Drug Substance(s)	AZD5672	**SYNOPSIS**	(For national authority use only)
Study Code	D1710C00002		
Date	20 November 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 B: Multiple Ascending Dose

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

Study centre

Guy's Drug Research Unit Quintiles Limited (GDRU), 6 Newcomen Street, London, SE1 1YR, UK

Study dates		**Phase of development**
First subject enrolled	10 October 2006	Clinical pharmacology (I)
Last subject completed	22 December 2006	

Objectives (Part B)

Primary

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

Secondary

- To investigate the pharmacodynamic effects of AZD5672 after multiple 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.

Exploratory

- To provide pharmacogenetic data for the AZD5672 project that can be pooled with genetic data from other AZD5672 studies for exploration of the influence of genotype on variability in PK disposition, PD response, tolerability and safety.

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 B of the study only. Part B was of a randomised, double-blind, placebo-controlled, multiple ascending dose design, conducted at a single centre.

Target subject population and sample size

It was planned that a maximum of 3 dose levels would be explored, each with 12 subjects, ie, a total of 36 subjects.

Investigational product and comparator: 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 3:1 ratio. The lowest dose of AZD5672 was 100 mg once daily chosen by the Safety Review Committee (SRC) after review of the safety, tolerability and PK data from the single ascending dose part of the study (Part A). Subsequent doses were 250 mg and 300 mg; these doses were chosen by the SRC following review of the safety, tolerability and PK data from the preceding cohort(s).

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

AZD5672 50 mg	06-009734AZ
AZD5672 100 mg	06-009996AZ
Placebo	06-009737AZ; 06-009967AZ

Duration of treatment

Cohorts 1 and 2 received an oral dose of AZD5672 100 mg, 250 mg or placebo daily for a maximum period of 10 days. Cohort 3 received an oral dose of AZD5672 300 mg or placebo daily for a maximum period of 28 days.

Variables

- **Pharmacokinetic**

  Plasma: AUC, $AUC_{(0-t)}$, $AUC_{(0-24)}$, AUC_{τ}, C_{max}, C_{min}, $C_{ss,max}$, $C_{ss,min}$, $t_{½}$, t_{max}, $t_{ss,max}$, CL/F, Vz/F, R_{ac}. Urine: A_e, $F_{e(0-24)}$, $CL_{R(0-24)}$.

- **Pharmacodynamic**

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

- **Pharmacogenetics**

  CCR5 Δ32 genotype data.

- **Safety**

  Adverse events, clinical chemistry, haematology, urinalysis, 12-Lead ECG, QTc interval, 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 healthy volunteer received.

No interim analyses were planned during this study. However, blinded data were reviewed by a safety review committee after each dose, in order to ensure healthy volunteer safety and to inform dosing increments.

In order to expedite analysis and interpretation of the QTc data to facilitate consultation with the Regulatory Authorities, an unplanned interim analysis on unblinded ECG data was carried out prior to Clean File. The unblinding was not carried out due to safety reasons. An interim statistical analysis plan and SOP deviation documentation were prepared, and the study team remained blind.

Subject population

A total of 32 healthy volunteers were allocated into 3 cohorts. Cohort 1 included 11 subjects (2 placebo and 9 AZD5672 100 mg subjects), Cohort 2 included 12 subjects (3 placebo and 9 AZD5672 250 mg subjects) and Cohort 3 included 9 subjects (2 placebo and 7 AZD5672 300 mg subjects). In total, 25 subjects received active treatment and 7 subjects received placebo. There were no protocol deviations, all subjects completed the study and all were included in the analyses.

Demographic and baseline characteristics are summarised in Table S1. All 32 subjects were male, the age range was 18 to 50 y (mean age 25 y), and 25 (78%) subjects were White. 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 AZD5672 100 mg; 5 (16%) of the study population was heterozygous for the variant and 26 (81%) were homozygous wild-type.

