Drug Substance(s)	AZD9056	**SYNOPSIS**	(For national authority use only)
Study Code	D1520C05289		
Date	11 October 2005		

A randomised, single-blind, placebo-controlled, single centre Phase I study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of ascending single oral doses of AZD9056 tablets in healthy Japanese male subjects

Study centre(s)

Sekino Clinical Pharmacology Clinic, 3-28-3, Ikebukuro, Toshima-ku, Tokyo 171-0014, Japan.

Study dates		**Phase of development**
First subject enrolled	06 October 2004	Clinical pharmacology (I)
Last subject completed	28 December 2004	

Objectives

The primary objectives of this study were:

1. to investigate the safety and tolerability of AZD9056 by assessment of AEs, 12-lead ECG, BP, pulse rate, body temperature, safety laboratory tests (haematology, clinical chemistry, urinalysis), and physical examination

2. to investigate the PK of AZD9056 by assessment of plasma concentrations of AZD9056, and estimation of the following PK parameters for AZD9056; AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{½\lambda z}$, CL/F, Vz/F

when given as an oral tablet in ascending single doses to healthy Japanese male subjects.

The secondary objectives of this study were:

1. to investigate the PD effects of AZD9056 by assessment of the *ex vivo* ATP-stimulated IL-1β release from leucocytes in whole blood (a biomarker of $P2X_7$ signalling)

2. to perform a preliminary investigation into PK/PD relationship of AZD9056 by assessment of relationship between relating plasma concentration data and effects on *ex vivo* ATP-stimulated IL-1β release from leucocytes in whole blood

3. to provide samples to allow investigation of genetic factors that may influence the ADME, PD effects and tolerability of AZD9056 (genes that may be investigated include MDR-1, CYP3A, $P2X_7$ receptor, and IL-1β)

when given as an oral tablet in ascending single doses to healthy Japanese male subjects.

Study design

This was a randomised, single-blind, placebo-controlled, single centre, Phase I study to determine the safety, tolerability, PK and PD of AZD9056 carried out in healthy Japanese male subjects, using a parallel group design with a fixed placebo group.

In total, six ascending dose levels in the planned range of 30 to 1200 mg were given orally using tablets of appropriate strength.

Twenty subjects were allocated into 2 cohorts (A and B) of 10 subjects. Within each cohort, 8 subjects received 3 active doses of AZD9056, and 2 subjects received 3 corresponding placebo doses, in a series of single ascending doses in separate treatment visits. Subjects in Cohorts A received AZD9056 30 mg, 200 mg and 800 mg or placebo. Subjects in Cohorts B received AZD9056 60 mg, 500 mg and 1200 mg or placebo.

Target subject population and sample size

Japanese healthy male subjects aged 20 to 55 years, inclusive. It was planned to randomise 20 subjects into the study.

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

AZD9056 was provided as 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. Placebos were also provided.

Batch number:P7040 (5 mg), P6657 (50 mg), P6576 (100 mg), P6577 (300 mg), P6526 (placebo to 5 mg) and P6888 (placebo to 50, 100, 300 mg).

The doses administered during the study were: 30, 60, 200, 500, 800, 1200 mg AZD9056.

Duration of treatment

Single dose; with each subject receiving a maximum of 3 single doses of ascending strengths or placebo, at 3 separate treatment visits.

Variables

- **Pharmacokinetic**

  Plasma concentrations of AZD9056, PK parameters (AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{½\lambda z}$, CL/F, Vz/F for AZD9056)

- **Pharmacodynamic**

  ex vivo ATP-stimulated interleukin-1β release from leucocytes in whole blood

- **Pharmacogenetics**

  $P2X_7$ receptor, MDR-1, CYP3A and IL-1β gene

- **Safety**

  AEs, 12-lead ECG, BP, pulse rate, body temperature, safety laboratory tests (haematology, clinical chemistry, urinalysis), ophthalmological test and physical examination

Statistical methods

PK, PD and safety data were summarised using descriptive statistics. Where appropriate these data were additionally presented graphically.

Subject population

In total, 47 subjects were enrolled and 20 of them were randomized into this study (10 each for cohort A and 10 each for cohort B). Subject population and disposition are summarized in Table S 1 and Table S 2, respectively. All subjects were Japanese male. Age of the subjects ranged from 22 to 36 years and body weight was from 57 to 92 kg. All subjects completed the study. Safety population analysed was 16 for AZD9056 (8 each for 6 dose groups) and 4 for placebo (2 each for 6 dose groups). Pharmacokinetics population analysed was 16 for AZD9056 (8 each for 6 dose groups). Pharmacodynamics population analysed was 16 for AZD9056 (8 each for 6 dose groups) and 4 for placebo (2 each for 6 dose groups). Each subjects had 3 dosing occasions; 30 mg, 200 mg and 800 mg in cohort A and 60 mg, 500 mg and 1200 mg in cohort B.

