AstraZeneca

Drug product:	AZD9056; 100, 400 and 600 mg	**SYNOPSIS**	
Drug substance(s):	AZD9056		
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A Phase I, Double-Blind, Placebo-Controlled, Randomised, Group Comparative Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of AZD9056 in Healthy Volunteers

Study centre

This was a single centre study carried out at the AstraZeneca Clinical Pharmacology Unit (Alderley Park), Mereside, Alderley Park, Macclesfield, SK10 4TG.

Publications

None at the time of this report.

Study dates		**Phase of development**
First subject enrolled	21 October 2002	Clinical pharmacology (I)
Last subject completed	06 March 2003	

Objectives

Primary objective:

- To investigate the safety, tolerability and pharmacokinetics (PK) of multiple ascending doses of AZD9056.

Secondary objectives:

- To investigate the pharmacodynamics (PD) of multiple ascending doses of AZD9056, specifically the effect of AZD9056 on the biomarker – ATP-stimulated IL-1β release.

- To perform a preliminary investigation into the PK/PD (ATP-stimulated IL-1β release) relationship following multiple ascending doses of AZD9056.

Study design

This was a single centre, double-blind, placebo-controlled, randomised, group comparative study to investigate the safety, tolerability, PK and PD of AZD9056 when given as multiple doses to healthy volunteers.

Three dose levels were investigated: 100, 400 and 600 mg.

Target subject population and sample size

It was originally planned to include 36 healthy male and female volunteers aged between 20 and 65 years inclusive. However, an additional cohort of 12 subjects was dosed at the 400 mg dose level; the final planned number of subjects was therefore 48. The actual number of subjects randomised was 47.

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

AZD9056 was provided as 100 and 300 mg tablets for oral administration at doses of 100, 400 and 600 mg. The 100 mg dose comprised of one tablet (100 mg tablet), the 400 mg dose comprised of 2 tablets (100 and 300 mg tablets) and the 600 mg dose of 2 tablets (2 x 300 mg tablets). A matching placebo was also provided and the corresponding number of tablets given.

Batch numbers:	Placebo	P6527
	100 mg AZD9056	P6497
	300 mg AZD9056	P6535

Duration of treatment

It was planned that each subject would receive either 100, 400 or 600 mg AZD9056 or matching placebo for 10 consecutive days.

Criteria for evaluation (main variables)

All safety and PK variables were used to assess the primary objective. The PD and PK variables were used to assess the secondary objectives.

Pharmacokinetic

Day 1: maximum observed plasma concentration (C_{max}), minimum observed plasma concentration (C_{min}), time taken to achieve observed C_{max} (t_{max}), area under plasma concentration versus time curve to 24 hours ($AUC_{(0-24)}$); Day 10 (ie, steady state [ss]): trough concentration at steady state ($C_{min,ss}$), $C_{max,ss}$, $t_{max,ss}$, $AUC_{(0-24)ss}$, terminal half-life of the drug in plasma ($t_{½}$), apparent plasma clearance at steady state (CL_{ss}/F) and apparent terminal volume of distribution at steady state ($V_{z,ss}/F$); accumulation ratio ($C_{min,ss}/C_{min}$).

Safety

Haematology, clinical chemistry (including ACTH and cortisol), urinalysis, faecal occult bloods, 12-lead ECG, blood pressure, pulse, telemetry and adverse events.

Pharmacodynamic

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

Pharmacogenetics

$P2X_7$ receptor, MDR1, Cytochrome P450, 3A, 2C9, 2C19 and 2D6. The results will be reported in a separate pooled analysis.

Statistical methods

All data were summarised using descriptive statistics and, where appropriate, graphical methods. No formal statistical comparisons were made. The PK variables were derived using non-compartmental analysis prior to summarisation. The safety data was analysed using the Safety dataset and the PK and IL-1β data were analysed using the Per Protocol dataset. The exploratory PK/PD analysis was performed using the Safety dataset.

Subject population

A total of 48 subjects was planned to take part in this study. Forty-seven subjects were randomised (11 in the 100 mg dose group [Cohort A], and 12 each to the two 400 mg dose groups [Cohorts B and C] and the 600 mg dose group [Cohort D]). All randomised subjects received at least one administration of study drug. Three subjects in each cohort were randomised to placebo.

There was a higher number of male subjects in all groups and all subjects were Caucasian.

Thirteen subjects discontinued from the study. Two discontinuations were due to AEs (one in Cohort B and one in Cohort C). The subject in Cohort B subsequently experienced a SAE, and as a result the remainder of Cohort B were also discontinued from the study.

Two subjects (Subjects 13 and 35) were excluded from the Per Protocol dataset. These subjects each discontinued from the study due to AEs after 5 days' administration of 400 mg AZD9056; their PK data were therefore incomplete.

