AstraZeneca

Drug product:	AZD9056; 400 mg (300 mg + 100 mg)	**SYNOPSIS**	
Drug substance(s):	AZD9056		
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A Non-Randomised, Single-Blind, Placebo-Controlled Study to Investigate the Effect of AZD9056 (400 mg Oral Dose for 5 Days) on Cytochrome P450 3A4 Using the Probe Drug Midazolam (7.5 mg Oral Dose) in Healthy Volunteers

Study centre

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

Publications

None at the time of this report.

Study dates

First subject enrolled 24 April 2003

Last subject completed 23 June 2003

Phase of development

Clinical pharmacology (I)

Objectives

Primary objective

The primary objective of this study was to assess the effect of AZD9056 on the clearance (CL/F) of orally administered midazolam.

Secondary objectives

The secondary objectives of the study were:

1. to investigate the effect of AZD9056 on the following midazolam PK parameters: AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, V_z/F and $t_{½}$

2. to further investigate the pharmacokinetic (PK) profile of AZD9056

3. to further investigate the safety and tolerability of AZD9056, including when a single dose of midazolam is taken at steady state by assessment of vital signs, ECG, haematology, clinical chemistry, urinalysis and adverse events

4. to provide pharmacogenetic data for the AZD9056 project that can be pooled with genetic results from other AZD9056 studies to allow the investigation of the influence of genotype on PK disposition (and PD response where appropriate).

Study design

This was a non-randomised, single-blind, placebo-controlled study to investigate the effect of AZD9056 (400 mg/day for 5 days) on the clearance of orally administered midazolam (7.5 mg) when given to healthy volunteers.

Target subject population and sample size

Healthy male and female subjects, aged between 18 to 65 years inclusive.

Sixteen subjects were included to ensure that there were at least 13 subjects eligible for the primary analysis of the study.

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

AZD9056 was administered orally as a 100 mg and a 300 mg tablet daily for 5 days. Placebo to AZD9056 (hereafter referred to as placebo) was administered orally as 2 tablets, which matched the active tablets, for 5 days. Midazolam was also administered orally as a 7.5 mg tablet on Day 5 of both active and placebo groups.

The batch numbers were:

AZD9056 100 mg tablets	Batch P6734
AZD9056 300 mg tablets	Batch P6577
Placebo tablets	Batch P6527
Midazolam 7.5 mg tablets	Batch X1359 (assigned by Charnwood QA) Manufacturer's Batch No B1516

Duration of treatment

Subjects were administered placebo for 5 days and, following a washout period of at least 2 days, AZD9056 for 5 days. On Day 5 of dosing in each treatment period, subjects received a single dose of midazolam immediately after receiving the final dose of placebo/AZD9056.

Criteria for evaluation (main variables)

Pharmacokinetics

- Primary variable: Midazolam clearance (CL/F).
- Secondary variables: Standard pharmacokinetic parameters of midazolam and AZD9056: maximum plasma concentration (C_{max}), time taken to achieve C_{max} (t_{max}), area under the plasma concentration-time curve during a dosing interval ($AUC_{(0-t)}$), area under the plasma concentration-time curve from zero to infinity (AUC), half-life ($t_{½}$), apparent total plasma clearance (CL/F) and apparent terminal volume of distribution (V_z/F).

Safety

- Secondary variables: Standard safety assessments included adverse events reports, clinical laboratory data (haematology, clinical chemistry and urinalysis), 12-lead ECG, blood pressure and pulse rate.

Pharmacogenetics

Pharmacogenetic parameters included MDR1 (P-gp gene), Cytochrome P450 3A. The results will be included in a future pooled analysis.

Statistical methods

The midazolam PK parameters were derived using non-compartmental analysis; these parameters (including the primary variable, clearance) were analysed using a hierarchical analysis of variance with factors for subject and treatment. Prior to the analysis, the data were logarithmically transformed using natural logs, the difference on a log scale equating to a ratio on the original scale. There was deemed to be no statistically significant effect of AZD9056 on midazolam clearance if the 90% confidence interval of the geometric mean ratio was within the no effect boundaries of 0.80 to 1.25 as used for equivalence studies. For the secondary PK parameters the ratios and confidence intervals were calculated; however, these analyses are deemed exploratory as the study was not powered for these parameters.

All data, including safety data, were summarised using descriptive statistics and, where appropriate, graphical methods.

Subject population

It was planned that a total of 16 subjects would take part in the study. All 16 subjects completed the study and were included in the safety and per-protocol data sets. No subjects discontinued from the study.

Subject demographics and disposition are summarised in Table S1.