Table S1 Demographic and baseline characteristics of the safety analysis set

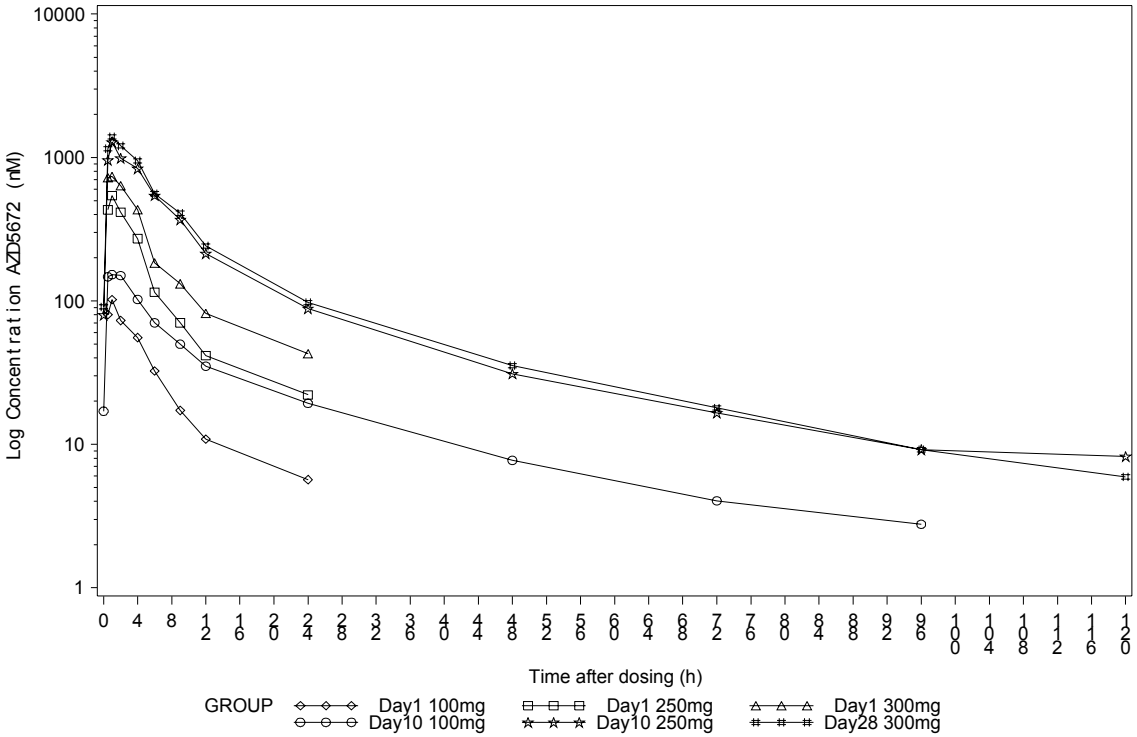
	Category or statistic	Placebo (n=7)	AZD5672 100 mg (n=9)	AZD5672 250 mg (n=9)	AZD5672 300 mg (n=7)	Total (n=32)
Demographic characteristics						
Sex	N	7	9	9	7	32
	Male	7 (100%)	9 (100%)	9 (100%)	7 (100%)	32 (100%)
	Female	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Age (years)	N	7	9	9	7	32
	Mean (SD)	24 (4.2)	26 (9.2)	25 (6.3)	26 (4.3)	25 (6.3)
	Range	19-31	20-50	18-35	19-31	18-50
Race	N	7	9	9	7	32
	White	7 (100%)	7 (78%)	5 (56%)	6 (86%)	25 (78%)
	Black	0 (0%)	1 (11%)	2 (22%)	0 (0%)	3 (9%)
	Asian	0 (0%)	0 (0%)	0 (0%)	1 (14%)	1 (3%)
	Other	0 (0%)	1 (11%)	2 (22%)	0 (0%)	3 (9%)
Key baseline characteristics						
Weight (kg)	n	7	9	9	7	32
	Mean (SD)	84.2 (9.80)	76.3 (9.20)	79.1 (8.54)	76.6 (9.23)	78.9 (9.23)
	Range	70.3-96.1	63.8-87.9	64.9-92.5	62.2-92.9	62.2-96.1
BMI (kg/m^2)	n	7	9	9	7	32
	Mean (SD)	25.5 (2.02)	24.2 (2.75)	25.2 (1.84)	24.7 (1.46)	24.9 (2.07)
	Range	23.3-29.3	20.8-28.4	21.4-27.2	21.8-26.6	20.8-29.3
CCR5 Δ32 genotype	n	7	9	9	7	32
Homozygote wild type	n (%)	5 (71%)	5 (56%)	9 (100%)	7 (100%)	26 (81%)
Heterozygote	n (%)	2 (29%)	3 (33%)	0 (0%)	0 (0%)	5 (16%)
Homozygote variant	n (%)	0 (0%)	1 (11%)	0 (0%)	0 (0%)	1 (3%)

BMI Body Mass Index

Summary of pharmacokinetic results

A plot of AZD5672 plasma concentration data is presented in Figure S1.