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

Table S1 Subject demographics

		Cohort A (n=11)		Cohort B (n=12)		Cohort C (n=12)		Cohort D (n=12)		Total (n=47)	
		Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active
N randomised		3	8	3	9	3	9	3	9	12	35
Sex [a]	Male	3 (100%)	6 (75%)	3 (100%)	7 (78%)	3 (100%)	9 (100%)	3 (100%)	8 (89%)	12 (100%)	30 (86%)
	Female	0	2 (25%)	0	2 (22%)	0	0	0	1 (11%)	0	5 (14%)
Race [a]	Caucasian	3 (100%)	8 (100%)	3 (100%)	9 (100%)	3 (100%)	9 (100%)	3 (100%)	9 (100%)	12 (100%)	35 (100%)
Age (years)	Mean	45	38	33	40	37	40	42	41	39	40
	SD	12.8	11.2	11.0	12.3	7.2	10.3	16.2	9.4	11.4	10.4
	Median	42	36	28	41	39	39	51	41	41	39
	Min	34	25	26	23	29	26	23	23	23	23
	Max	59	57	46	64	43	63	51	57	59	64

a N and % of subjects

Table S2 Subject disposition

	Cohort A (n=11)		Cohort B (n=12)		Cohort C (n=12)		Cohort D (n=12)		Total placebo
	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	(n=12)
Safety dataset	3	8	3	9	3	9	3	9	12
Per Protocol	3	8	3	8	3	8	3	9	12
Total discontinued	0	0	3	9	0	1	0	0	3
Completed	3	8	0	0	3	8	3	9	9

Pharmacokinetic and pharmacodynamic results

The pharmacokinetic (PK) data indicated that the rate of absorption into the systemic circulation is independent of dose and the number of doses given (range of median value t_{max} on Day 1 and Day 10 was 3 to 4 hours). Steady state plasma concentrations were achieved after 3 to 4 days of single daily doses which is consistent with the measured $t_{½}$ (range of the geometric mean values 16.8 to 17.9 hours), and the range of the geometric mean accumulation ratio across the doses was 1.7 to 2.1 and was predictable from single dose data obtained in the single ascending dose (SAD) study (D1520C05215).

The results of the pharmacokinetic analysis at Day 10 are shown in Table S3.

Table S3 Summary of pharmacokinetic parameters for AZD9056 for Day 10 (Geometric mean and range; Per Protocol dataset)

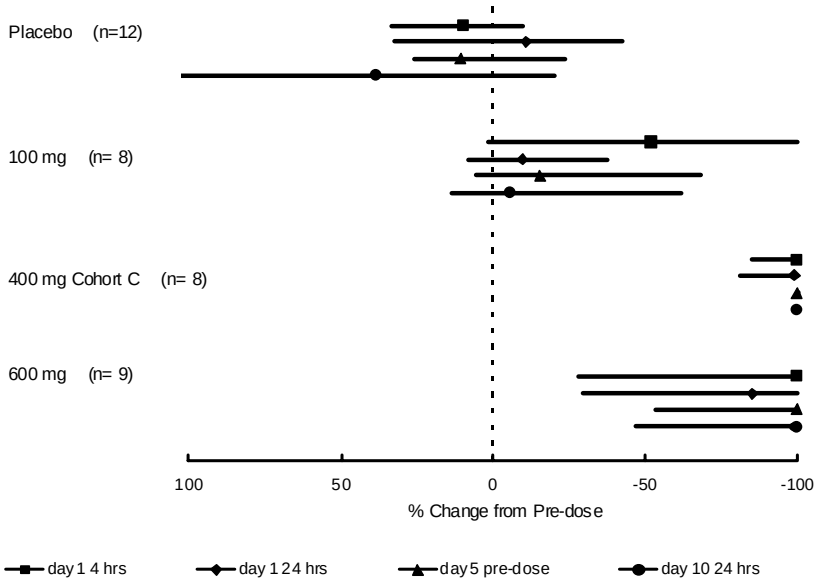
Parameter	100 mg Cohort A (n=8)	400 mg Cohort C (n=8)	600 mg Cohort D (n=9)
$AUC_{(0-24)ss}$ (nM.h)	6144 (3736-9024)	33584 (27840-44916)	39344 (18203-56065)
$C_{max,ss}$ (nM)	495 (378-715)	2640 (1840-3560)	3406 (2500-4210)
$C_{min,ss}$ (nM)	124.0 (57.0-224.0)	899.1 (706.0-1250.0)	907.7 (393.0-1600.0)
R_{ac}	2.1 (1.7-2.7)	2.0 (1.6-2.6)	1.7 (0.9-4.4)
$t_{max,ss}$ (h)[a]	3 (1-5)	4 (3-8)	3 (3-8)
$t_{½}$ (h)	17.76 (14.96-20.19)	16.77 (15.38-18.24)	17.85 (13.63-22.74)

a $t_{max,ss}$ values are median (rather than geometric mean)

There was intersubject heterogeneity in the amount of IL-1β released pre-dose, following the addition of ATP to LPS-primed leucocytes in whole blood. In addition, several different types of release patterns were identified. The majority of the subjects exhibited a typical response where ATP stimulated the release of IL-1β such that the amount released increased to a plateau as the concentration of ATP increased. However, 12 subjects had measurable amounts of IL-1β in the incubation in the absence of ATP. Addition of agonist resulted in a concentration-related increase in IL-1β in 10 of these subjects; for the other 2 subjects, there was no increase in IL-1β with increasing concentrations of ATP up to 5 mM.