Table S1 Subject demographics

		Total
Number dosed		16
Demographic Characteristics		
Sex (N and % of subjects)	Male	16 (100%)
Age (years)	Mean (SD) Range	40 (7.2) 25 to 50
Race (N and % of subjects)	Caucasian	16 (100%)
Height (cm)	Mean (SD) Range	179 (7.8) 164 to 194
Weight (kg)	Mean (SD) Range	81 (10.5) 57 to 102
BMI (kg/m^2)	Mean (SD) Range	25.4 (2.40) 20.2 to 29.4

N Number; SD Standard Deviation

Pharmacokinetic results

The mean plasma clearance of midazolam was reduced by approximately 60%, from a geometric mean value of 71.0 L/h (n=15) for the placebo treatment limb, to 29.3 L/h when co-administered with AZD9056 (n=16); the corresponding geometric mean ratio and 90% CI was 0.415 (0.367 to 0.469). Clearance could be calculated for all subjects except Subject 13 for the placebo limb, and was consistently lower in all individuals after AZD9056 dosing.

AZD9056 also had a clear effect on the other midazolam PK parameters, in particular, exposure in terms of AUC and C_{max}. Midazolam AUC was increased over 2-fold in the presence of AZD9056; the geometric mean ratio (90% CI) was 2.412 (2.134 to 2.725). There was an approximate 1.8-fold increase in C_{max}, with a 90% CI of 1.818 (1.391 to 2.376).

The geometric mean half-life of midazolam increased by approximately 25% when co-administered with AZD9056. The geometric mean value in the absence and presence of AZD9056 was 3.88 and 4.85 hours, respectively.

The results of the analyses are shown in Table S2.

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

Treatment Comparisons	PK Parameter	N	Ratio	90% Confidence Interval
AZD9056 plus Midazolam / Midazolam	CL/F	15	0.415	(0.367 , 0.469)
	C_{max}	16	1.818	(1.391 , 2.376)
	$AUC_{(0-t)}$	16	2.453	(2.179 , 2.762)
	AUC	15	2.412	(2.134 , 2.725)
	$t_{½}$	15	1.250	(1.148 , 1.362)
	V_z/F	15	0.518	(0.478 , 0.561)

Safety results

Adverse events are summarised in Table S3 (categories of adverse event) Table S4 (most common adverse events in decreasing order of frequency).

Table S3 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	Enrolment (n=16)	Placebo (n=16)	Placebo + Midazolam (n=16)	AZD9056 (n=16)	AZD9056 + Midazolam (n=16)	Total (n=16)
SAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinued Study Drug due to AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other Significant AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any AE	1 (6%)	3 (19%)	7 (44%)	10 (63%)	7 (44%)	13 (81%)
	Total number of adverse events					
Adverse Events	1	9	11	20	12	53

Table S4 Number (%) of subjects with the most commonly reporteda adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Adverse event (preferred term)	Enrolment (n=16)	Placebo (n=16)	Placebo + Midazolam (n=16)	AZD9056 (n=16)	AZD9056 + Midazolam (n=16)
Somnolence	0 (0%)	1 (6%)	5 (31%)	0 (0%)	5 (31%)
Headache	1 (6%)	2 (13%)	0 (0%)	2 (13%)	1 (6%)
Dysgeusia	0 (0%)	0 (0%)	0 (0%)	3 (19%)	1 (6%)
Lethargy	0 (0%)	0 (0%)	2 (13%)	1 (6%)	0 (0%)

a Adverse events occurring at an incidence of 2 or more subjects having an AE in a treatment period

Overall AZD9056 was well tolerated. There were no deaths or serious adverse events, no discontinuations due to adverse events, and no other significant adverse events.

There were 52 adverse events with onset after the start of dosing during the study, reported by 13 subjects. A greater number of AEs was reported on AZD9056 alone treatment days (20 AEs in 10 subjects) compared to placebo alone (9 AEs in 3 subjects). Twelve AEs were reported by 7 subjects on the AZD9056 plus midazolam treatment day, and 11 AEs by 7 subjects on the placebo plus midazolam treatment day.

The majority of AEs (42) were mild in intensity; 10 were considered to be moderate and one was considered to be severe (abdominal discomfort on Day 4 of AZD9056 treatment). For 17 AEs, there was considered to be a reasonable possibility that the event may have been caused by the study drug (11, 3 and 3 AEs reported on AZD9056, AZD9056 plus midazolam, and placebo plus midazolam dosing days, respectively).

The most commonly reported AE was somnolence (11 events in 9 subjects); 10 of these were reported on midazolam dosing days, and occurred with the same frequency in both treatment periods. Dysgeusia was reported on 8 occasions by a total of 3 subjects (19%), each following AZD9056 treatment. Other commonly reported AEs were headache and lethargy, occurring with a similar frequency in both treatment periods. GI symptoms were more commonly reported following AZD9056 treatment compared to placebo.

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 clinically important changes in vital signs, 12-lead ECG, physical findings or other observations related to safety during the study.