPSIS**	
Drug substance(s)	AZD9056		
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A Double-Blind, Placebo-Controlled, Randomised Study in Healthy Volunteers to Determine the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Doses of AZD9056

Study centre

AstraZeneca Clinical Pharmacology Unit (Nottingham) Queen's Medical Centre, Derby Road, Nottingham NG7 2UH.

Publications

None at the time of this report.

Study dates		**Phase of development**
First subject enrolled	10 June 2002	Clinical pharmacology (I)
Last subject completed	02 October 2002	

Objectives

Primary:

- The primary objective of the study was to determine the safety, tolerability and pharmacokinetics of single ascending doses of AZD9056 in healthy volunteers by the assessment of safety parameters and pharmacokinetic parameters.

Secondary:

- To determine the pharmacodynamic effects of single ascending doses of AZD9056 by assessment of the *ex vivo* adenosine triphosphate (ATP)-stimulated IL-1β release from leucocytes in whole blood (a biomarker of $P2X_7$ signalling).

- To investigate the pharmacokinetic/pharmacodynamic relationship of AZD9056 by relating plasma concentration data to the effects on *ex vivo* ATP-stimulated IL-1β release.

Study design

This study was a double-blind, randomised, single ascending dose study using a parallel group design with a fixed placebo group. The study was performed at the AstraZeneca Clinical Pharmacology Unit (AZCPU) in Nottingham. Subjects were recruited from the AZCPU volunteer panel and from Chiltern International (a contract research organisation [CRO]).

Twenty-eight subjects were allocated into 3 cohorts. Within each cohort, subjects were randomised to receive either AZD9056 or placebo throughout the study. This treatment was received at Visits 2, 3 and 4, such that a total of 9 doses was administered across the 3 cohorts. Subjects returned for the post-study follow-up at Visit 5. In addition, 3 subjects from Cohort A had an additional treatment visit (Visit 6) to supplement the small number of subjects remaining eligible for dosing in Cohort C for the final dose administration; this visit took place following Visit 5, and subjects attended for a second post-study follow-up visit (Visit 7).

In this study, dose escalation was guided by estimates of predicted systemic exposure instead of using fixed, predetermined dose increments. Potential systemic exposure was estimated from drug concentration data obtained throughout the study using Bayes theorem. With the information derived using this methodology, it was possible for the Safety Review Committee to make a more informed decision of subsequent doses to ensure that the anticipated C_{max} would not exceed the toxicity limit for exposure.

Target subject population and sample size

Healthy volunteers (males and post-menopausal/surgically sterile females) aged 20 to 55 years, inclusive. It was planned to randomise 30 subjects into the study. The actual number of subjects randomised was 28, and all subjects were male.

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

AZD9056 was provided as a tablet, or series of tablets, for oral use. The tablets were provided as a single strength tablet or a combination of tablet strengths in order to allow different doses to be given based on predicted systemic exposures. Matching placebos were also provided.

Batch numbers: P6516 (5 mg), P6496 (10 mg), P6497 (100 mg), P6535 (300 mg), P6526 (placebo to 5 mg), P6527 (placebo to 10, 100 and 300 mg).

The doses administered during the study were: 5, 10, 30, 60, 200, 500, 800, 1500 and 3000 mg AZD9056.

Duration of treatment

It was planned that each subject would receive 3 single doses of ascending strengths, or placebo, at 3 separate treatment visits. However, 3 subjects from Cohort A had an additional treatment visit and were administered a 4th dose (3000 mg AZD9056 or placebo); this was done to supplement the small number of subjects remaining eligible for dosing in Cohort C for the final dose administration.

Criteria for evaluation (main variables)

Safety (primary endpoints)

Adverse events, clinical chemistry, haematology, urinalysis, plasma adrenocorticotrophic hormone (ACTH), plasma cortisol, 12-lead electrocardiogram (ECG), blood pressure and pulse, respiratory rate and aural body temperature and telemetry.

Pharmacokinetic

Maximum plasma concentration (C_{max}), time taken to achieve maximum plasma concentration (t_{max}), area under the plasma concentration versus time curve to the last measurable sampling point (AUC_t), area under the plasma concentration versus time curve extrapolated to infinity (AUC), the terminal half-life of the drug in plasma ($t_{½}$), apparent plasma clearance (CL/F), apparent terminal volume of distribution (V_Z/F).

Pharmacodynamic

Ex vivo ATP-stimulated IL-1β release from leucocytes in whole blood primed with lipopolysaccharide.

Statistical methods

All data were summarised using descriptive statistics and, where appropriate, graphical methods. The pharmacokinetic (PK) variables were derived using non-compartmental analysis prior to summarisation. No formal statistical comparisons were made.

