Drug Substance	AZD5672	**SYNOPSIS**	(For national authority use only)
Study Code	D1710C00013		
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A randomised, placebo-controlled, single-blind, single centre phase I study to assess the safety, tolerability and pharmacokinetics of ascending single oral doses of AZD5672 in healthy Japanese male volunteers

Study centre(s)

Kyushu Clinical Pharmacology Research Clinic,
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Study dates		**Phase of development**
First subject enrolled	17 March 2007	Clinical pharmacology (I)
Last subject completed	4 July 2007	

Objectives

Primary objective: To investigate safety and tolerability of single ascending doses of AZD5672 in healthy Japanese male volunteers.

Secondary objective: To investigate PK profile of AZD5672 following single ascending doses in healthy Japanese male volunteers.

Study design

This was a randomised, single-blind, placebo-controlled, single centre, parallel group, Phase I study to determine the safety, tolerability and PK of AZD5672 carried out in healthy Japanese male volunteers. In total, five ascending dose levels in the range of 15 to 400 mg were given orally.

Target subject population and sample size

It was planned that a maximum of 5 dose levels would be explored, each with 9 healthy Japanese volunteers, ie, a total of 45 volunteers.

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

The following investigational products were used:

- AZD5672 capsule 5 mg: (batch No. 07-010642AZ)
- AZD5672 capsule 25 mg: (batch No. 07-010644AZ)
- AZD5672 capsule 100 mg: (batch No. 07-010643AZ)
- AZD5672 placebo capsule 1: (batch No. 07-010647AZ)
- AZD5672 placebo capsule 2: (batch No. 07-010648AZ)

AZD5672 capsule was dispersed in water by homogenisation to produce a solution/suspension prior to oral administration and given as a single dose of 15 mg, 50 mg, 150 mg, 225 mg and 400 mg.

Duration of treatment

Each subject received a single dose of AZD5672 or placebo.

Variables

- **Pharmacokinetic**

  Plasma concentration of AZD5672, PK parameters (C_{max}, t_{max}, AUC, $AUC_{(0-t)}$, $AUC_{(0-24)}$, $t_{½}$, Vz/F and CL/F for AZD5672)

- **Pharmacogenetics**

  MDR-1 and CYP3A gene

- **Safety**

  AE, safety laboratory tests (haematology, clinical chemistry, urinalysis), 12-lead ECG, BP, pulse rate, body temperature, pupillometry, ophthalmology test

Statistical methods

PK and safety data were summarised using descriptive statistics. Where appropriate these data were additionally presented graphically.

Subject population

A total of 76 enrolled Japanese healthy male volunteers from a single centre entered this study and 45 subjects were randomised; the first subject entered on 17 March 2007, and the last subject completed the study on 4 July 2007. All randomized 45 subjects completed the study. All subjects were included in the safety and pharmacokinetic analyses.

The data from the subjects who took the active drug (ie, AZD5672) was summarised in each dose level, and the data from the subjects who took the placebo from five dose levels was added together as one control group. All groups contained similar groups of subjects as shown by the demographics in Table S1.

There are three subjects whose BMIs were less than 19 kg/m^2 in the table, but according to the height and weight on medical record, their actual BMIs were between 19 kg/m^2 and 27 kg/m^2 (refer to the footnotes for further information), and thus these were not deviations.

Table S1 Demographic and baseline characteristics of the full data set

Demographic characteristic		Placebo (n=15)	AZD5672					Total (n=45)
			15 mg (n=6)	50 mg (n=6)	150 mg (n=6)	225 mg (n=6)	400 mg (n=6)	
Race (n)	Japanese	15	6	6	6	6	6	45
Sex (n)	Male	15	6	6	6	6	6	45
Medical history: past (n)	Yes	0	0	0	0	0	0	0
	No	15	6	6	6	6	6	45
Medical history: current (n)	Yes	0	0	0	0	0	0	0
	No	15	6	6	6	6	6	45
Age (years)								
Mean		22	21	22	23	24	24	22
SD		1.7	1.1	2.1	1.9	4.3	2.3	2.4
Min		20	20	20	20	21	21	20
Median		21	21	22	23	23	24	21
Max		25	23	26	25	32	26	32
Weight (kg)								
Mean		63	63	66	57	63	60	62
SD		8.7	7.7	8.4	7.7	4.7	8.8	8.0
Min		51	54	57	50	54	53	50
Median		61	62	64	55	64	57	61
Max		81	75	80	71	68	76	81

