Drug Substance(s)	AZD9056	**SYNOPSIS**	(For national authority use only)
Study Code	D1520C00002		
Date	27 April 2005		

An Open, Non-Randomised, Crossover Study to Investigate the Effect of AZD9056 (50 mg Oral Dose for 5 Days) on Cytochrome P450 3A Using the Probe Drug Midazolam (7.5 mg Oral and 1 mg Intravenous Dose) in Healthy Subjects

Study centre

AstraZeneca Clinical Pharmacology Unit, E floor, South Block, Queens Medical Centre, Derby Road, Nottingham, NG7 2UH.

Study dates		**Phase of development**
First subject enrolled	06 September 2004	Clinical pharmacology (I)
Last subject completed	22 November 2004	

Objectives

Primary:

To investigate the effects of daily dosing of oral AZD9056 (50 mg) for 5 days on the PK parameters of both oral and iv administered midazolam.

Secondary:

1. To provide data that can be pooled with the midazolam information gathered following daily dosing of AZD9056 at 400 mg to investigate the relationship between dose of AZD9056 plus midazolam exposure. Data will form part of a pooled analysis to be reported separately.
2. To investigate the pharmacokinetics of AZD9056 upon multiple daily dosing of 50 mg.
3. To provide data to evaluate modelling predictions against observed data. Data will form part of a pooled analysis to be reported separately.
4. To further investigate the safety and tolerability of AZD9056.

5. 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

Single centre, open, non-randomised, drug:drug interaction study.

Target subject population and sample size

12 male and female healthy volunteers, aged 18 to 65 years inclusive.

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

AZD9056 administered orally as a single 50 mg tablet; batch number P6882A.

Midazolam administered orally as a 7.5 mg tablet (batch number X1539) and as an intravenous (iv) bolus of 1 mg (batch number X1541).

Duration of treatment

At Visit 2, subjects were administered a single 7.5 mg tablet of midazolam. Six hours later, they were administered 1 mg midazolam by iv bolus injection.

At Visit 3, subjects were administered 50 mg AZD9056 for 5 days. On Day 5, they were also administered 7.5 mg oral midazolam and 1 mg iv midazolam, as for Visit 2.

There was a washout period of 6 days between Visits 2 and 3.

Variables

- **Pharmacokinetic**

  Midazolam:
  Pharmacokinetic parameters were estimated from compartmental modelling in the presence and absence of AZD9056: K_a, CL, CLi, V_c, V_t, $t_{½}$, T_{lag}, t_{max}, $C_{max\ oral}$, AUC_{oral}, $C_{max\ iv}$ and AUC_{iv}; F, F_g and F_h as measures of bioavailability.

  AZD9056:
  Pharmacokinetic parameters were calculated using non-compartmental analysis: $AUC_{(0\text{-}24)}$, C_{max}, $C_{max,ss}$, C_{min}, $C_{min,ss}$, t_{max}, $t_{max,ss}$, $t_{½,ss}$, CL/F, V_z/F and R_{ac}.

- **Pharmacodynamic**

  There were no pharmacodynamic measurements in this study.

- **Pharmacogenetics**

  Genotyping will form part of a possible future pooled analysis to explore factors that affect the pharmacokinetic and/or pharmacodynamic effects of AZD9056; it is not reported as part of this study.

- **Safety**

  Adverse events, haematology, clinical chemistry, urinalysis, 12-lead ECG, blood pressure and pulse.

Statistical methods

The pharmacokinetic and safety data are summarised using standard summary statistics such as the mean, standard deviation, median and range for continuous variables, and frequencies and percentages for categorical data. No formal statistical testing was performed as the study was not formally powered and was exploratory in nature.

Subject population

Twelve subjects were included in the study. Of these, 10 subjects completed the study and 2 subjects discontinued from the study. Twelve subjects were analysed for safety and 10 subjects were analysed for PK. The first subject entered the study on 07 September 2004 and the last subject completed the study 22 November 2004. No female subjects were enrolled.

Subject 7 was not administered the 5th dose of AZD9056, nor any midazolam, at Visit 3. Subject 8 was not administered any study medication at Visit 3. These subjects were not included in the per protocol dataset. Subject 8 was included in the AE summaries, but not in other safety summaries for the second treatment period.

Table S1 Subject population and disposition

Characteristic	Statistic or category	Total (n=12)
Demographic characteristics		
Gender (N and % of subjects)	Male	12 (100%)
Age (years)	Mean (SD)	35 (9.7)
	Range	22 to 54
Race (N and % of subjects)	Caucasian	11 (92%)
	Black	1 (8%)
Disposition		
Number (%) of subjects	Enrolled	24
	Entered	12 (50%)
	Completed	10 (83%)
	Discontinued	2 (16.6%)
Number of subjects analysed for all doses	Safety	12 (100%)
	Per Protocol	10 (83%)

Summary of pharmacokinetic results

Following administration of AZD9056 at a dose of 50 mg once daily for 5 days, the geometric mean clearance of midazolam was reduced by 18% (36.7 vs 30.2 L/h). The geometric mean half-life showed an increase of 16% (2.3 vs 2.7 hours). In addition, in the presence of AZD9056 geometric mean midazolam AUC increased during both the oral (276 vs 356 nM.h) and iv (83.6 vs 102 nM.h) phases, suggesting weak inhibition (as defined by Bjornsson *et al* 2003) of CYP3A. Absolute bioavailability was estimated to be 0.44 in the absence of AZD9056, and 0.57 in the presence of AZD9056. These trends were consistent among 9 of the 10 subjects.

