Drug product:	Not applicable	**SYNOPSIS**	
Drug substance(s):	AZD5672		
Study code:	D1710C00008		
Date:	12 December 2007		

An Open, Phase I Trial to Assess the Pharmacokinetics and Safety and Tolerability of a Single Oral Dose of AZD5672 in Male and Female Patients of Non-Childbearing Potential, with Active Rheumatoid Arthritis

Study centres

Five centres in Hungary.

Publications

None.

Study dates

First subject enrolled 07 February 2007

Last subject completed 23 July 2007

Phase of development

Clinical pharmacology (I)

Objectives

Primary

To investigate the PK profile of AD5672 following a single dose in patients with active RA.

Secondary

To investigate the safety and tolerability of single doses of AZD5672 in patients with active RA.

Exploratory

To retrospectively explore the contribution of polymorphisms in genes determining drug disposition to the PK profile of AZD5672. (The pharmacogenetic data are not presented in this Clinical Study Report.)

Study design

Open, single dose design, in patients aged 18 to 80 years, with preference for final 33% of patients to be >65 years.

Target subject population and sample size

Fifteen patients with active RA.

Investigational product: dosage, mode of administration and batch numbers

AZD5672 100 mg administered orally (dispersed in water) in fasted conditions. Batch numbers: 06-009734AZ and 07-010632AZ.

Duration of treatment

Single dose.

Criteria for evaluation (main variables)

Pharmacokinetics

Area under plasma concentration-time curve from time zero to infinity (AUC), area under plasma concentration-time curve from zero to the last measurable time point t ($AUC_{(0-t)}$), area under plasma concentration-time curve from zero to 24 hours ($AUC_{(0-24)}$), maximum observed plasma (peak) drug concentration (C_{max}), observed plasma concentration at 24 hours following drug administration (C_{min}), terminal elimination half life ($t_{½}$), observed time to reach peak or maximum concentration or maximum response following drug administration (t_{max}), apparent clearance following extravascular administration (CL/F), apparent volume of distribution (V_z/F).

Amount excreted in urine (A_e) over a 24-hour period post-dose at Visit 3 (urine was collected at intervals: 0 to 6, 6 to 12 and 12 to 24 hours), observed fraction of dose excreted unchanged in the urine from zero to 24 hours following dosing ($F_{e(0-24)}$) and apparent oral renal clearance ($CL_{R(0-24)}$).

Safety

Adverse events, clinical chemistry, haematology, urinalysis, ECG, blood pressure, pulse.

Statistical methods

Data for patients who were dosed with the study treatment (AZD5672) were included in the study.

No interim analyses were planned during the study. However, a planned review of the data was conducted by a safety review committee (SRC) after 6 patients aged 18 to 65 years had been dosed with AZD5672, in order to ensure patient safety prior to administering AZD5672 to patients aged over 65.

No formal statistical analyses were performed in this study. Summary measures of plasma concentrations and derived PK parameters were produced. Safety and tolerability variables are also summarised.

Subject population

Of the 15 patients, 12 (80%) were female and 3 (20%) were male. All of the patients were White. The mean age was 59 years (range 44 to 69 years). Three patients (20%) were aged over 65 years. Ten patients (67%) (all female, mean age 61 years) reported a medical history of hypertension; for 9 of these patients this was a current controlled condition for which they were receiving treatment.

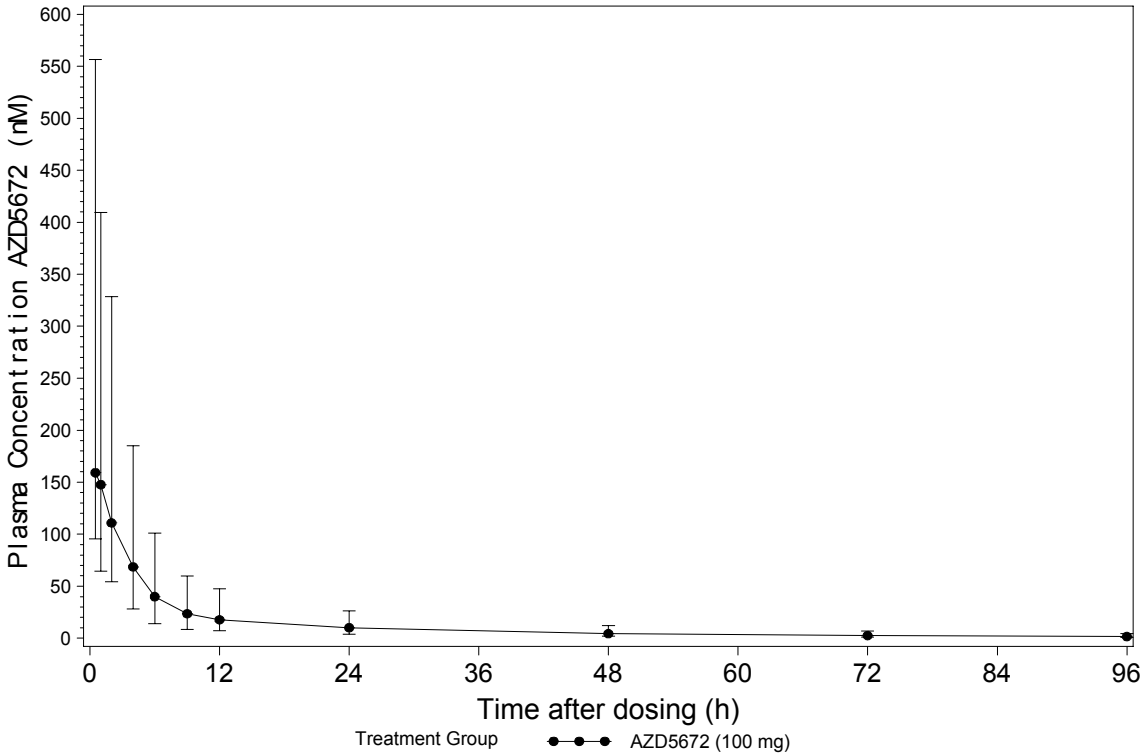
All 15 patients who received AZD5672 (100 mg) completed the study and were included in both the Safety and Per Protocol analysis sets.

