Drug Substance	AZD9056	**SYNOPSIS**	(For national authority use only)
Study Code	D1520C00005		
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A randomised, single-blind, placebo-controlled, single centre phase I study to assess the safety, tolerability and pharmacokinetics of multiple doses of AZD9056 tablets in healthy Japanese male subjects

Study centre(s)

Osaka Pharmacology Clinical Research Hospital
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Study dates		**Phase of development**
First subject enrolled	25 September 2007	Clinical pharmacology (I)
Last subject completed	5 December 2007	

Objectives

The primary objective was to investigate the safety and tolerability of AZD9056 when given as multiple doses to healthy Japanese male subjects.

The secondary objective was to investigate the Pharmacokinetics (PK) of AZD9056 when given as multiple doses to healthy Japanese male subjects

Study design

This study was a randomised, single-blind, placebo-controlled, multiple oral dose study carried out at a single centre to assess the safety, tolerability and PK of AZD9056 in healthy male Japanese volunteers. The study consisted of 2 groups: each group received 10 single daily doses of 100 or 400 mg tablet of AZD9056 or matched placebo.

Target subject population and sample size

A total of 24 young healthy male Japanese volunteers aged 21 to 36 years were randomised. On each dose level, 9 subjects received AZD9056 and 3 received matched placebo.

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

The following investigational products were provided:

- AZD9056 50 mg tablet (batch number: 07-010822AZ)
- AZD9056 200 mg tablet (batch number: 07-010821AZ)
- AZD9056 placebo tablet (batch number: 07-010603AZ)

Two tablets of either AZD9056 50 mg, 200 mg or matching placebo were taken orally once daily after meal.

Duration of treatment

Each subject received either 100 or 400 mg AZD9056 or matching placebo for 10 consecutive days.

Variables

- **Pharmacokinetic**

  Plasma concentrations of AZD9056
  PK parameters:
  C_{max}, t_{max}, C_{min} and $AUC_{(0-24)}$ for Day 1
  $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $AUC_{(0-24),ss}$, $t_{½}$, $CL_{,ss}/F$, $V_{z,ss}/F$, $R_{ac}[C_{min}]$ and $R_{ac}[AUC_{(0-24)}]$ for Day 10

- **Pharmacogenetics**

  MDR-1, CYP3A and $P2X_7$ receptor gene

- **Safety**

  Adverse events (AEs), 12-lead electrocardiogram (ECG), blood pressure (BP), pulse rate, body temperature, safety laboratory tests (haematology, clinical chemistry, urinalysis) and physical examination

Statistical methods

Data were described as listings and individual graphs, and were summarised using descriptive statistics for each dose level. When applicable geometric mean and coefficient of variation were also presented. Demographic and all safety data of the subjects were listed for each subject and summarised for each dose level using descriptive statistics. In addition, all abnormal results in laboratory data were also listed for each subject. Plasma concentrations of AZD9056 at each time point were summarised for each dose level using descriptive statistics: including geometric mean and coefficient of variation. The safety and PK data were analysed using the Safety dataset and Per Protocol analysis set, respectively.

Subject population

A total of 38 healthy male subjects from a single centre entered this study. Twenty-four (24) subjects were randomised and received at least one administration of study drug. All randomised subjects (9 AZD9056 100 mg, 9 AZD9056 400 mg, 6 placebo) received study drug on all 10 treatment days and completed the study. The first subject entered on 25 September 2007, and the last subject completed the study on 5 December 2007.

All of the randomised subjects were male Japanese. The mean age and body mass index (BMI) of randomised subjects were 25.7 years (range 21 to 36 years) and 20.84 kg/m^2 (range 19.1 to 23.3 kg/m^2), respectively. The treatment groups were well balanced with regards to demography and subject characteristics, thus differences in demography were not likely to influence the results and their interpretation.

The demographic and key baseline characteristics of study subjects are summarized in Table S1.

Table S1 Summary of demographic data and baseline characteristics

		Placebo	AZD9056		Total
			100 mg	400 mg	
N		6	9	9	24
Sex	Male	6 (100%)	9 (100%)	9 (100%)	24 (100%)
Ethnic group	Japanese	6 (100%)	9 (100%)	9 (100%)	24 (100%)
Age (years)	n	6	9	9	24
	Mean	23.3	27.2	25.7	25.7
	SD	2.50	5.49	3.08	4.19
	Min	21	21	21	21
	Median	22.5	24.0	25.0	24.0
	Max	28	36	30	36
Height (cm)	n	6	9	9	24
	Mean	172.57	172.42	173.20	172.75
	SD	5.340	3.957	6.423	5.111
	Min	164.2	166.2	163.2	163.2
	Median	171.75	172.70	174.30	173.05
	Max	178.4	178.8	181.7	181.7
Weight (kg)	n	6	9	9	24
	Mean	63.28	61.70	61.92	62.18
	SD	5.030	4.638	5.287	4.810
	Min	57.2	53.4	52.1	52.1
	Median	63.60	61.90	62.00	61.95
	Max	69.6	69.2	69.5	69.6
BMI (kg/m^2)	n	6	9	9	24
	Mean	21.27	20.74	20.64	20.84
	SD	1.655	1.260	1.318	1.348
	Min	19.1	19.3	19.1	19.1
	Median	21.85	20.80	20.50	20.85
	Max	22.9	23.3	23.0	23.3
Medical history	No	6 (100%)	9 (100%)	9 (100%)	24 (100%)
	Yes	0	0	0	0
Surgical history	No	6 (100%)	9 (100%)	9 (100%)	24 (100%)
	Yes	0	0	0	0

Summary of pharmacokinetic results

From the plasma concentrations at pre-dose and 4 hours post-dose it appears that steady state was achieved after 3 to 4 days following daily doses of 100 and 400 mg.

