Drug Substance(s)	AZD5672	**SYNOPSIS**	(For national authority use only)
Study Code	D1710C00001		
Date	19 July 2007		

A Phase I, 3-part Study to Assess the Safety and Tolerability, Pharmacokinetics (including Food Effect) and Pharmacodynamics of Oral Doses of AZD5672 Following Single and Multiple Doses Administered for up to 28 Days in Healthy Volunteers

Part A: Single Ascending Dose

NOTE: This Clinical Study Report documents only Part A of the 3-part study, Protocol number D1710C00011. Parts B and C are reported separately.

Study centre

AstraZeneca Clinical Pharmacology Unit,
Queen's Medical Centre, Nottingham, NG7 2UH. UK.

Study dates		**Phase of development**
First subject enrolled	8 May 2006	Clinical pharmacology (I)
Last subject completed	20th Sept 2006	

Objectives (Part A)

Primary

- To investigate the safety, tolerability and pharmacokinetics of single ascending doses of AZD5672 in healthy volunteers.

Secondary

- To investigate the pharmacodynamic effects of AZD5672 after single doses of AZD5672 or placebo using the CCR5 internalisation assay.
- To investigate the relationship between pharmacokinetic and pharmacodynamic effects of AZD5672 using the CCR5 internalisation assay.

- To investigate the influence of the CCR5 Δ32 variant on the response (pharmacodynamic and safety) to AZD5672.

Study design

This Phase I study consisted of 3 separate parts designed to investigate the safety and tolerability, pharmacokinetics (including food effect) and pharmacodynamics of oral doses of AZD5672 administered for up to 28 days in healthy volunteer subjects. This Clinical Study Report documents Part A of the study only. Part A was of a randomised, double-blind, placebo-controlled, single ascending dose design, conducted at a single centre.

Target subject population and sample size

It was planned that a maximum of 9 dose levels would be explored, each with 9 subjects, ie, a total of 81 subjects.

Investigational product and comparators: dosage, mode of administration and batch numbers

AZD5672 and placebo were supplied as capsules, to be dispersed in purified water, and administered as a suspension. Within each cohort, subjects were randomised to receive AZD5672 or placebo in a 2:1 ratio.

The lowest dose of AZD5672 was 5 mg. Subsequent doses were 15 mg, 50 mg, 150 mg, 225 mg, 400 mg and 600 mg; these doses were chosen by the Safety Review Committee (SRC) following review of the blinded safety, tolerability and PK data from the preceding cohort(s). Dose escalation was stopped after the 7th dose level (600 mg) because the exposure data met the protocol-defined stopping criteria for dose escalation.

Batch numbers for each of the batches of AZD5672 and placebo capsules used were as follows:

AZD5672 1 mg	06-008075AZ
AZD5672 5 mg	06-008077AZ
AZD5672 25 mg	06-008113AZ
AZD5672 100 mg	06-008112AZ
Placebo	06-008082AZ, 06-008083AZ

Duration of treatment

Each subject received a single dose of AZD5672 or placebo

Variables

- **Pharmacokinetic**

  Area under plasma concentration-time curve (AUC), $AUC_{(0-t)}$, $AUC_{(0-24)}$ maximum plasma concentration (C_{max}), half-life ($t_{½}$), time to reach peak or maximum

concentration (t_{max}), apparent clearance (CL/F), and apparent volume of distribution Vz/F).

- **Pharmacodynamic**

  CCR5 expression, expressed as: CCR5 internalisation at 100nM MIP1β, basal CCR5 expression and % inhibition of pre-dose response.

- **Pharmacogenetics**

  CCR5 Δ32 genotype data.

- **Safety**

  Adverse events, clinical chemistry, haematology, urinalysis, 12-Lead ECG, QTc interval, ECG telemetry, blood pressure, pulse, pupillometry.

Statistical methods

Each variable was summarised using standard summary statistics, according to the treatment (placebo or AZD5672) and dose the subject received.