The majority of patients (12 patients, 80%) had RA functional capacity class II. Two patients (13%) were class III and one (7%) was class I. The dates of RA diagnosis ranged from 1982 to January 2006, thus the duration of patients' disease ranged from 1 to 25 years. The DAS28 scores ranged from 3.3 to 7.6. All 15 patients were taking a Disease Modifying Anti-Rheumatoid Drug (DMARD) for their RA. Nine patients (60%) were taking methotrexate and 6 patients (40%) were taking other DMARDS. Ten of the patients (67%) were also taking glucocorticoids.

Pharmacokinetic results

Concentrations of AZD5672 were detected up to 96 hours in 14 patients. AZD5672 was rapidly absorbed; median t_{max} was 0.5 hours (range 0.5 to 4 hours). There was considerable inter-individual variability in the extent of absorption of AZD5672 in fasted patients (geometric mean [range]: $AUC_{(0-t)}$ 1213 nM.h [354 to 2889 nM.h] and C_{max} 200 nM [44 to 542 nM]). The geometric mean terminal half-life of AZD5672 in patients was approximately 27 hours. The large V_Z/F value (geometric mean 4751 L) suggested AZD5672 was widely distributed throughout the body. CL/F was moderate (geometric mean 120 L/h).

Figure S1 Plot of geometric mean with SD of AZD5672 concentration against time



The geometric mean $F_{e(0-24)}$ (observed fraction of dose excreted unchanged in the urine from zero to 24 hours following dosing) following 100 mg AZD5672 was 4.3% (range 1.6% to 8.5%). The geometric mean $CL_{R(0-24)}$ (apparent oral renal clearance from 0 to 24 hours following AZD5672 administration) was 7.5 L/h (range 3.8 to 14.3 L/h).

Safety results

There were no deaths, SAEs, discontinuations due to AEs or other significant AEs during this study. A total of 3 AEs (haematuria x 2, dyspepsia) was reported by 2 subjects after the start of treatment in the study.

There were no clinically relevant changes in the mean or individual values of any haematology parameter. With the exception of one patient who had a transaminase increase (74 U/L) at Follow-up, and one other patient who had increases in serum creatinine and urea on Day 3, there were no clinically relevant changes in the mean or individual values of any clinical chemistry parameter. One patient had blood in the urine during the study, and the urine tested positive for leucocyte esterase and bacteria; the patient subsequently reported 2 AEs of haematuria and spontaneously reported a history of haematuria (not databased). There were no other clinically relevant post-treatment urinalysis results.

Table S1 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Adverse Event	AZD5672 (100 mg) n=15
Number of Patients:	
SAE	0 (0%)
Deaths	0 (0%)
Discontinued Study Drug due to AE	0 (0%)
Other Significant AE	0 (0%)
Any AE	2 (13%)
Total Number of AEs	3

Table S2 Number (%) of patients who had at least 1 adverse event, by preferred term (safety analysis set)

MedDRA Preferred Term Name	AZD5672 (100 mg) n=15
Dyspepsia	1 (7%)
Haematuria	1 (7%)

Eight patients demonstrated asymptomatic significant drops in postural SBP (>20 mmHg) during the study; of these, one patient had the drop at pre-dose only, and 2 patients had the drops at screening as well as post-treatment. Six of the 8 patients were receiving medication for hypertension. Two patients had asymptomatic postural drops in diastolic blood pressure of more than 10 mmHg. Two patients had abnormal overall ECG findings after the start of treatment (one had 1st grade AV block at 4 hours post-dose; the other had ventricular extrasystoles at 4, 24 and 48 hours post-dose [ventricular extrasystoles had been reported in the patient's medical history]).