For 100 and 400 mg doses the t_{max} was 5 hours post-dose both on Day 1 and Day 10. At steady state the $t_{½}$ for 100 and 400 mg doses were 15.7 and 14.1 hours, respectively. From Day 1 to Day 10 the C_{min} and $AUC_{(0-24)}$ increased within the range of 1.3 to 1.5 fold for both doses, and the accumulation ratios were predictable from the $t_{½}$ values. The PK parameters after multiple dosing were predictable from single dose data.

The summary of pharmacokinetic parameters for AZD9056 on Day 10 is shown in Table S2.

Table S2 Summary of pharmacokinetic parameters for AZD9056 on Day 10

Parameter	100 mg (n=9)	400 mg (n=9)
$C_{max,ss}$ (nM)	409 (23.6)	2170 (22.3)
$t_{max,ss}$ (h)	5.00 (3.00-5.00)	5.00 (3.00-5.00)
$C_{min,ss}$ (nM)	95.4 (38.5)	620 (28.0)
$AUC_{(0-24),ss}$ (nM.h)	4880 (27.9)	28900 (20.3)
$t_{½}$ (h)	15.7 (12.2)	14.1 (13.6)
$CL_{,ss}/F$ (L/h)	48.9 (27.9)	33.0 (20.2)
$V_{z,ss}/F$ (L)	1100 (37.0)	672 (17.0)
R_{ac} [C_{min}]	1.33 (21.8)	1.46 (20.7)
R_{ac} [$AUC_{(0-24)}$]	1.42 (12.3)	1.40 (16.9)

Geometric mean and CV (%) except for $t_{max,ss}$ (median and range)
R_{ac} [C_{min}] and R_{ac} [$AUC_{(0-24)}$] are calculated as $C_{min,ss}/C_{min}$ and $AUC_{(0-24),ss}/AUC_{(0-24)}$, respectively

Summary of safety results

In this study, AZD9056 demonstrated an acceptable safety profile and to be well tolerated. There were no deaths, serious adverse events, discontinuation due to AE or any other significant AE.

In total 12 adverse events were reported during the study by a total of 7 (29.2%) out of 24 subjects. By doses, 6 (66.7%) out of 9 subjects in 100 mg dose group had 10 adverse events, no subject out of 9 subjects in 400 mg dose group had any adverse event, whereas 1 (16.7%) out of 6 subjects in the placebo group had 2 adverse events. All adverse events reported following AZD9056 administration were considered by the investigator to have been possibly or probably caused by the investigational product. All adverse events were mild intensity, and resolved with no action taken.

Adverse events were observed more frequently in the active group than in the placebo group. The incidence of adverse event was higher in 100 mg dose group rather than 400 mg, so there was no evident dose dependent effect of AZD9056 on the incidence and intensity of adverse events.

There were no clinically significant changes or trends in any laboratory parameter, ECG and vital signs measured during the study. There were no clinically relevant findings in physical examination.

Adverse events are summarised in Table S3 and Table S4.

Table S3 Summary of adverse events (Safety analysis set)

	Placebo	**AZD9056**		**Total**
	(n=6)	**100 mg (n=9)**	**400 mg (n=9)**	**(n=24)**
Number (%) of subjects*:				
Any adverse events	1 (16.7%)	6 (66.7%)	0	7 (29.2%)
Any serious adverse events	0	0	0	0
Any adverse events leading to death	0	0	0	0
Any adverse events leading to the study discontinuation	0	0	0	0
Any adverse events with mild intensity	1 (16.7%)	6 (66.7%)	0	7 (29.2%)
Any adverse events with moderate intensity	0	0	0	0
Any adverse events with severe intensity	0	0	0	0
Any other significant adverse events	0	0	0	0
Any drug-related adverse events	0	6 (66.7%)	0	6 (25.0%)
Number of events:				
All adverse events	2	10	0	12
All adverse events with mild intensity	2	10	0	12
Drug-related adverse events	0	10	0	10

* Subjects with multiple events in the same category are counted only once in that category. Subjects with more than 1 category are counted once in each of those categories.

Table S4 Number (%) of subjects who had at least 1 adverse event by system organ class and preferred term (Safety analysis set)

System organ class*	Placebo	AZD9056		Total
Preferred term*	(n=6)	100 mg (n=9)	400 mg (n=9)	(n=24)
INVESTIGATIONS	**1 (16.7%)**	**3 (33.3%)**	**0**	**4 (16.7%)**
BLOOD AMYLASE INCREASED	0	2 (22.2%)	0	2 (8.3%)
LIPASE INCREASED	0	2 (22.2%)	0	2 (8.3%)
BLOOD BILIRUBIN INCREASED	1 (16.7%)	0	0	1 (4.2%)
INFECTIONS AND INFESTATIONS	**1 (16.7%)**	**1 (11.1%)**	**0**	**2 (8.3%)**
NASOPHARYNGITIS	1 (16.7%)	1 (11.1%)	0	2 (8.3%)
CARDIAC DISORDERS	**0**	**1 (11.1%)**	**0**	**1 (4.2%)**
ATRIOVENTRICULAR BLOCK FIRST DEGREE	0	1 (11.1%)	0	1 (4.2%)
GASTROINTESTINAL DISORDERS	**0**	**1 (11.1%)**	**0**	**1 (4.2%)**
ABDOMINAL PAIN	0	1 (11.1%)	0	1 (4.2%)
DIARRHOEA	0	1 (11.1%)	0	1 (4.2%)

* MedDRA version 10.1

Number of subjects with adverse events sorted by system organ class followed by preferred term in decreasing order of total frequency. A subject can have one or more preferred terms reported under a given system organ class.