Figure S1 Plot of arithmetic mean of AZD5672 log concentration against time – safety analysis set



The median t_{max} after a single dose and at steady state was 1 h for all dose groups. The steady state gmean $t_{1/2}$ was 29.06 h for the 100 mg group, 29.32 h for the 250 mg group, and 26.09 h for the 300 mg group; this was independent of dose. The sampling regimen used to obtain C_{min} estimated steady state to occur between Days 5 and 11. V_z/F, at steady state, was high and decreased with increasing dose, at 100 mg the gmean V_z/F was 5067 L, decreasing to 1924 L at 250mg and 1740 L at 300mg. CL/F also had an inverse relationship with dose, the gmean CL/F at 100 mg was 120.9 L/h, 45.47 L/h at 250 mg and 46.22 L/h at 300 mg. After both the first and last dose, at all dose levels, potential therapeutic plasma concentrations (C_{min} values greater than 3 x pA_2; 2.28 nM) of AZD5672 were achieved across the dosing interval ($C_{ss,min}$ of 18.72, 82.25 and 94.85 nM on Days 10 for 100 mg and 250 mg, and Day 28 for 300 mg AZD5672, respectively).

There was a non-linear relationship between dose and exposure (as measured by AUC and C_{max}) following the first dose of AZD5672 and at steady state: a greater than proportional increase in gmean $C_{ss,max}$ and AUC_τ between 100 mg and 250 mg (for a 2.5 fold increase, $C_{ss,max}$ increased 7.4-fold and AUC_τ increased 6.6-fold); however, between 250 mg and 300 mg there were approximately dose-proportional increases in $C_{ss,max}$ and AUC_τ. In addition, the observed geometric mean values (range 2.3 to 3.3) for AZD5672 were greater than predicted from the $t_{1/2}$ data observed in the single ascending dose study (the $t_{1/2}$ from the SAD study (D1710C0001) was 17 h, from this $t_{1/2}$ the R_{ac} was calculated to be 1.60).

Overall, these data suggest that AZD5672 has non-linear plasma pharmacokinetics upon multiple dosing.

The fraction of AZD5672 excreted in the urine (as measured by $F_{e(0-24)}$) appeared to be dose proportional at all doses and times assessed; on Day 1, the gmean $F_{e(0-24)}$ was 3.1% (range 1.6% to 4.6%, CV 33.6%) for 100 mg, increasing 2.4-fold to 7.5% (range 3.3% to 17.6%, CV 63.9%) for the 250 mg dose. At steady state (Day 10), $F_{e(0-24)}$ was approximately 3-fold greater than $F_{e(0-24)}$ measured on Day 1 for 100 mg and 250 mg AZD5672. Renal clearance (as measured by $CL_{R(0-24)}$) appeared independent of dose and time; gmean $CL_{R(0-24)}$ ranged from between 8.5 L/h to 13.5 L/h across all doses and timepoints measured.

Summary of pharmacodynamic results

The mean % inhibition of pre-dose response for placebo 24h post-dose on Day 1 was -13.1% (range -60.1% to 12.6%), pre-dose on Day 10 was 13.7% (range 1.5% to 41.1%) and pre-dose Day 28 was 18.5% (range 13.8% to 23.2%). Close to maximal % inhibition of pre-dose CCR5 internalisation (85%), was observed 24 h post single dose of 100 mg and 250 mg AZD5672, with mean±SD of 82.7±3.86 and 81.1±4.34, respectively. The extent of inhibition was slightly less and more variable following a single dose of 300 mg AZD5672, the mean±SD was 69.8±17.31.

A trend indicating less inhibition of the pre-dose CCR5 internalisation was observed at steady state than at 24 h post-dose on Day 1: for AZD5672 100 mg and 250 mg on Day 10, mean ±SD was 71.0±17.91 and 76.6±12.65, respectively; on Day 28 for 300 mg, mean ±SD was 58.0±18.45.

On Day 1, there was greater variability in the % inhibition from pre-dose in the 300 mg group (range 45.1% to 85.0%) than in the 100 mg (range 74.2% to 85.0%) and 250 mg groups (range 74.1% to 85.0%). At steady state, all treatment groups had greater variability than after a single dose, but this was similar across the treatment groups (100 mg range 31.3% to 85.0% on Day 10; 250 mg range 46.4% to 85.0% on Day 10; 300 mg range 32.7% to 77.9% at 28 days).

There was a trend of a return towards baseline at 100 mg AZD5672 suggesting reversibility, evidenced by a decline in inhibition at 96 h. AZD5672 inhibited CCR5 internalisation to 64.2% of pre-dose 96 h at 100 mg. There was no discernable change for 250 mg AZD5672 and at 300 mg there was a definite change but this could have been biased by one individual subject.