No interim analyses were planned during this study. However, blinded data were reviewed by a safety review committee after each dose.

Subject population

In total, 62 subjects were allocated into 7 cohorts; the first cohort had 8 subjects and the remaining 6 cohorts had 9 subjects each. In total, 41 subjects received active treatment and 21 subjects received placebo (Table S1). There were no protocol deviations or violations that were judged to have the potential to affect the data collected or the results, and all subjects were included in all the summaries. Hence, the per protocol and safety analysis sets were identical.

The subjects were mostly male and Caucasian. The age range was 18 y to 52 y (mean age 31 y). Small differences between treatment groups in baseline characteristics are not considered to have influenced interpretation of study data. Only one subject was variant homozygous for the CCR5 Δ32 variant genotype, and this subject received placebo; 19% of the study population was heterozygous for the variant and 79% were homozygous wild-type.

Table S1 Demographic and baseline characteristics of the safety analysis set

Demographic or baseline characteristic		Treatment group								
		Placebo (n=21)	AZD5672 5mg (n=5)	AZD5672 15mg (n=6)	AZD5672 50mg (n=6)	AZD5672 150mg (n=6)	AZD5672 225mg (n=6)	AZD5672 400 mg (n=6)	AZD5672 600 mg (n=6)	Total (n=62)
Demographic characteristics										
Sex n (% subjects)	Male	20 (95%)	5 (100%)	6 (100%)	6 (100%)	5 (83%)	5 (83%)	6 (100%)	6 (100%)	59 (95%)
	Female	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	1 (17%)	0 (0%)	0 (0%)	3 (5%)
Age (years)	Mean (SD)	29 (8.8)	30 (4.3)	34 (8.3)	37 (8.0)	32 (12.9)	32 (11.0)	26 (7.7)	30 (8.5)	31 (9.0)
	Range	18 to 52	23 to 34	23 to 43	21 to 43	20 to 50	21 to 50	20 to 41	20 to 42	18 to 52
Race n (%subjects)	Caucasian	19 (90%)	5 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	4 67%	6 (100%)	58 (94%)
	Black	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
	Oriental	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 33%	0 (0%)	2 (3%)
Other baseline characteristics										
Weight: males (kg)	Mean (SD)	79 (9.2)	80 (13.2)	86 (11.3)	85 (7.1)	72 (6.1)	81 (11.4)	77 (9.3)	75 (8.9)	80 (9.8)
	Range	64 to 94	60 to 96	65 to 95	73 to 94	62 to 77	68 to 94	66 to 92	65 to 87	60 to 96
Weight: females (kg)	Mean (SD)	69 -	-	-	-	75 -	49 -	-	-	64 (13.6)
	Range	-	-	-	-	-	-	-	-	49 to 75
BMI Males (kg/m2)	Mean (SD)	24 (2.3)	25 (3.1)	26 (4.3)	27 (2.6)	22 (3.1)	25 (3.9)	24 (2.5)	24 (1.9)	25 (2.9)
	Range	20 to 28	21 to 29	18 to 30	24 to 30	19 to 26	21 to 30	22 to 27	23 to 27	18 to 30
BMI Females (kg/m2)	Mean (SD)	26 -	-	-	-	28 -	22 -	-	-	25 (3.2)
	Range	-	-	-	-	-	-	-	-	22 to 28
CCR5 Δ32 genotype										
Homozygote wild type		17 (81%)	3 (60%)	6 (100%)	2 (33%)	5 (83%)	6 (100%)	5 (83%)	5 (83%)	49 (79%)
Heterozygote		3 (14%)	2 (40%)	0 -	4 (67%)	1 (17%)	0 -	1 (17%)	1 (17%)	12 (19%)
Homozygote variant		1 (5%)	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (2%)

BMI Body Mass Index.
Note: weight and BMI data given above are rounded to nearest whole number