Randomisation code break

The randomisation code was broken in advance of clean file, after data collection was complete, for 13 subjects experiencing gastrointestinal (GI) and visual effects. This was done so that these adverse event (AE) data could be presented to the Independent Ethics Committee considering the protocol for the multiple ascending dose (MAD) study. The blind was also

broken for another subject who was withdrawn from the study following dosing at Visit 3 due to elevated liver function test (LFT) results; this subject had received placebo. This decision was made by the Safety Review Committee due to the acute elevation of the LFTs. In each case, the code break was performed by the Director of Drug Safety and the Clinical Study Team Responsible Drug Safety Scientist. The Project Physician was also unblinded, and to minimise the potential bias did not participate in the finalisation of the statistical analysis plan or in the blinded data review; medical opinion was instead provided by the Principal Investigator.

Subject population

A total of 30 subjects was planned to take part in this study. Twenty-eight subjects were randomised (10 each to Cohorts A and B, and 8 to Cohort C). No female subjects were randomised. All randomised subjects received at least one administration of study drug.

Six subjects discontinued from the study (3 following placebo, 2 following 30 mg AZD9056, and one following 500 mg AZD9056). Two discontinuations were due to AEs (chest infection following 30 mg AZD9056 and upper respiratory tract infection following placebo; see safety section).

Four subjects were excluded from the Per Protocol dataset at the 3000 mg dose. Three subjects were excluded because they received loperamide for diarrhoea on the day of dosing and one was excluded because he vomited approximately 30 minutes after dosing.

Subject demographics and disposition are summarised in Table S1 and Table S2, respectively.

Table S1 Subject demographics (Safety dataset)

		Cohort A (n=10)		Cohort B (n=10)		Cohort C (n=8)		Total
		Placebo	Active	Placebo	Active	Placebo	Active	(n=28)
	N	3	7	3	7	1	7	28
Sex	Male	3(100%)	7(100%)	3(100%)	7(100%)	1(100%)	7(100%)	28(100%)
	Female	0	0	0	0	0	0	0
Race	Caucasian	3(100%)	7(100%)	3(100%)	5(71%)	1(100%)	6(86%)	25(89%)
	Black	0	0	0	2(29%)	0	0	2(7%)
	Other	0	0	0	0	0	1(14%)	1(4%)
Age	Mean	27	31	30	36	31	39	34
(years)	SD	4.0	6.5	8.7	8.6		7.1	7.7
	Median	25	33	28	33	31	39	33
	Minimum	25	20	23	27	31	26	20
	Maximum	32	38	40	52	31	50	52

The slight differences in demographic characteristics among the 3 cohorts were not considered to have any impact on the results of the study.

Table S2 Subject disposition

	Cohort A (n=10)		Cohort B (n=10)		Cohort C (n=8)		Total Placebo (n=7)
	Placebo	Active	Placebo	Active	Placebo	Active	
N randomised	3	7	3	7	1	7	7
5 mg/10 mg/30 mg							
Safety dataset	3	7	3	7	1	7	7
Per Protocol dataset	3	7	3	7	1	7	7
60 mg/200 mg/500 mg							
Safety dataset	2	7	3	7	1	5	6
Per Protocol dataset	2	7	3	7	1	5	6
800 mg/1500 mg/3000 mg							
Safety dataset	1	7	2	7	1	4	4
Per Protocol dataset	1	7	2	7	1	2	4
3000 mg							
Safety dataset	1	2	-	-	-	-	1
Per Protocol dataset	1	0					1
Discontinued	2	0	1	0	0	3	3

Pharmacokinetic and pharmacodynamic results

The PK parameters are summarised in Table S3.

Table S3 Summary of pharmacokinetic parameters for AZD9056 (Geometric mean and range; Per Protocol dataset)

