AstraZeneca

Drug product:	AZD9056 200 mg tablet, 25 mg iv	**SYNOPSIS**	
Drug substance(s):	AZD9056		
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An Open, Randomised, 2-way Crossover Study to Establish the Absolute Bioavailability of AZD9056 in Tablet Formulation (200 mg) Compared With an Intravenous Formulation (25 mg), in Healthy Volunteers

Study centre

A single centre study in which 12 volunteers were randomised to treatment. The study was conducted at the AstraZeneca Clinical Pharmacology Unit (Nottingham), E floor, South Block, Queen's Medical Centre, Derby Road, Nottingham, NG7 2UH.

Publications

None at the time of this report.

Study dates		**Phase of development**
First subject enrolled	24 September 2002	Clinical pharmacology (I)
Last subject completed	12 November 2002	

Objectives

Primary objective

To determine absolute bioavailability of the tablet formulation of AZD9056, compared with an intravenous formulation. Pharmacokinetic assessments were used to determine the absolute bioavailability.

Secondary objective

To assess the safety and tolerability of AZD9056 as a tablet formulation.

Study design

This was an open label, randomised, 2-way crossover study.

Target subject population and sample size

Healthy male and female volunteers aged 18 to 65 years recruited from the volunteer panel at AstraZeneca Clinical Pharmacology Unit at Nottingham (AZCPU).

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

AZD9056 was provided as two 100 mg tablets for oral administration, and as a 100 mL intravenous (iv) infusion of 25 mg.

Duration of treatment

Subjects received a single dose of iv and oral administrations of AZD9056 (one treatment per visit, tablet or iv), according to the randomisation code. There was a washout period of 7 days between treatment administrations.

Criteria for evaluation (main variables)

Pharmacokinetics

Plasma concentration and pharmacokinetic parameters of AZD9056.

Safety

Safety and tolerability assessments: adverse events, supine blood pressure and pulse, 12-lead ECG, 24-hour ambulatory cardiac monitoring, safety laboratory tests and physical examination.

Pharmacogenetic

At Visit 2, subjects who had consented provided a blood sample for genotyping. DNA samples will be analysed for MDR1 and Cytochrome P450, 3A, 2C9, 2C19 and 2D6 polymorphism. The results will be included in a future pooled analysis.

Statistical methods

Non-compartmental analysis was used to characterise the pharmacokinetic profile of each formulation of AZD9056.

Pharmacokinetic data, safety data, including adverse events, laboratory data, blood pressure and pulse rate, 12-lead ECG and 24-hour ambulatory cardiac monitoring, have been summarised by tablet and iv formulation using descriptive statistics and graphical output where appropriate.

No formal statistical comparisons have been made.

Subject population

A total of 12 subjects was planned to take part in this study. Twelve subjects were randomised and received at least one administration of study drug. One subject discontinued from the study drug treatment due to an AE (ventricular bigeminy) after receiving 200 mg ADZ9056 orally. Eleven subjects received both treatments and completed the study. All subjects were included in the Safety and Per Protocol datasets for the doses they received.

Table S1 Subject demographics

Characteristic	N	Statistic or Category	Total
Gender	12	Male	12 (100%)
Race	12	Caucasian	12 (100%)
Age (years)	12	Mean (SD) Median (range)	33 (8.1) 36 (21-42)
Weight (kg)	12	Mean (SD) Median (range)	82 (10.3) 81 (63-100)
Height (cm)	12	Mean (SD) Median (range)	176 (5.3) 177 (163-182)
Body Mass Index (kg/m^2)	12	Mean (SD) Median (range)	26 (2.4) 27 (24-30)

Pharmacokinetic results

The mean absolute bioavailability was estimated as 62%, with a range of 38 to 79% and a 95% confidence interval for the mean of 55 to 69%.

There was evidence of secondary peak at 5 hours post-dose in the mean plasma concentration profiles for both the tablet and the iv formulations.

The geometric mean $t_{½}$ was approximately the same for each formulation (18 hours for iv and 16 hours for oral). The average plasma clearance was 29 L/h, and the average volume of distribution was 735 L. The median t_{max} was shorter for the iv infusion (2 hours) than for the oral tablet (3 hours).

Table S2 Summary of the absolute bioavailabilty data (%)

N	Mean	SD	Median	Minimum	Maximum	95% Confidence Inteval
11	62	10.1	61	38	79	(55, 69)

Safety results

There was a total of 30 AEs during the study, experienced by 8 (67%) of the 12 subjects; 13 AEs were reported (by 4 subjects [36%]) during the iv dosing limb and 17 AEs were reported (by 7 subjects [58%]) during the oral dosing limb. Except for one (ventricular bigeminy), none of the AEs was considered to have a reasonable possibility of a causal relationship with study treatment. One subject had study drug discontinued due to an AE (ventricular bigeminy). There were no deaths or other SAEs and no other significant AEs. The majority of AEs were mild or moderate in intensity; 3 AEs (reported by one subject) were considered to be severe. The only AEs that were reported by more than one subject were cannula site reaction, cough, defaecation urgency, headache, loose stools and vomiting – each reported by 2 subjects.

There were no clinically significant treatment-related changes in any laboratory parameter measured during the study. There were no results outside the reference range that were considered to be of clinical relevance. There were no clinically important changes in vital signs or physical findings during the study. An AE of ventricular bigeminy, determined from 24-hour cardiac monitoring, was recorded for one subject after receiving oral AZD9056; occasional episodes of bigeminy were already present in this subject at enrolment, and multiple episodes were also observed during the second treatment period, although the subject was not dosed. There were no other clinically important ECG findings during the study.

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= 12	iv n= 11	Oral n= 12
Number of subjects:			
SAE	0 (0%)	0 (0%)	0 (0%)
Deaths	0 (0%)	0 (0%)	0 (0%)
Discontinued study drug due to AE	0 (0%)	0 (0%)	1 (8%)
Other significant AE	0 (0%)	0 (0%)	0 (0%)
Any AE	0 (0%)	4 (36%)	7 (58%)
Total number of AEs		13	17

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 the most commonly reported[a] adverse events as summarised over all treatment groups (safety analysis set)

Preferred term	Enrolment n= 12	iv n= 11	Oral n= 12
Cannula site reaction	0 (0%)	2 (18%)	0 (0%)
Cough	0 (0%)	0 (0%)	2 (17%)
Defaecation urgency	0 (0%)	0 (0%)	2 (17%)
Headache	0 (0%)	0 (0%)	2 (17%)
Loose stools	0 (0%)	0 (0%)	2 (17%)
Vomiting NOS	0 (0%)	0 (0%)	2 (17%)

[a] Adverse events reported by more than one subject at any dose level are listed in this table.