A greater fraction of midazolam escaped gut metabolism than escaped liver metabolism, but the differential effect on F_g and F_h was not affected by the presence of AZD9056.

There is an accumulation of AZD9056 from Day 1 to Day 5; the geometric mean R_{ac} was 1.55 (range 0.85 to 1.96). The estimate of $t_{½,ss}$ (20.5 hours) suggests that steady state for AZD9056 would be achieved by Day 4 to 5, the time of midazolam co-administration. This is supported by the similarity in observed C_{min} values pre- and 24 hours post-dose on Day 5.

Table S2 Summary of the ratio of the pharmacokinetic parameters of midazolam in the presence and absence of AZD9056

Treatment Comparisons	Parameter	N	Geometric mean ratio	90% Confidence interval
AZD9056 + MDZ / MDZ	CL	10	0.82	(0.742, 0.912)
	$t_{½}$ (h)	10	1.16	(1.070, 1.260)
	$C_{max\ oral}$ (nM)	10	1.03	(0.726, 1.462)
	AUC_{oral} (nM.h)	10	1.29	(1.128, 1.468)
	$C_{max\ iv}$ (nM)	10	0.90	(0.763, 1.061)
	AUC_{iv} (nM.h)	10	1.22	(1.097, 1.348)
	F_g	10	0.95	(0.858, 1.052)
	F_h	10	1.11	(0.989, 1.255)
	$F_{rel.absol.}$ / $F_{visit\ 2}$	10	1.28	(1.125, 1.467)

Summary of safety results

Overall AZD9056 was well tolerated and this study did not identify any issues that would preclude further development of this compound. There were 2 discontinuations due to adverse events; one of these subjects had not received any AZD9056. There were no deaths or serious adverse events, and no other significant adverse events during the study.

There were 16 adverse events with onset after the start of dosing during the study, reported by 7 subjects. Five AEs were reported by 4 subjects in the midazolam treatment period, and 11 AEs by 5 subjects in the AZD9056 plus midazolam treatment period. Two AEs were reported during the enrolment period.

The majority of AEs (15) were mild in intensity; 3 were considered to be moderate. For one AE, there was considered to be a reasonable possibility that the event may have been caused by the study drug; this was reported in the midazolam alone period.

The most commonly reported AE after the onset of treatment was cough: 2 events in 2 subjects, both reported in the midazolam alone period. All other AEs after the onset of treatment were reported on only one occasion.

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

There were no treatment-related clinically important changes in vital signs, 12-lead ECG, physical findings or other observations related to safety during the study.

Table S3 Number (%) of subjects who had at least 1 adverse event in any category and total numbers of adverse events (safety dataset)

Category of adverse event	Enrolment (n=12)	MDZ (n=12)	AZD9056+MDZ (n=12)	Total (n=12)
Number of subjects				
SAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinued study drug due to AE	1 (8%)	0 (0%)	1 (8%)	2 (17%)
Other significant AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any AE	2 (17%)	4 (33%)	5 (42%)	8 (67%)
Total number of AEs	2	5	11	18

Table S4 Number (%) of subjects with adverse events sorted by decreasing order of frequency as summarised over all treatment groups (safety dataset) by Preferred Term

Preferred term	Enrolment (n=12)	MDZ (n=12)	AZD9056+MDZ (n=12)
Cough	0 (0%)	2 (17%)	0 (0%)
Headache	1 (8%)	0 (0%)	1 (8%)
Abdominal pain	0 (0%)	0 (0%)	1 (8%)
Arthropod bite	0 (0%)	1 (8%)	0 (0%)
Back pain	0 (0%)	0 (0%)	1 (8%)
Catheter site related reaction	0 (0%)	1 (8%)	0 (0%)
Diplopia	0 (0%)	1 (8%)	0 (0%)
Hiccups	0 (0%)	0 (0%)	1 (8%)
Injection site paraesthesia	0 (0%)	0 (0%)	1 (8%)
Nasopharyngitis	0 (0%)	0 (0%)	1 (8%)
Otitis externa	0 (0%)	0 (0%)	1 (8%)
Pharyngolaryngeal pain	0 (0%)	0 (0%)	1 (8%)
Rash pustular	0 (0%)	0 (0%)	1 (8%)
Ventricular extrasystoles	1 (8%)	0 (0%)	0 (0%)