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

Study centre(s)

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Study dates		**Phase of development**
First subject enrolled	20 November 2007	Clinical pharmacology (I)
Last subject completed	20 February 2008	

Objectives

Primary objective: To investigate safety and tolerability of multiple doses of AZD5672 in healthy Japanese male volunteers by assessment of adverse events (AE), safety laboratory tests (haematology, clinical chemistry, urinalysis), 12-lead electrocardiogram (ECG), blood pressure (BP), pulse rate (PR), body temperature, pupillometry

Secondary objective: To investigate pharmacokinetic (PK) profile of AZD5672 following multiple doses in healthy Japanese male volunteers by assessment of plasma concentration of AZD5672 and PK parameters

Study design

This was a randomised, single-blind, placebo-controlled, multiple oral dose Phase I study carried out at a single centre to assess the safety, tolerability and PK of AZD5672 in healthy Japanese male volunteers. The study consisted of 2 groups: each group received 10 single daily doses of 100 or 225 mg capsule of AZD5672 or matched placebo.

Target subject population and sample size

A total of 24 healthy male Japanese volunteers aged 20 to 29 years were randomised and received at least one administration of investigational product. All randomised subjects (9 AZD5672 100 mg, 9 AZD5672 225 mg, 6 placebo) received study drug on all 10 treatment days and completed the study.

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

The following investigational products were provided:

- AZD5672 capsule 25 mg (batch number: 07-011807AZ)
- AZD5672 capsule 100 mg (batch number: 07-011809AZ)
- AZD5672 placebo capsule 1 (batch number: 07-011889AZ)
- AZD5672 placebo capsule 2 (batch number: 07-011808AZ)

AZD5672 and placebo were supplied as capsules, to be dispersed in purified water, and administered as a suspension. Either AZD5672 100 mg, 225 mg or matched placebo was taken orally once daily.

Duration of treatment

Each subject received either 100 or 225 mg of AZD5672 or matched placebo for 10 consecutive days.

Variables

- **Pharmacokinetic**
  - Plasma concentration of AZD5672
  - PK parameters

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

- **Pharmacogenetics**

  Multidrug resistance-1 (MDR-1) and CYP3A gene

- **Safety**

  AEs, safety laboratory tests (haematology, clinical chemistry, urinalysis), 12-lead ECG, BP, PR, body temperature and pupillometry

Statistical methods

Demographic and safety data 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 AZD5672 at each time point were summarised for each dose level using descriptive statistics including geometric mean and coefficient of variation. The PK variables were listed for each subject, and summarised using descriptive statistics including the geometric mean and coefficient of variation (CV) for each dose level (except for t_{max} and $t_{max,ss}$). The safety and PK data were analysed using the Safety analysis set and PK analysis set, respectively. Data were also displayed graphically.

Subject population

A total of 37 healthy Japanese 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 AZD5672 100 mg, 9 AZD5672 225 mg, 6 placebo) received study drug on all 10 treatment days and completed the study; all randomised subjects were included in analysis set. The first subject entered on 20 November 2007, and the last subject completed the study on 20 February 2008.

The mean age and Body Mass Index (BMI) of randomised subjects was 22.4 years (range 20 to 29 years) and 21.78 kg/m^2 (range 18.8 to 25.3 kg/m^2), respectively. There was 1 subject whose BMI was less than 19 kg/m^2, but according to the height and weight on medical record, his actual BMI was 19.016 kg/m^2 (refer to the footnote for further information) and thus this is not a deviation. The demographic and baseline characteristics of randomised subjects were similar between treatment groups, and thus the treatment groups were comparable.

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

Table S1 Demographic and baseline characteristics (Safety analysis set)

		Placebo		AZD5672				Total	
				100 mg		225 mg			
n		6		9		9		24	
Sex, Male	n	6	(100%)	9	(100%)	9	(100%)	24	(100%)
Race, Japanese	n	6	(100%)	9	(100%)	9	(100%)	24	(100%)
Age (years)	n	6		9		9		24	
	Mean	22.2		22.9		22.1		22.4	
	SD	1.2		2.6		1.2		1.8	
	Min	21		20		20		20	
	Median	22.0		22.0		22.0		22.0	
	Max	24		29		24		29	
Weight (kg)	n	6		9		9		24	
	Mean	63.0		64.6		64.0		64.0	
	SD	12.2		6.6		5.9		7.8	
	Min	50		54		55		50	
	Median	60.0		63.0		65.0		64.0	
	Max	82		74		75		82	
Height (cm)	n	6		9		9		24	
	Mean	170.8		172.7		169.8		171.1	
	SD	7.0		3.7		5.2		5.2	
	Min	163		168		162		162	
	Median	168.5		174.0		169.0		170.0	
	Max	180		178		180		180	
BMI (kg/m^2)	n	6		9		9		24	
	Mean	21.40		21.64		22.18		21.78	
	SD	2.41		1.81		1.19		1.73	
	Min	18.8*		19.1		20.1		18.8	
	Median	21.15		20.90		22.10		21.85	
	Max	25.3		24.2		24.0		25.3	
Medical history (past)	No	6	(100%)	9	(100%)	9	(100%)	24	
Medical history (current)	No	6	(100%)	9	(100%)	9	(100%)	24	

* The height and body weight were recorded on case report form (CRF) as 163 cm and 50 kg, respectively. However, according to the medical record, the actual values were 162.8 cm and 50.4 kg, respectively; thus the actual BMI was 19.016 kg/m^2.