Summary of pharmacokinetic/pharmacodynamic correlations

The plasma concentration response plot for AZD5672 vs % inhibition of pre-dose CCR5 internalisation *ex vivo*, suggested that the magnitude of the response was variable. In several subjects, the dose administered resulted in close to maximal inhibition across the dose interval; in others, the magnitude of the response was variable, particularly following multiple dosing to steady state. These factors put together make the scope for observing a subjective exposure-response relationship difficult.

Summary of pharmacogenetics results

Mean (±SD) pre-dose CCR5 basal expression (median fluorescence) was lower in the CCR5 Δ32/+ heterozygotes 164.8 (67.25) than CCR5 +/+ wild type homozygotes 199.7 (70.31) though there was considerable inter-individual variability in both genotype groups. No CCR5 expression was detected for the homozygous variant subject.

From the limited data available from this study, there is no clear evidence of an effect of the CCR5 Δ32 variant on the pharmacodynamic response to AZD5672. At steady state there was slightly less inhibition of CCR5 internalisation in heterozygous subjects. The only heterozygous subjects dosed active AZD5672 in the study were in the 100 mg dose group; 5 subjects were homozygous wild type and 3 subjects were heterozygous. At 100 mg Day 10 pre-dose the mean % inhibition of pre-dose response was 73.5% (range 63.7% to 85.0%) for the homozygous wild-type subjects and 67.0% (range 31.3% to 85.0%) for the heterozygous subjects. Similarly, at 72 h mean inhibition of pre-dose response for the homozygous wild type and heterozygous subjects were 80.4% (range 72.2% to 85.0%) and 64.6% (range 56.9% to 79.1%), respectively. Finally, at 96 h the homozygous wild type subjects were inhibited to 67.6% (range 46.3% to 85.0%) and the heterozygous subjects to 59.8% (range 30.7% to 77.8%).

The PK/PD response was steep, and there were no clear differences between CCR5 Δ32 -/+ heterozygote subjects and CCR5 +/+ wildtype homozygote subjects in PK/PD relationship.

Summary of safety results

There were no deaths, serious AEs or discontinuations from the study due to AEs. One subject receiving AZD5672 300 mg experienced an 'other significant AE' of blurred vision; this was not considered to be due to AZD5672.

A total of 71 AEs were reported by 21 subjects. A greater number of AEs were reported in the AZD5672 300 mg group (32 in 6 [86%] subjects) than in the 100 mg group (10 in 5 [56%] subjects), the 250 mg group (10 in 6 [67%] subjects), and the placebo group (19 in 4 [57%] subjects). This was expected as the subjects receiving AZD5672 300 mg were dosed for 28 days compared with 10 days for the other treatment groups. In addition, one subject in the AZD5672 300 mg group experienced 14 AEs during the study, possibly skewing the data. Seven (22%) of the AEs in the AZD5672 300 mg group occurred before Day 10; this was comparable to the other AZD5672 groups. The majority (25 [78%]) of the AEs in the AZD5672 300 mg group were reported after Day 10; 6 (50%) of the AEs reported by matched placebo were reported after Day 10. The most commonly reported AEs were headache, pharyngolaryngeal pain, dizziness, epistaxis, and postural dizziness. These AEs occurred both in subjects receiving placebo and subjects receiving AZD5672, and did not appear to be related to AZD5672 dose.

Most of the AEs were mild in severity; no subjects experienced severe AEs. One (14%) subject in the AZD5672 300 mg group experienced an AE of moderate intensity (vomiting). Seventeen (53%) subjects across all treatment groups had 47 (66%) AEs which were considered by the investigator to have been possibly or probably caused by study drug.

There did not appear to be any differences between the treatment groups in any laboratory parameter, or in pupilometry.

Small decreases from baseline in mean supine and standing systolic blood pressure across all timepoints in the study were observed in the AZD5672 groups; these decreases appeared greater in the 250 mg and 300 mg groups than the 100 mg group, and were not seen in the placebo group (mean change from baseline in supine systolic blood pressure ranging from -10 to 2 mmHg [300 mg]; -12 to 2 mmHg [250 mg]; -6 to 8 mmHg [100 mg]; and 0 to 18 mmHg [placebo]); however there was considerable variability within individual subjects. No differences between the treatment groups were seen in change from baseline in mean supine or standing diastolic blood pressure, or pulse.

ECG data revealed no effect of AZD5672 on any ECG variable, with the exception of RR interval. It was observed that the RR interval on Days 1, 8 and 28 was shorter in the AZD5672 treatment groups than the placebo group. This appeared to show a trend towards a treatment-related effect; however there were low numbers of subjects in each treatment group and large inter-subject variability. In addition, there were no corresponding changes in pulse rate. Change from baseline data indicate a shortening of RR interval and slight QTcF prolongation in the placebo group compared with the AZD5672 groups.