AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5672
Study Code	D1710C00020
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An Open-Label, Single-Centre, Parallel Group, Phase I Study To Compare the Pharmacokinetics of AZD5672 Single Dose in Patients with Renal Impairment and Healthy Volunteers

Study dates:	First healthy volunteer/patient enrolled: 3 July 2008 Last healthy volunteer/patient completed: 12 February 2009
Phase of development:	Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centre(s)

This study was conducted at 1 centre in Germany. The principal investigator was Dr Angelika Weil, APEX GmBH, Munich, Germany. The first subject (throughout this synopsis the term subject refers collectively to both healthy volunteers and patients with renal impairment unless otherwise specified) was enrolled on 3 July 2008 and the last subject completed all study procedures on 12 February 2009.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to investigate the pharmacokinetics (PK) of a single dose of AZD5672 in patients with renal impairment by comparing with healthy volunteers.

The secondary objective of this study was to determine the safety and tolerability of AZD5672 in patients with renal impairment by comparing with healthy volunteers.

The exploratory objective of this study was to provide samples to allow investigation of genetic factors that might help explain some of the variability observed in the PK and/or tolerability of AZD5672. Any data formed as part of a pooled analysis will be reported separately.

Study design

This was an open label study in up to 3 renal patient groups (mild, moderate and severe) and matched healthy volunteers. Eight patients with moderate renal impairment and matched healthy volunteers were recruited initially and received a single oral dose of AZD5672 100 mg. Data from these participants were reviewed by an informal safety review committee (SRC) to decide whether recruitment of patients with mild and/or severe renal impairment should then be triggered. Following this review, the SRC thought it appropriate to recruit patients with severe renal impairment with a matching healthy volunteer group. The German Competent Authority agreed with this proposal.

Target subject population and sample size

Initially, up to 24 patients with renal impairment and up to 16 healthy volunteers were to be recruited. Following SRC review this was amended to 16 patients with moderate and severe renal impairment (according to their measured creatinine clearance [CLcr]) and up to 16 healthy volunteers matched by age, gender and weight with a preference for approximately 8 patients in each of the renal impairment groups.

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

AZD5672 100 mg (2 x 50 mg) as tablets for oral administration; batch number 08-012857AZ.

Duration of treatment

AZD5672 was administered as a single oral dose; however, the duration of the study for all healthy volunteers and patients with renal impairment was up to 6 weeks (screening period of up to 3 weeks, followed by a 7-day investigational period with a 2-week follow-up period).

Criteria for evaluation - pharmacokinetics (primary variables)

The primary variables used were the ADZ5672 PK parameters area under plasma concentration-time curve from zero to time to the last quantifiable plasma concentration ($AUC_{(0-t)}$) and maximum plasma (peak) drug concentration (C_{max}). The following parameters were also calculated for each subject: area under the plasma concentration time curve from zero to infinity (AUC), terminal elimination half-life ($t_{1/2}$), apparent oral clearance following extravascular dosing (CL/F), volume of distribution (apparent) during terminal (λz) phase following extravascular dosing (V_z/F), and time to reach peak or maximum concentration following drug administration (t_{max}).

Plasma samples were analysed for AZD5672 protein binding to determine the percentage AZD5672 unbound (free). From this, the unbound (free) PK parameters for AZD5672 were to be determined by multiplying the relevant PK parameter by the percentage AZD5672 unbound (free). An apparent period effect in terms of unbound (free) AZD5672 concentrations (which influenced the subsequent interpretation of the resulting unbound [free] AZD5672 PK parameters) was observed. Thus, only total AZD5672 PK parameters are presented as the primary PK analysis set.

PK parameters derived from urinary concentrations: the cumulative amount of unchanged drug excreted into urine from 0 to time 24 h; cumulative amount of unchanged drug excreted into urine from 0 to time 48 h; fraction of systemically available drug excreted into urine over period 0-24 h; fraction of systemically available drug excreted into urine over period 0-48 h, renal clearance over the period 0-24 h, and renal clearance over the period 0-48 h ($CL_{R(0-48)}$).

Criteria for evaluation - safety (main variables)

Safety variables included: adverse events (AEs), laboratory data (clinical chemistry, haematology and urinalysis), 12-lead electrocardiograms (ECGs), continuous cardiac monitoring, blood pressure and pulse.

