AstraZeneca

Drug product:	AZD9056 tablet 300 mg	**SYNOPSIS**	
Drug substance(s):	AZD9056		
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An Open, Randomised, Single Dose 2-way Crossover Study to Investigate the Effect of Food on the Pharmacokinetic Characteristics of AZD9056 (Tablets (300 mg)), in Healthy Subjects

Study centre

Single centre (Alderley Park Clinical Pharmacology Unit, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG).

Publications

None at the time of this report.

Study dates		**Phase of development**
First subject enrolled	11 March 2003	Clinical pharmacology (I)
Last subject completed	22 April 2003	

Objectives

Primary objective:

- To investigate the effect of food on the pharmacokinetic characteristics of AZD9056 as a tablet formulation.

Secondary objectives:

- To investigate the safety and tolerability of AZD9056 administered as a tablet formulation in fed and fasted states.
- To provide genetic data on the absorption, distribution, metabolism and excretion of AZD9056. Data will form part of pooled analyses.

Study design

This was an open label, randomised, 2-way crossover, single dose study to investigate the effect of food on the pharmacokinetic characteristics of AZD9056 when given as single 300 mg dose to healthy volunteers in fed and fasted states.

Target subject population and sample size

Healthy male and female subjects, aged between 18 and 75 years inclusive.

Eighteen subjects were randomised to ensure that at least 16 subjects completed the study.

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

AZD9056 was dosed orally as a single 300 mg tablet. The batch number was P6577 and the expiry date 11 September 2003.

Duration of treatment

Subjects were dosed on 2 occasions during the study, with a washout of at least 7 days between doses.

Criteria for evaluation (main variables)

Pharmacokinetics

Primary variables: Visits 2/3, Day 1 - 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_t), area under the plasma concentration-time curve extrapolated to infinity (AUC).

Half-life ($t_{½}$), apparent total plasma clearance (CL/F) and apparent terminal volume of distribution (V_z/F) were also determined, although they were not used to address any of the study objectives.

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

Secondary variables: MDR1 (P-gp gene), Cytochrome P450, 3A, 2C9, 2C19 and 2D6. These data will be included in future pooled analyses; they are not included in this clinical study report.

Statistical methods

All data were summarised using descriptive statistics, and where appropriate, graphical methods. The PK variables were derived using non-compartmental analysis prior to

summarisation. No formal confirmatory hypothesis testing was made. However, testing was performed in an exploratory capacity in order to assess whether there were differences in AUC_t, AUC, C_{max} and t_{max} in the fed and fasted state.

Subject population

It was planned that a total of 18 subjects would take part in the study. Eighteen subjects were randomised (9 in each of the fed/fasted and fasted/fed groups). All randomised subjects received the study drug on 2 occasions. All 18 subjects were included in the safety and Per Protocol data sets. The groups were generally well balanced in terms of demographic characteristics. No subjects discontinued from the study.

Subject demographics and disposition are summarised in Table S1.

Table S1 Subject population and disposition

		Fed/Fasted	Fasted/Fed	Total
Population				
N randomised		9	9	18
Demographic characteristics				
Sex (N and % of subjects)	Male	7 (78%)	8 (89%)	15 (83%)
	Female	2 (22%)	1 (11%)	3 (17%)
Age (years)	Mean (SD)	40 (15.3)	40 (10.7)	40 (12.8)
	Range	20 to 62	19 to 55	19 to 62
Race (N and % of subjects)	Caucasian	9 (100%)	9 (100%)	18 (100%)
	Black	0 (0%)	0 (0%)	0 (0%)
	Oriental	0 (0%)	0 (0%)	0 (0%)
	Other	0 (0%)	0 (0%)	0 (0%)
Disposition				
N (%) of subjects who:	Completed	9 (100%)	9 (100%)	18 (100%)
	Discontinued	0 (0%)	0 (0%)	0 (0%)
Number of subjects analysed for:	Safety [a]	9	9	18
	Pharmacokinetics	9	9	18

a Number of subjects who took at least one dose of study treatment and had at least one data point after dosing

N Number; SD Standard Deviation

Pharmacokinetic results

The primary objective of the study investigated the effect of food on the pharmacokinetic (PK) characteristics of AZD9056 as a tablet formulation.

