Drug Substance	AZD2207	**SYNOPSIS**	(For national authority use only)
Study Code	D3180C00009		
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A Randomized, Single-blind, Placebo-Controlled, Single-Centre Phase I Study to Assess the Safety, Tolerability and Pharmacokinetics after Single Ascending Oral Doses of AZD2207 in Japanese Healthy Male Subjects

Study dates

First subject enrolled 4 July 2007

Last subject completed 1 October 2007

Phase of development

Clinical pharmacology (I)

Objectives

Primary objective:

The primary objective of this study was to evaluate the safety and tolerability of single ascending oral doses of AZD2207 in Japanese healthy male subjects, by assessment of adverse events (AEs), laboratory variables, vital signs, physical examination and electrocardiogram (ECGs).

Secondary objectives:

- To evaluate the pharmacokinetics of AZD2207 after single ascending oral doses to Japanese healthy male subjects.

- To collect and store DNA samples for potential future research into genes which may influence pharmacokinetic (PK) profile, drug disposition, efficacy, safety and tolerability of AZD2207.

Study design

This was a randomized, single blind, placebo-controlled, Phase I study designed to investigate the safety, tolerability, and pharmacokinetics after single ascending oral doses of AZD2207 to Japanese healthy male subjects.

Target subject population and sample size

A total of 24 healthy male subjects aged between 20 and 40 inclusive, were planned to be enrolled in the study and randomized to one of three groups of 8 subjects (Group 1, 2, and 3) to receive 2 mg and 8 mg AZD2207 (Group 1), 30 mg and 100 mg AZD2207 (Group 2), 200 mg and 400 mg AZD2207 (Group 3). Within each group of 8 subjects, 6 subjects received study drug and 2 subjects received placebo. One subject withdrew voluntarily after the first period and was replaced by another subject in Period 2. The actual number of subjects randomized was 25.

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

AZD2207 oral capsules (0.5 mg [batch number H 1845-01-02], 5 mg [batch number H 1846-01-03] and 50 mg [batch number H 1847-01-03]) and matching placebo capsules for 0.5 mg [batch number H 1848-01-03], 5 mg [batch number H 1849-01-04] and 50 mg [batch number H 1850-01-04] were administered to subjects.

Subjects were randomized to receive single oral doses of 2 mg (4 x 0.5 mg capsules), 8 mg (1 x 5 mg and 6 x 0.5 mg capsules), 30 mg (6 x 5 mg capsules), 100 mg (2 x 50 mg capsules), 200 mg (4 x 50 mg capsules) and 400 mg (8 x 50 mg capsules).

Duration of treatment

Subjects received a single dose of 2 mg, 8 mg, 30 mg, 100 mg, 200 mg or 400 mg AZD2207 or placebo. The duration of subject participation was for up to approximately 8 weeks including the enrolment visit, treatment period, and follow up visit.

Variables

The primary variables were the safety and tolerability of AZD2207. Secondary variables included the PK of AZD2207.

- **Safety**

  Adverse events (AEs)

  ECGs

  Vital signs measurements (body temperature, blood pressure [BP] and pulse rate)

  Laboratory measurements (haematology, clinical chemistry and urinalysis)

  Physical examination

- **Pharmacokinetic**

  Plasma concentration of AZD2207

  C_{max}, $t_{½}$, t_{max}, AUC and AUC_{0-t} for AZD2207

Statistical methods

All PK and safety data were listed for each individual subject and summarised descriptively by treatment.

Safety data included adverse events, haematology and clinical chemistry, ECGs, vital signs and physical examination.

Dose proportionality was performed by employing a power model: a model with an interaction between PK parameter (C_{max}, AUC and AUC_{0-t}) and dose group.

Subject population

A total of 24 healthy male volunteers from a single centre were planned to be randomized and entered onto this study. The first subjects entered on 4 July 2007 and the last subjects completed the study on 1 October 2007. The 24 subjects were randomized to one of three groups of 8 subjects (Group 1, 2, and 3) to receive 2 mg and 8 mg AZD2207 (Group 1), 30 mg and 100 mg AZD2207 (Group 2), 200 mg and 400 mg AZD2207 (Group 3). Within each group of 8 subjects, 6 subjects received study drug and 2 subjects received placebo. One subject withdrew voluntarily after the first period and was replaced by another subject. The actual number of subjects randomized was 25. The mean weight, height and BMI were similar across all treatment groups indicating the well balanced nature of the subject demographic characteristics. There were no protocol deviations that led to exclusion of data from the safety or PK summaries. All subjects were included in the safety analysis and the PK analysis.