Table S1 Demographic and baseline characteristics of the full data set

Demographic characteristic	Placebo (n=15)	AZD5672					Total (n=45)
		15 mg (n=6)	50 mg (n=6)	150 mg (n=6)	225 mg (n=6)	400 mg (n=6)	
Height (cm)							
Mean	172	171	175	170	171	170	172
SD	8.1	4.3	7.2	8.1	4.4	5.9	6.7
Min	158	165	166	161	163	165	158
Median	174	171	177	168	172	167	171
Max	189	178	182	184	175	180	189
BMI (kg/m^2)							
Mean	21.1	21.3	21.6	19.6	21.6	20.8	21.0
SD	2.15	1.97	2.87	0.82	1.90	2.18	2.07
Min	18.8 [1]	19.0	19.0	18.9 [2]	18.9 [3]	19.0	18.8
Median	20.8	21.2	20.3	19.2	21.3	19.8	20.4
Max	26.4	23.7	26.1	21.0	24.1	23.5	26.4

Data derived from Table 11.1.4.1 and Table 11.1.4.2, Section 11.

1: On CRF, height and body weight were recorded as 174 cm and 57 kg, respectively. However, according to medical record, the actual values were 173.7 cm and 57.4 kg, respectively, and thus BMI was 19.02 kg/m^2.

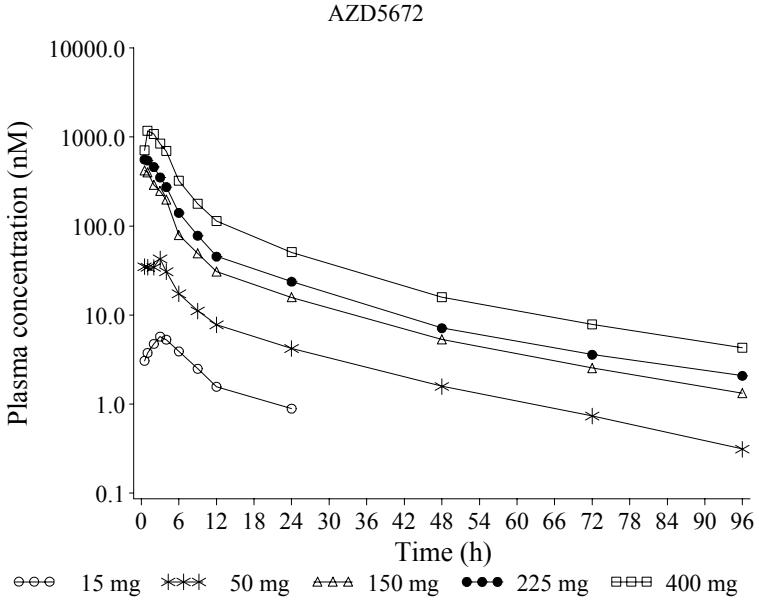
2: On CRF, height and body weight were recorded as 166 cm and 52 kg, respectively. However, according to medical record, the actual values were 166.0 cm and 52.4 kg, respectively, and thus BMI was 19.02 kg/m^2.

3: On CRF, height and body weight were recorded as 169 cm and 54 kg, respectively. However, according to medical record, the actual values were 168.5 cm and 54.2 kg, respectively, and thus BMI was 19.09 kg/m^2.

Summary of pharmacokinetic results

Mean AZD5672 plasma concentrations following administration of single oral doses of AZD5672 are shown in Figure S1.

Figure S1 **Mean AZD5672 plasma concentrations following administration of single oral doses of AZD5672 (6 subjects per dose level)**



Derived from Figure 11.2.1.2.3.