Treatment group	AUC (ng.h/mL)	C_{max} (ng/mL)	Half life (h)	t_{max} (h)[a]	CL/F (L/h)
5 mg (n=7)	79 (54-108)	4 (3-5)	17.8 (10.3-26.0)	5 (3-5)	63.4 (46.0-92.0)
10 mg (n=7)	142 (72-248)	8 (5-12)	17.7 (10.8-23.2)	3 (1-6)	70.0 (40.0-139.0
30 mg (n=7)	622 (512-799)	35 (20-51)	20.2 (16.0-26.3)	3 (1-5)	48.2 (38.0-59.0)
60 mg (n=7)	1405 (1090-1635)	79 (60-107)	19.3 (16.3-22.7)	3 (1-5)	42.9 (37.0-55.0)
200 mg (n=7)	5350 (2700-7758)	351 (229-448)	18.7 (16.0-23.2)	3 (2-5)	37.5 (26.0-74.0)
500 mg (n=5)	18189 (14364-21555)	973 (750-1215)	18.9 (17.4-21.2)	4 (3-5)	27.4 (23.0-35.0)
800 mg (n=7)	28909 (24091-32056)	1522 (1224-1751)	17.4 (15.8-19.7)	4 (3-5)	27.6 (25.0-33.0)
1500 mg (n=7)	52968 (28138-75041)	2350 (1957-2937)	16.7 (13.4-19.6)	5 (4-9)	28.4 (20.0-53.0)
3000 mg (n=2)	96580 (95893-97271)	3403 (3084-3754)	20.1 (17.6-23.0)	7 (5-9)	31.0 (31.0-31.0)

a t_{max} values are median (range).
nM values for C_{max} and AUC are presented in the main body of this report.

The geometric mean $t_{½}$ (range: 16.7 to 20.2 hours) was similar across all the doses received. For doses of 5 to 1500 mg, the median t_{max} was in the range of 3 to 5 hours. At the 3000 mg dose, the t_{max} values obtained from the Per Protocol dataset were 5 and 9 hours. There was a general trend indicating a decrease in CL/F and V_z/F for doses between 5 and 500 mg, whereupon a plateau appeared to be reached. These changes were reflected in the non-proportional increase in AUC and C_{max} with dose.

The percentage change from pre-dose in the area under the curve for the ATP-stimulated IL-1β release from LPS-primed leucocytes in whole blood over the whole ATP concentration curve ($AUC_{IL-1β}$) data are summarised in Table S4.

Table S4 Summary of the median (and range) percentage change from pre-dose in the $AUC_{IL-1β}$ (Per Protocol dataset)

Treatment	Active			Placebo		
	N	4 hours	24 hours	N	4 hours	24 hours
Total Placebo				36	6.0 (-34.6 to 52.7)	2.3 (-52.2 to 41.7)
5 mg	7	-9.9 (-21.8 to 81.0)	-8.3 (-19.9 to 2.0)	3	40.9 (10.1 to 52.7)	-9.8 (-34.2 to 11.4)
10 mg	7	15.2 (-44.5 to 37.9)	25.4 (-5.7 to 46.1)	3	31.0 (15.4 to 47.2)	5.9 (-3.3 to 36.2)
30 mg	7	-37.9 (-53.7 to -25.2)	-40.0 (-63.1 to 51.0)	1	-29.6 (-29.6 to -29.6)	-52.2 (-52.2 to -52.2)
60 mg	7	-48.0 (-88.7 to -5.6)	-8.2 (-70.2 to 18.6)	2	-6.5 (-8.3 to -4.6)	11.8 (-1.4 to 25.0)
200 mg	7	-93.9 (-100.0 to -34.8)	-54.2 (-94.4 to -44.6)	3	-11.4 (-34.6 to 33.6)	-28.0 (-35.9 to 30.0)
500 mg	5	-100.0 (-100.0 to -97.4)	-100.0 (-100.0 to -93.6)	1	-16.2 (-16.2 to -16.2)	-2.5 (-2.5 to -2.5)
800 mg	7	-100.0 (-100.0 to -80.7)	-100.0 (-100.0 to -79.7)	1	2.5 (2.5 to 2.5)	26.9 (26.9 to 26.9)
1500 mg	7	-100.0 (-100.0 to -29.6)	-100.0 (-100.0 to -43.4)	2	17.8 (9.6 to 25.9)	4.6 (-32.6 to 41.7)
3000 mg	2	-100.0 (-100.0 to -100.0)	-100.0 (-100.0 to -100.0)	2	-24.4 (-28.8 to -20.0)	32.6 (26.9 to 38.3)

There was an increase in the release of IL-1β from lipopolysaccharide (LPS)-stimulated leucocytes in whole blood with increasing concentrations of ATP. This response showed considerable heterogeneity between subjects although there was less intra-individual variability of baseline measurements. There was a decrease in $AUC_{IL-1β}$ with increasing AZD9056 dose, with a median reduction of 100% at 4 and 24 hours post-dose at doses of 500 mg and above. The effect on $AUC_{IL-1β}$ appeared to be related to plasma concentrations of

AZD9056 in the majority of patients, and reversibility was demonstrated within the dynamic range of the assay. Exploratory analyses suggested a relationship between $AUC_{IL\text{-}1\beta}$ and AZD9056 plasma concentration, which could be described by an inhibitory E_{max} model.