Examination of the PK parameters indicated that there was an increase in exposure (ie, AUC, AUC_t, C_{max}) when AZD9056 300 mg was administered with food in this exploratory study. The ratio of the adjusted geometric means fed:fasted for AUC and AUC_t were 1.27 and 1.26, respectively (90% CIs 1.18 to 1.37 and 1.17 to 1.37, respectively) and 1.17 for C_{max} (90% CI 1.00 to 1.38). The analysis indicated that there was no difference in the adjusted least squared mean t_{max} in the fed state compared to fasted; the least square mean difference was 0 (90% CI -1.3 to 1.3). The adjusted geometric mean $t_{½}$ was similar. The results of the analysis are shown in Table S2.

Table S2 Summary of pharmacokinetic parameters (adjusted geometric mean and range) and statistics for AZD9056

Parameter	Ratio of adjusted geometric mean (fed/fasted)	90% CI	Geometric mean (range) Fasted	Fed
AUC (nM.h)	1.27	(1.18, 1.37)	18585 (11588, 32545)	23569 (15518, 38200)
AUC_t (nM.h)	1.26	(1.17, 1.37)	17926 (10846, 31617)	22644 (15223, 36830)
C_{max} (nM)	1.17	(1.00, 1.38)	1173 (469, 1980)	1375 (876, 2100)
t_{max} (h)	0.00 [a]	(-1.3, 1.3)	(1, 9)	(1, 6)
$t_{½}$ (h)	ND	ND	15.34 (12.05, 18.89)	15.49 (12.72, 18.61)
CL/F (L/h)	ND	ND	38.5 (22.0, 61.8)	30.4 (18.7, 46.1)
V_z/F (L)	ND	ND	853 (451, 1637)	679 (386, 1030)

a The mean value for t_{max} is the least squared mean (LSM) of the difference between fed and fasted
ND Not done.

Safety results

Adverse events (AEs) are summarised in Table S3 (categories of AE) and Table S4 (most common AEs 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	Number (%) of subjects who had an adverse event in each category[a]		
	Enrolment n= 18	300 mg Fed n= 18	300 mg Fasted n= 18
Serious adverse events not leading to death	0 (0%)	0 (0%)	0 (0%)
Serious adverse events leading to death	0 (0%)	0 (0%)	0 (0%)
Discontinuations of study treatment due to AEs	0 (0%)	0 (0%)	0 (0%)
Other significant adverse events	0 (0%)	0 (0%)	0 (0%)
Any adverse events	2 (11%)	8 (44%)	8 (44%)
Total number of AEs	3	11	19

a Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.

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

Preferred Term	Enrolment n= 18	300 mg Fed n= 18	300 mg Fasted n= 18
Cannula site reaction	0 (0%)	4 (22%)	3 (17%)
Headache	1 (6%)	1 (6%)	2 (11%)
Loose stools	0 (0%)	0 (0%)	3 (17%)
Nausea	0 (0%)	1 (6%)	2 (11%)
Venipuncture site bruise	1 (6%)	1 (6%)	0 (0%)
Abdominal pain lower	0 (0%)	1 (6%)	0 (0%)
Abdominal pain NOS	0 (0%)	0 (0%)	1 (6%)
Anorexia	0 (0%)	1 (6%)	0 (0%)
Constipation	0 (0%)	1 (6%)	0 (0%)
Cough	0 (0%)	1 (6%)	0 (0%)
Dizziness	0 (0%)	0 (0%)	1 (6%)
Dry mouth	0 (0%)	0 (0%)	1 (6%)
Dry skin	0 (0%)	0 (0%)	1 (6%)
Dyspepsia	0 (0%)	0 (0%)	1 (6%)
Epigastric discomfort	0 (0%)	0 (0%)	1 (6%)
Fatigue	0 (0%)	0 (0%)	1 (6%)
Injury NOS	0 (0%)	0 (0%)	1 (6%)

Overall, AZD9056 300 mg was well tolerated in fasting and fed states, and this study did not identify any issues that would preclude further development of this compound. There were no deaths or serious adverse events, no discontinuations due to adverse events, and no other significant adverse events during the study.

A total of 30 AEs was reported after the onset of dosing in the study, by 12 subjects. A greater number of AEs was reported by subjects in the fasted state (19) compared to the fed state (11); the number of subjects reporting AEs was the same in both groups (8 subjects). Gastrointestinal symptoms (loose stools, nausea) were reported more frequently in the fasted state. The majority of AEs (30) were mild in intensity; none was considered to be severe. Eight AEs were considered to have a reasonable possibility of a causal relationship with study treatment, 7 in the fasted limb (reported by 2 subjects) and one in the fed limb.

There were no clinically significant 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 AEs. There were no clinically

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