There was considerable inter-individual variability in the rate and extent of absorption of AZD5672. A double peak was observed in the plasma-concentration profiles in some subjects. The median t_{max} was in the range of 0.75 to 3.0 hours. The geometric mean C_{max} and AUC increased greater than the dose-proportional manner throughout the dose studied. However, in the dose range between 150 mg and 400 mg, the increase of exposure was close to dose-proportional manner. The terminal phase observed with the higher doses is not observed with the 15 mg dose. In the dose range between 50 mg and 400 mg, the geometric mean terminal half-life was approximately 20 hours. The apparent volume of distribution (Vz/F) and oral clearance (CL/F) decreased over the dose range studied but appeared to be of a similar magnitude over the 150-400 mg dose range.

Summary of safety results

AZD5672 at doses up to 400 mg was shown to be well tolerated and demonstrated a safety profile similar to placebo. A total of 5 AEs were reported after the start of study treatment in 4 subjects (2 in one subject in the placebo group which were not considered to be related to study medication by the investigator, and 3 in three subjects in the AZD5672 treatment groups which were considered by the investigator to be related to study medication). There was no suggestion of an increase in the number, frequency and the severity of AEs with increasing dose. There were no deaths, SAEs, discontinuations due to AEs or other significant AEs during this study.

A summary of adverse events in each category is presented in Table S2, and number of subjects in the safety population who had at least 1 AE is presented in Table S3.

Table S2 Number of subjects who had an adverse event in any category (safety analysis set)

	Placebo	AZD5672					Total
	(n=15)	15 mg (n=6)	50 mg (n=6)	150 mg (n=6)	225 mg (n=6)	400 mg (n=6)	(n=45)
Number of subjects*:							
Any adverse events	1	1	0	0	1	1	4
Serious adverse events	0	0	0	0	0	0	0
Adverse events leading to death	0	0	0	0	0	0	0
Adverse events leading to the study discontinuation	0	0	0	0	0	0	0
Adverse events with severe intensity	0	0	0	0	0	0	0
Any drug-related adverse events	0	1	0	0	1	1	3
Total number of recorded:							
Any adverse events	2	1	0	0	1	1	5
Serious adverse events	0	0	0	0	0	0	0
Adverse events leading to death	0	0	0	0	0	0	0
Adverse events leading to the study discontinuation	0	0	0	0	0	0	0
Adverse events with severe intensity	0	0	0	0	0	0	0
Any drug-related adverse events	0	1	0	0	1	1	3

*: 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 in each of those categories.
Data derived from Table 11.3.2.1, Section 11.

Table S3 Number of subjects in the safety population who had at least 1 adverse event, grouped by system organ class and preferred term (safety analysis set)

MedDRA system organ class name	Placebo	AZD5672					Total
MedDRA preferred term name	(n=15)	15 mg (n=6)	50 mg (n=6)	150 mg (n=6)	225 mg (n=6)	400 mg (n=6)	(n=45)
GASTROINTESTINAL DISORDERS	1	0	0	0	0	0	1
ABDOMINAL PAIN	1	0	0	0	0	0	1
DIARRHOEA	1	0	0	0	0	0	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	1	0	0	0	0	1
PYREXIA	0	1	0	0	0	0	1
INVESTIGATIONS	0	0	0	0	1	0	1
C-REACTIVE PROTEIN INCREASED	0	0	0	0	1	0	1
VASCULAR DISORDERS	0	0	0	0	0	1	1
ORTHOSTATIC HYPOTENSION	0	0	0	0	0	1	1

Data derived from Table 11.3.2.2, Section 11.

There were no laboratory findings of clinical concern. There were 3 occasions on which CRP was increased but as one of these occurred in placebo, one occurred 8 days after administration and the other occurred in connection with AE (pyrexia) observed at the lowest dose level (15 mg), the overall conclusion is that these were unlikely to be related to dosing with AZD5672.

There were no clinically relevant changes from baseline in the vital signs measurements. No association between AZD5672 and critical ECG parameters, including QTc, was observed. There were no clinically relevant changes in the pupil diameter values and ophthalmological tests measurements.