At steady state (ie, Day 4 onwards) trough plasma concentrations for the 100 mg AZD9056 dose, the median $AUC_{IL-1β}$ response had not changed substantially compared to baseline values (Figure S1). However at t_{max} (ie, 4 hours) at steady state the median percentage reduction in $AUC_{IL-1β}$ was greater than or equal to 70%. At doses of 400 and 600 mg the median percentage reduction in $AUC_{IL-1β}$ was greater than 90% both at t_{max} and at trough steady state plasma concentrations, although the range of values was large in Cohorts B (400 mg) and D (600 mg). The majority of this variability arises from the individuals that had measurable amounts of IL-1β in the absence of ATP. Although AZD9056 does substantially inhibit the ATP stimulated IL-1β release, it does not reduce IL-1β that is not attributed to addition of ATP, possibly with the exception of one subject. Since calculation of $AUC_{IL-1β}$ does not involve subtraction of the baseline IL-1β levels, for these individuals it is not possible to record 100% inhibition of $AUC_{IL-1β}$ hence the apparent lower response for these individuals. By 96 hours post-dose the median $AUC_{IL-1β}$ was close to baseline for Cohort C (400 mg), indicating reversibility of the inhibition of ATP-stimulated IL-1β release within the dynamic range of the assay. For Cohort D at 96 hours post-Dose 10, the median percentage reduction in $AUC_{IL-1β}$ was substantially less than that observed at steady state trough plasma concentrations.

Figure S1 **Median and range of the percentage change from pre-dose AUC IL-1β at 24 hours post-dose and at steady state (Per Protocol dataset)**



Safety results

Adverse events are summarised in Table S4 (categories of adverse event) and Table S5 (most common adverse events in decreasing order of frequency).

Table S4 **Number (%) of subjects 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=12	100 mg n=8	400 mg n=18	600 mg n=9
Number of subjects:				
SAE	0 (0%)	0 (0%)	1 (6%)	0 (0%)
Deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinued study drug due to AE	0 (0%)	0 (0%)	2 (11%)	0 (0%)
Any AE	10 (83%)	6 (75%)	15 (83%)	7 (78%)
Total number of AEs	53	10	68	21

Table S5 Number (%) of subjects with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

MedDRA PREFERRED TERM NAME	Placebo n=12	100 mg n= 8	400 mg n=18	600 mg n= 9
HEADACHE	4 (33%)	0	6 (33%)	2 (22%)
PHARYNGITIS	2 (17%)	1 (13%)	3 (17%)	1 (11%)
UPPER RESPIRATORY TRACT INFECTION NOS	3 (25%)	0	3 (17%)	1 (11%)
LOOSE STOOLS	3 (25%)	0	3 (17%)	0
CANNULA SITE REACTION	2 (17%)	0	3 (17%)	0
PARAESTHESIA	2 (17%)	0	3 (17%)	0
ABDOMINAL PAIN NOS	3 (25%)	0	0	1 (11%)
RASH PAPULAR	3 (25%)	0	1 (6%)	0
DIARRHOEA NOS	1 (8%)	0	0	2 (22%)
EPISTAXIS	1 (8%)	0	2 (11%)	0
NASAL CONGESTION	1 (8%)	0	2 (11%)	0
RASH FOLLICULAR	1 (8%)	0	2 (11%)	0
CONSTIPATION	0	0	2 (11%)	0
RHINORRHOEA	0	0	2 (11%)	0
FACIAL NEURALGIA NOS	0	2 (25%)	0	0
RIGORS	2 (17%)	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.

There was one SAE during the study (AZD9056 400 mg). Two subjects were discontinued from the study due to AEs (one of whom had the SAE).

A total of 152 AEs occurred after the onset of dosing during the study, reported by 38 (81%) of the 47 subjects. A similar proportion of subjects experienced AEs in each dose group, including placebo. For 34 of the 99 AEs reported following AZD9056 administration (6, 17 and 11 AEs at the 100, 400 and 600 mg doses, respectively), it was considered that there was a reasonable possibility that the event may have been caused by the investigational product. The majority of AEs were mild or moderate in intensity; one AE was considered to be severe. The most commonly reported AEs were headache, pharyngitis, URTI and loose stools; these were reported with a similar or greater frequency in the placebo group as in any of the AZD9056 dose groups.

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, occurring with a similar 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. 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.