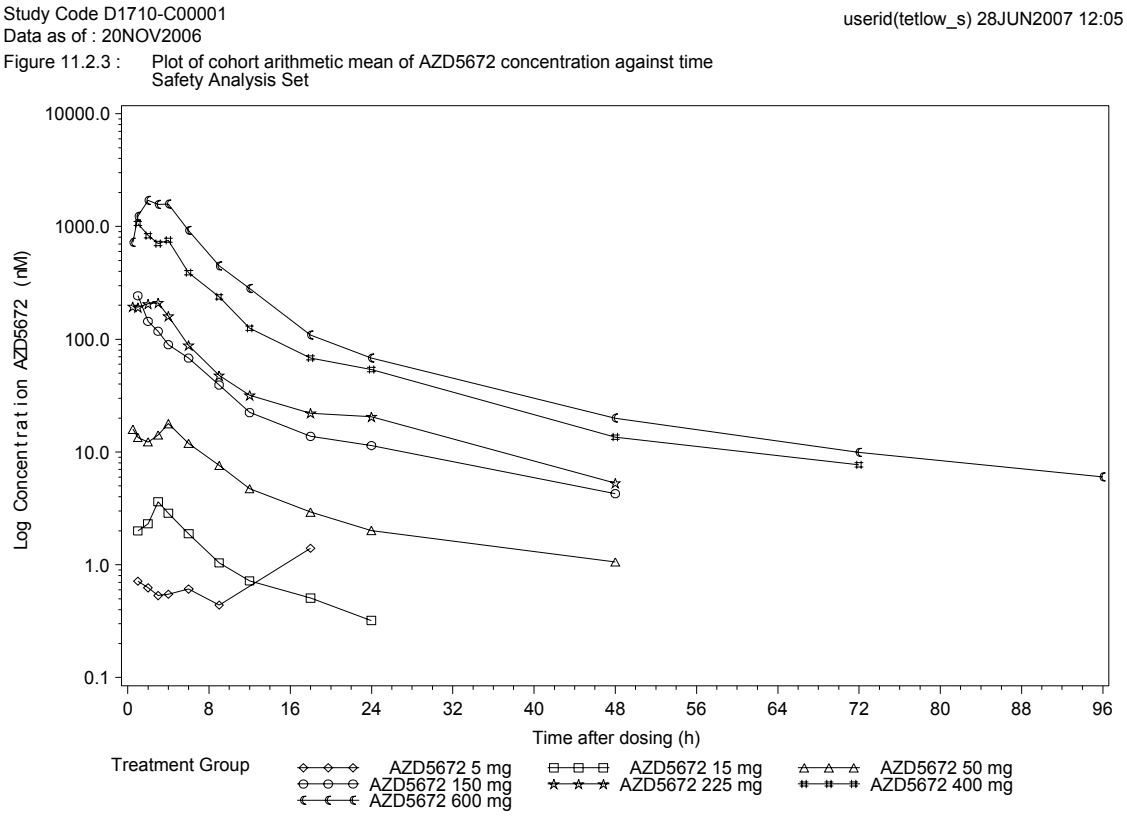
Summary of pharmacokinetic results

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

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. t_{max} varied between 0.5 h and 6.1 h, independent of dose. The geometric mean C_{max} for AZD5672, attained at 600 mg, was 1799 nM (range 1220 nM to 2690 nM). The decline from C_{max} in plasma concentrations was reasonably parallel across the dose range, and AZD5672 was measurable up to 24 h for 15 mg, 48 h for 50 mg to 225 mg, 72 h for 400 mg and 96 h for 600 mg AZD5672. Where terminal half-life of AZD5672 could be robustly measured (doses 50 mg to 600 mg) the geometric mean value was approximately 17 h, and it appeared to be independent of dose. The apparent volume of distribution during the terminal phase, calculated as Vz/F, was high and decreased with increasing dose, from geometric mean 9163 L at 50 mg to 1817 L at 600mg AZD5672. Clearance (CL/F) decreased with increasing dose, from geometric mean 367.6 L/h at 50mg to 67.7 L/h at 600mg AZD5672.