Table S 1 Subject population

Demographic or baseline characteristic		Treatment group			
		Placebo	Active		Total
			Cohort A	Cohort B	
Population					
N randomised		4	8	8	20
Demographic characteristics					
Sex (N)	Male	4	8	8	20
	Female	0	0	0	0
Age (years)	Mean (SD)	29.5 (2.9)	25.3 (3.5)	26.5 (4.5)	26.6 (4.0)
	range	26 to 33	22 to 31	22 to 36	22 to 36
Ethnic group	Japanese	4	8	8	20
Height (cm)	Mean (SD)	177.8 (9.6)	175.9 (5.9)	172.4 (4.1)	174.9 (6.2)
	range	168 to 187	167 to 184	164 to 177	164 to 187
Weight (kg)	Mean (SD)	72.8 (13.7)	62.4 (4.7)	66.3 (7.0)	66.0 (8.4)
	range	62 to 92	57 to 68	57 to 76	57 to 92
BMI (kg/m^2)	Mean (SD)	22.88 (2.30)	20.14 (0.90)	22.26 (1.93)	21.54 (1.98)
	range	21.3 to 26.3	18.9* to 21.7	19.9 to 26.0	18.9 to 26.3
Baseline characteristics					
Alcohol, Current Consumption	No	4	8	6	18
	Yes	0	0	2	2
Nicotine use (Smoking)	Non Smoker	4	8	8	20
Medical History	No	4	8	8	20
Disposition					
N of subjects who	Completed	4	8	8	20
	Discontinued	0	0	0	0

* Before rounded up for CRF, the height is 174.9 cm and the weight is 58.4 kg. Using these values, BMI was 19.09.

Table S 2 Summary of analysis sets

		Cohort A			Cohort B		
	Placebo*	AZD9056			AZD9056		
		30mg	200mg	800mg	60mg	500mg	1200mg
Safety analysis[a]	12	8	8	8	8	8	8
PK analysis	0	8	8	8	8	8	8
PD analysis	12	8	8	8	8	8	8

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing.
* Count represents the number of observations, not the number of subjects.

Summary of pharmacokinetic results

Following single oral administration, plasma concentration of AZD9056 reached maximum (C_{max}) at 2.0 to 5.5 hours (t_{max}) after the administration. The median t_{max} increased at over 500 mg doses suggesting the reduction of the rate of absorption at the higher doses. There was a trend indicating a decrease in CL/F and Vz/F for doses between 30 and 500 mg, thereafter a plateau appeared to be reached. However, this is thought to be an increase of bioavailability of AZD9056 with increase with dose rather than a change in the elimination of AZD9056 from systemic circulation. This view is supported by the dose independent elimination half-life of AZD9056 (approximately 13 to 16 hours) observed at all doses studied. Across the dose range studied the exposure of AZD9056 was non-proportional with dose; dose normalized C_{max} and AUC showed an increase at doses up to 500 mg then seemed to reach a plateau thereafter.

Summary of pharmacodynamic results

AZD9056 showed concentration-related inhibition of ATP-induced IL-1β release. At doses above 500 mg, the median percentage reduction from pre-dose $AUC_{IL-1\beta}$ was about 90% or more at both 4 and 24 hours. At the 200 mg dose, there was a differentiation in the magnitude of the percentage reduction of $AUC_{IL-1\beta}$ at 4 and 24 hours, illustrating reversibility, although the effect had not returned to baseline. The percentage change in $AUC_{IL-1\beta}$ following dosing with placebo ranged from -32.4% to 27.9%.

Summary of pharmacokinetic/pharmacodynamic correlations

Observation of the plot of residuals suggests that goodness of fit of the model to data seems acceptable, since the residuals appears to be distributed evenly about 0. Exploratory analyses suggested a relationship between $AUC_{IL-1\beta}$ and AZD9056 plasma concentration, which could be described by an inhibitory E-max model.

Summary of population pharmacokinetics

Not applicable

Summary of pharmacogenetics

The consent for the genetic test was obtained from all the randomised subjects except 1 subject (E0001013: Subject No. 09) before collection of blood sample. Any blood sample for genetic test was not collected from the subject (E0001013: Subject No.09). The purpose of the genetic component of the study was to generate data for use in future retrospective analyses. Future analyses will explore genetic factors, which may influence the disposition, efficacy, safety and tolerability to AZD9056. The results of the genetic analyses will not form part of the clinical study report for this study. The results may be pooled with genetic data from other studies on AZD9056 to generate hypotheses to be tested in future studies.