Table S 1 Demographic characteristics of the whole study population

Demographic characteristic	**Treatment**						
	Placebo (n=6)	**AZD2207 2 mg (n=6)**	**AZD2207 8 mg (n=6)**	**AZD2207 30 mg (n=6)**	**AZD2207 100 mg (n=6)**	**AZD2207 200 mg (n=6)**	**AZD2207 400 mg (n=6)**
Age (yrs)							
mean	27.8	26.8	26.8	25.2	24.0	23.2	23.2
range	(23.0 - 30.0)	(22.0 - 31.0)	(22.0 - 31.0)	(23.0 - 30.0)	(23.0 - 28.0)	(20.0 - 34.0)	(20.0 - 34.0)
Height (cm)							
mean	170.5	171.6	171.6	172.7	172.0	170.9	170.9
range	(164.0 - 176.5)	(163.0 - 184.0)	(163.0 - 184.0)	(165.3 - 187.3)	(165.3 - 187.3)	(166.7 - 177.0)	(166.7 - 177.0)
Weight (kg)							
mean	62.1	61.3	61.3	64.9	66.9	63.0	63.0
range	(52.7 - 70.3)	(54.9 - 71.0)	(54.9 - 71.0)	(53.4 - 82.2)	(53.4 - 82.2)	(56.0 - 74.0)	(56.0 - 74.0)
BMI (kg/m2)							
mean	21.3	20.8	20.8	21.9	22.8	21.5	21.5
range	(19.4 - 24.3)	(19.4 - 23.6)	(19.4 - 23.6)	(19.3 - 26.2)	(19.3 - 26.3)	(19.8 - 25.0)	(19.8 - 25.0)

Summary of pharmacokinetic results

A summary of the pharmacokinetic variables for Japanese subjects is provided in Table S 2. The mean C_{max} and AUC values increased with dose but were less than dose proportional. The lowest exposure was observed with the 2 mg dose and the highest with the 400 mg dose. T_{max} was reached between 0.67 to 5 hours post-dose and increased with dose although there was no clear pattern. The mean elimination half-life ($t_{½}$) did not show any clear dose-dependent changes.

Based on a power regression model, dose proportionality was analysed for an interaction between the PK parameters (C_{max}, AUC and AUC_{0-t}) and dose group. The results from the power regression model showed that the 95% CIs for the PK parameters C_{max}, AUC, and AUC_{0-t} did not contain 1, suggesting that AZD2207 dose proportionality could not be confirmed in this dose range.

Summary of safety results

No safety or tolerability concerns were identified in this study of single doses up to 400 mg AZD2207. Overall, AZD2207 was well tolerated as single doses up to 400 mg. There were no deaths or serious adverse events (SAEs) in this study and none of the subjects withdrew due to an adverse event.

Five subjects out of 19 receiving active treatment (AZD2207) reported a total of 10 AEs during the study, and one subject out of 6 receiving placebo reported 2 AEs during the study. All were considered mild in intensity and none of the AEs were considered to be causally related with the study treatment. All of these AEs resolved without intervention. The most commonly reported AEs were diarrhoea (reported by 3 subjects) and nausea (reported by 3 subjects). The majority of the AEs were reported by subjects receiving either the 100 mg dose or the 400 mg dose.

There were no clinically significant changes in the haematology, clinical chemistry, or urinalysis parameters in any of the subjects. No safety issues were raised based on vital signs or ECG recordings and no clinically significant physical findings or other safety findings were made during the study.

Table S 2 Mean (SD) for PK parameters for AZD2207

Treatment	N	AUC (nmol*h/L)	AUCt (nmol*h/L)	Cmax(nmol/L)	tmax (h)a	$t^{1/2}$ (h)	CL/F L/h)
AZD2207 002 mg	6	124.91 (54.25)	102.38 (40.22)	18.43 (6.71)	1.83 (1.5-3.5)	17.67 (11.71)	29.58 (17.72)
AZD2207 008 mg	6	556.00 (157.57)	467.47 (158.07)	53.03 (19.55)	1.92 (1-3)	23.31 (8.19)	25.57 (17.48)
AZD2207 030 mg	6	1671.25 (927.37)	1599.15 (888.83)	137.97 (73)	2.61 (0.67-5)	20.11 (6.89)	38.23 (16.67)
AZD2207 100 mg	6	3661.82 (1579.61)	3575.87 (1560.5)	215.17 (51.88)	2.33 (1.5-3.5)	16.83 (3.65)	52.45 (27.39)
AZD2207 200 mg	6	7347.63 (2000.28)	7260.94 (2022.13)	436.83 (95.58)	1.86 (0.67-3)	17.92 (2.63)	47.57 (30.81)
AZD2207 400 mg	6	9262.33 (2595.15)	9192.93 (2563.61)	494.17 (160.33)	3.36 (0.67-5)	20.22 (2.92)	75.88 (48.76)
AZD2207 total					2.32 (0.67-5)	19.44 (6.26)	46.92 (22.8)

[a] Median t_{max} values are given