Safety results

Overall, AZD9056 was shown to demonstrate a good safety profile, with no serious effects on major organ function at doses up to 3000 mg. The maximum tolerated dose was 1500 mg, and was defined by the frequency and severity of visual and other central nervous system (CNS) symptoms, and GI symptoms. There was a total of 138 AEs with onset after the start of dosing during the study, experienced by 26 (93%) of the 28 subjects. Of these, 14 (50%) subjects experienced at least one AE that was considered to have a reasonable possibility of a causal relationship with study treatment. There were no deaths or other serious AEs. Two subjects were discontinued due to respiratory tract infection AEs. One subject had received placebo and the other had received 30 mg AZD9056. In each case, the AE was considered not to have a reasonable possibility of a causal relationship with study drug. The majority of AEs were mild or moderate in intensity; 12 AEs (reported by 7 subjects) were considered to be severe. The most commonly reported AEs at the higher doses (greater than or equal to 1500 mg) were visual disturbances, diarrhoea, dysgeusia, dizziness and nausea.

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

Table S5 Number (%) of subjects who had at least one adverse event in any category, and total numbers of adverse events (Safety dataset)

Category of adverse event	Placebo n=18[a]	5 mg n= 7	10 mg n= 7	30 mg n= 7	60 mg n= 7	200 mg n= 7	500 mg n= 5	800 mg n= 7	1500 mg n= 7	3000 mg n= 6
Number of subjects:										
SAE	0	0	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0	0	0
Discontinued study drug due to AE	1 (6%)	0	0	1 (14%)	0	0	0	0	0	0
Any AE	6 (33%)	2 (29%)	6 (86%)	6 (86%)	6 (86%)	3 (43%)	3 (60%)	6 (86%)	6 (86%)	6 (100%)
Total number of AEs	11	3	11	23	7	3	6	17	25	32

a Number of placebo dosing occasions.

There were no clinically significant treatment-related changes or trends in any laboratory parameter measured during the study, and there were no results outside the reference range that were considered to be of clinical relevance or reported as AEs in subjects exposed to AZD9056. Some QTc increases were observed during the study; these were not considered to be clinically significant as they occurred with a similar magnitude and frequency both in subjects administered AZD9056 and in subjects administered placebo. Where these changes were observed in subjects receiving AZD9056, they did not appear to be related to dose or time post-dose. There were no other clinically important changes in vital signs, ECG,

physical findings or other observations related to safety during the study, except for those reported as AEs.

Table S6 Number (%) of subjects with the most commonly reported[a] adverse events, sorted by decreasing order of frequency in highest dose group (Safety dataset)

MedDRA PREFERRED TERM NAME	Placebo n=18[b]	5 mg n= 7	10 mg n= 7	30 mg n= 7	60 mg n= 7	200 mg n= 7	500 mg n= 5	800 mg n= 7	1500 mg n= 7	3000 mg n= 6
VISUAL DISTURBANCE NOS	0	0	0	0	0	0	0	0	2 (29%)	5 (83%)
DYSGEUSIA	0	0	0	1 (14%)	0	0	1 (20%)	3 (43%)	1 (14%)	4 (67%)
DIARRHOEA NOS	0	0	0	0	0	0	1 (20%)	3 (43%)	1 (14%)	4 (67%)
DIZZINESS	1 (6%)	0	1 (14%)	0	0	0	0	2 (29%)	2 (29%)	3 (50%)
NAUSEA	0	0	0	0	0	1 (14%)	0	0	2 (29%)	2 (33%)
HEADACHE NOS	1 (6%)	0	0	3 (43%)	1 (14%)	1 (14%)	0	1 (14%)	2 (29%)	0
ABDOMINAL DISTENSION	0	0	0	0	0	0	0	0	2 (29%)	0
DISTURBANCE IN ATTENTION	0	0	0	0	0	0	0	0	2 (29%)	0
VENIPUNCTURE SITE BRUISE	0	0	0	0	1 (14%)	0	0	2 (29%)	0	0
CANNULA SITE REACTION	0	1 (14%)	0	0	0	0	0	2 (29%)	0	0
ORTHOSTATIC HYPOTENSION	1 (6%)	0	2 (29%)	0	0	0	0	1 (14%)	0	0
PAIN IN LIMB	0	0	0	2 (29%)	0	0	0	0	0	0
GINGIVAL BLEEDING	0	0	2 (29%)	0	0	0	0	0	0	0

Multiple occurrences of an AE at the same dose are counted only once for that subject.

a Adverse events reported by more than one subject at any dose level are listed in this table.

b Number of placebo dosing occasions.