The geometric mean AUC attained at 600 mg AZD5672 was 13863 nM.h (range 9880 nM.h to 22700 nM.h). The relationship between AZD5672 exposure (AUC and C_{max}) and dose was non-linear. In general, the proportional increase in exposure was greater than the dose increment. Geometric mean AUC increased 65.6-fold for a 12-fold increase in dose from 50 mg to 600mg, and for a 40-fold increase in dose from 15 mg to 600 mg the median C_{max} increased 423-fold. The greatest increase in exposure occurred between 50 mg and 150 mg AZD5672, where for a 3-fold increase in dose C_{max} increased 11-fold and AUC increased almost 7-fold.

Figure S1 Mean AZD5672 plasma concentrations following administration of single oral doses of AZD5672



Summary of pharmacodynamic results

Inhibition of CCR5 internalisation was not observed in the placebo group. Following doses of 5 mg and 15 mg AZD5672 maximal mean (±SD) % inhibition of pre-dose CCR5 internalisation occurred after 2h (44.9 [8.91]% and 73.8 [13.1]%, respectively), and at subsequent measurements the activity declined. Following 50 mg AZD5672 inhibition of CCR5 internalisation was observed out to 24 h; at 2 h and 24 h, mean (±SD) inhibition of the pre-dose value was 77.7 (7.85)% and 76.5 (7.22)%, respectively. After doses of 225 mg and 400 mg, AZD5672 sustained mean (±SD) inhibition of pre-dose levels to 66.6 (27.46)% at 48 h, and 67.7 (15.39)% up to 72 h post dose, respectively. Administration of 600 mg AZD5672 resulted in inhibition for up to 4 days post-dose: at 96 h mean (±SD) inhibition of pre-dose CCR5 internalisation was 74.7 (13.82)%.

Summary of pharmacokinetic/pharmacodynamic correlations

The plasma concentration response curve for AZD5672 *vs* % inhibition of pre-dose CCR5 internalisation ex vivo was steep: in general >80% inhibition of the CCR5 response was

observed at plasma concentrations >2 nM. As AZD5672 plasma concentration increased there was an increase in the duration of the maximal observable % inhibition (>85%) of the pre-dose response. At the lower doses inhibition of CCR5 internalisation was observed beyond the decline in plasma AZD5672 concentration to below quantifiable levels.

Summary of population pharmacokinetics

Not applicable.

Summary of pharmacogenetics

Only one subject was a CCR5 Δ32/Δ32 variant homozygote, and this subject received placebo to 150mg AZD5672; 49 subjects (79%) were CCR5 +/+ wild-type homozygotes and 12 (19%) were CCR5 Δ32/+heterozygotes. Mean (±SD) basal pre-dose CCR5 expression (median fluorescence) was 180 (±125.0) in the CCR5 Δ32/+ heterozygotes, compared with 245 (±163.2) in the CCR5 +/+ wild-type homozygotes. There was no evidence of differences in pharmacodynamic response to AZD5672 between the heterozygotes and homozygous wild type subjects.

Summary of safety results

There was no evidence of an increase in the number of AEs in the AZD5672 treatment groups compared to placebo, and there was no increase in AEs with increasing dose. No deaths, treatment-emergent serious AEs, discontinuations due to AEs or other significant AEs occurred during this study. A total of 43 AEs were reported after the start of study treatment (14 in the placebo group and 29 in the AZD5672 treatment groups). Adverse events were reported by 9 subjects (43%) in the placebo group and 18 subjects (44%) in the AZD5672 treatment groups.

There were no clinically relevant changes from baseline in the mean or individual values of any laboratory parameter. Some postural falls in systolic and diastolic blood pressure were observed but there did not appear to be a dose relationship with AZD5672. No association between AZD5672 and critical ECG parameters, including QTc, was observed. There was no clear dose-related effect of treatment on pupil diameter.