Summary of pharmacokinetic results

From the plasma trough concentrations steady state appears to be achieved after 3 to 4 days following oral daily doses of 100 and 225 mg AZD5672.

The median t_{max} after first dose and at steady state was 1 hour for both dose groups. The geometric mean $t_{½}$ at steady state was 29.1 hours for the 100 mg group and 26.1 hours for the 225 mg group, which appeared to be independent of dose. The geometric mean R_{ac} for the $AUC_{(0-24)}$ were 2.29 and 2.36 for 100 and 225 mg dose, respectively, which were consistent with theoretical R_{ac} calculated from the $t_{½}$ at steady state. The R_{ac} for C_{min} were also similar for both doses (2.82 and 2.88, respectively).

There was a larger than proportional increase in both $AUC_{(0-24)}$ and C_{max} compared to the increase in dose on both Days 1 and 10. For a 2.25-fold increase in dose (100 to 225 mg), the $AUC_{(0-24),ss}$ and $C_{max,ss}$ increased 4.7-fold and 3.8-fold, respectively. A similar non-proportional increase was also seen following the first dose (4.6-fold for $AUC_{(0-24)}$, 3.9-fold for C_{max}).

The summary of pharmacokinetic parameters for AZD5672 on Day 10 is shown in Table S2.

Table S2 Summary of pharmacokinetic parameters for AZD5672 on Day 10 (PK analysis set)

Parameter	100 mg (n=9)	225 mg (n=9)
$AUC_{(0-24),ss}$ (nM.h)	1580 (38.3)	7460 (33.3)
$C_{max,ss}$ (nM)	298 (54.2)	1130 (50.5)
$C_{min,ss}$ (nM)	18.3 (45.0)	64.6 (29.3)
$t_{max,ss}$ (h)	1.00 (0.500-3.00)	1.00 (0.500-4.00)
$t_{½}$ (h)	29.1 (21.4)	26.1 (23.5)
$CL_{,ss}/F$ (L/h)	99.0 (38.3)	47.2 (33.2)
$V_{z,ss}/F$ (L)	4150 (58.5)	1780 (41.8)
$R_{ac}[C_{min}]$	2.82 (31.9)	2.88 (37.9)
$R_{ac}[AUC_{(0-24)}]$	2.29 (15.9)	2.36 (28.8)

Geometric mean and CV (%) except for $t_{max,ss}$ (median and range)

Summary of safety results

In this study, AZD5672 demonstrated a good safety profile and to be well tolerated. There were no deaths, serious AE, discontinuation due to AE or any other significant AE.

In total 4 adverse events were reported during the study by a total of 3 (12.5%) out of 24 subjects. By doses, no subject in 100 mg dose group had any adverse events, 2 (22.2%) subjects out of 9 subjects in 225 mg dose group had 2 adverse events, whereas 1 (16.7%) out

of 6 subjects in the placebo group had 2 adverse event. No adverse events were judged by the investigator as drug related to the investigational product. All adverse events were mild intensity, and resolved with no action taken. There were no apparent difference in the incidence and intensity of adverse event in the active group and placebo group.

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

Adverse events are summarised in Table S3 and Table S4.

Table S3 Summary of adverse events (Safety analysis set)

	Placebo	**AZD5672**	
		100 mg	**225 mg**
	(n= 6)	**(n= 9)**	**(n= 9)**
Number (%) of subjects*:			
Any adverse events	1 (16.7)	0 (0.0)	2 (22.2)
Any serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)
Any adverse events leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Any adverse events leading to the study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Any adverse events with mild intensity	1 (16.7)	0 (0.0)	2 (22.2)
Any adverse events with moderate intensity	0 (0.0)	0 (0.0)	0 (0.0)
Any adverse events with severe intensity	0 (0.0)	0 (0.0)	0 (0.0)
Any drug-related adverse events	0 (0.0)	0 (0.0)	0 (0.0)
Any other significant adverse events	0 (0.0)	0 (0.0)	0 (0.0)
Total number of recorded:			
All adverse events	2	0	2
All adverse events with mild intensity	2	0	2

*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.

Table S4 Summary of adverse events by system organ class (SOC) and preferred term (PT) (Safety analysis set)

MedDRA* SOC name / MedDRA PT name	Placebo (n= 6)		AZD5672 100 mg (n= 9)		AZD5672 225 mg (n= 9)	
	n (%)	Count	n (%)	Count	n (%)	Count
INVESTIGATIONS	**0 (0.0)**	**0**	**0 (0.0)**	**0**	**2 (22.2)**	**2**
MONOCYTE COUNT INCREASED	0 (0.0)	0	0 (0.0)	0	2 (22.2)	2
GASTROINTESTINAL DISORDERS	**1 (16.7)**	**1**	**0 (0.0)**	**0**	**0 (0.0)**	**0**
DIARRHOEA	1 (16.7)	1	0 (0.0)	0	0 (0.0)	0
VASCULAR DISORDERS	**1 (16.7)**	**1**	**0 (0.0)**	**0**	**0 (0.0)**	**0**
ORTHOSTATIC HYPOTENSION	1 (16.7)	1	0 (0.0)	0	0 (0.0)	0

Number of subjects with AEs, sorted by SOC followed by PT in decreasing order of frequencies (sorted by AZD5672 Total).
A subject can have one or more PTs reported under a given SOC.
* MedDRA: Medical dictionary for regulatory activities