Summary of safety results

A summary of adverse events in each category is presented in Table S 3.

Adverse events were reported by 1 ,1, 3, 2, 3 and 2 subjects in AZD9056 60 mg (cohort B), 200 mg (cohort A), 500 mg (cohort B), 800 mg (cohort A), 1200 mg (cohort B) and placebo, respectively. However, no serious adverse events were observed and no subjects were withdrawn due to adverse events.

Table S 3 Number (%) of subjects who had an adverse event in any category (safety analysis set)

		Cohort A			Cohort B		
	Placebo*	AZD9056			AZD9056		
		30mg	200mg	800mg	60mg	500mg	1200mg
	N=12	N=8	N=8	N=8	N=8	N=8	N=8
Number of subjects**:							
Any adverse events	2 (17)	0	1 (13)	2 (25)	1 (13)	3 (38)	3 (38)
Serious adverse events leading to death	0	0	0	0	0	0	0
Serious adverse events not leading to death	0	0	0	0	0	0	0
Discontinuations of study treatment due to adverse events	0	0	0	0	0	0	0
Other significant adverse events	0	0	0	0	0	0	0
Total number of recorded:							
Any adverse events	3	0	1	5	1	3	5
Serious adverse events leading to death	0	0	0	0	0	0	0
Serious adverse events not leading to death	0	0	0	0	0	0	0
Discontinuations of study treatment due to adverse events	0	0	0	0	0	0	0
Other significant adverse events	0	0	0	0	0	0	0

* N represents the number of observations, not the number of subjects.
**Subject with multiple events in the same category is counted only once in that category.
Subject with more than 1 category is counted once in each of those categories.

All adverse events by dose group (system organ and preferred term) are presented in Table S 4.

Most common adverse event was dizziness. Dizziness was reported by 1, 1, 2 and 2 subjects in AZD9056 200 mg (cohort A), 500 mg (cohort B), 800 mg (cohort A), 1200 mg (cohort B), respectively, and by 1 subject in placebo. However, all of the dizziness occurred after change

of position from supine to standing for blood pressure and pulse rate. All reported adverse events were mild in intensity. There were no clinically significant adverse events.

Drug-related adverse events assessed as causally related to the investigational product by the principal investigator were reported by 2 and 1 subject in AZD9056 1200 mg (cohort B) and placebo, respectively. There were abdominal pain upper, diarrhoea and headache assessed as causally related by the principle investigator in the AZD9056 1200 mg group. There were nausea and headache assessed as causally related by the principle investigator in the placebo group. All the drug-related adverse events were mild in intensity and resolved without any medical intervention.

There were no clinically significant treatment-related changes or trends in any laboratory parameter measured during study. There were no results outside the reference range that were considered to be of clinical relevance or reported AEs in subjects exposed to AZD9056.

There were no clinically important changes in vital signs, ECG, physical findings including neurological assessments (neurological, motor, cerebellar-vestibular, sensory systems) or othr observations (including ophthalmological test) related to safety during the study.

Table S 4 Number (%) of subjects in the safety population who had at least 1 adverse event, grouped by system organ class and preferred term (safety analysis set)

		Cohort A			Cohort B		
	Placebo*	AZD9056			AZD9056		
		30mg	200mg	800mg	60mg	500mg	1200mg
MedDRA System organ class and preferred term	N=12	N=8	N=8	N=8	N=8	N=8	N=8
NERVOUS SYSTEM DISORDERS	2 (17)	0	1 (13)	2 (25)	0	1 (13)	3 (38)
DIZZINESS	1 (8)	0	1 (13)	2 (25)	0	1 (13)	2 (25)
HEADACHE	1 (8)	0	0	0	0	0	1 (13)
GASTROINTESTINAL DISORDERS	1 (8)	0	0	0	0	1 (13)	2 (25)
ABDOMINAL PAIN UPPER	0	0	0	0	0	0	1 (13)
DIARRHOEA	0	0	0	0	0	0	1 (13)
ENTEROCOLITIS	0	0	0	0	0	1 (13)	0
NAUSEA	1 (8)	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	0	0	0	0	1 (13)	0	0
NASOPHARYNGITIS	0	0	0	0	1 (13)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	0	0	1 (13)	0
RHINORRHOEA	0	0	0	0	0	1 (13)	0

*N represents the number of observations, not the number of subjects.
MedDRA Version 7.1