Statistical methods

Each PK variable was summarised using standard summary statistics, according to the degree of renal impairment (normal renal function, or moderate or severe renal impairment). In addition to these standard summary statistics, the most appropriate plasma $AUC_{(0-t)}$ and C_{max} (unbound parameters for $AUC_{(0-t)}$ and C_{max} were to have been used if these could have been determined) for patients with renal impairment and matched healthy volunteers were statistically analysed using linear regression, fitting measured CLcr as an explanatory variable. A point estimate and 90% confidence interval for the ratio of the most appropriate plasma AZD5672 $AUC_{(0-t)}$ and C_{max} in patients with moderate renal impairment (30 mL/min) (and

severe [20 mL/min] renal impairment) compared to healthy volunteers with normal renal function (125 mL/min) were to be presented. Upon inspection of the data, an additional point estimate at 45 mL/min, representing the actual mean CLcr for patients with moderate renal impairment enrolled in this study, was included for exploratory analysis.

Subject population

Sixteen healthy volunteers and 16 patients with renal impairment received AZD5672. All 32 subjects completed the study. Most of the subjects (20 of the 32 subjects) were male and all 32 subjects were White. The mean age of subjects was 62 years (range: 36 years to 73 years).

Summary of pharmacokinetic results

A summary of the AZD5672 primary PK parameters, for patients with moderate or severe renal impairment with their matched healthy volunteers is presented in Table S1.

Table S1 Summary of pharmacokinetics for AZD5672 in healthy volunteers and patients with renal impairment (per protocol analysis set)

Group	Parameter	n	Geometric mean	CV (%)	Median	Min	Max
Cohort 1							
Healthy volunteer	$AUC_{(0-t)}$ (nM.h)	8	713.3	32.33	729	484	1030
	C_{max} (nM)	8	124.5	40.56	129	74.7	211
	$t_{1/2}$ (h)	7	27.18	16.81	26.3	21.3	36.3
Moderate renal impairment	$AUC_{(0-t)}$ (nM.h)	8	865.3	32.02	909	542	1221
	C_{max} (nM)	8	102.0	52.59	96.3	59.4	221
	$t_{1/2}$ (h)	7	30.70	15.58	31.7	25.6	37.8
Cohort 2							
Healthy volunteer	$AUC_{(0-t)}$ (nM.h)	8	790.5	22.96	775.7	611	1217
	C_{max} (nM)	8	101.5	30.06	105.0	66.2	165
	$t_{1/2}$ (h)	8	31.53	22.33	30.59	24.9	43.1
Severe renal impairment	$AUC_{(0-t)}$ (nM.h)	8	1432	63.12	1443	671	3210
	C_{max} (nM)	8	160.9	47.51	141.5	91.7	352
	$t_{1/2}$ (h)	8	31.46	21.96	31.72	23.8	45.2

CV Coefficient of variation.

$AUC_{(0-t)}$ was calculable for all subjects (n=32) and AUC was only calculable for 30 subjects; thus, $AUC_{(0-t)}$ has been used for the primary PK analysis in the study, where t=96 hours for all subjects. Patients with severe renal impairment had a 1.8-fold greater gmean $AUC_{(0-t)}$ compared with matched healthy volunteers, whereas the gmean $AUC_{(0-t)}$ in patients with moderate renal impairment was similar (1.2-fold greater) to that of the healthy volunteer

group (Table S1). Gmean C_{max} for AZD5672 was increased by 1.6-fold in patients with severe renal impairment compared with matched healthy volunteers; however, gmean C_{max} in patients with moderate renal impairment was similar (1.2-fold greater) to that of the healthy volunteer group (Table S1).

Data for the AUC of AZD5672 reflected that for the $AUC_{(0-t)}$ of AZD5672. Values for CL/F and V_z/F were consistent with the primary analysis. The range of $t_{1/2}$ and t_{max} values for patients with severe renal impairment were similar to those observed in the healthy volunteers and patients with moderate renal impairment, suggesting that the higher systemic AZD5672 exposures observed in patients with severe renal impairment resulted from an increase in the quantity of drug absorbed, rather than a decrease in the elimination of the drug from the systemic circulation.

The relationship between renal function (CLcr, explanatory variable) and log transformed PK parameters (C_{max} and $AUC_{(0-t)}$, dependant variables ie, total exposure) was investigated using linear regression models. The point estimates determined were used to produce a ratio of predicted AZD5672 exposures in patients with renal impairment compared with healthy volunteers with normal renal function. However, there were a number of factors which limited interpretation.

- Firstly, there was a lack of plasma AZD5672 exposure data in renal patients with CLcr values between 30 mL/min and 43 mL/min; therefore, the nature of the relationship between these values could not be assessed.

- Secondly, the observed data for patients with severe renal impairment was highly variable. For CLcr of 30 mL/min or lower (including a patient with moderate renal impairment who had borderline severe renal impairment with CLcr of 30.2), 5 patients had exposures in the same range as healthy volunteers and 4 patients had increased exposures with a range of increases from 2-fold to 4-fold over the average exposure for healthy volunteers.

Thus, it was only possible to make limited conclusions based on the pre-planned statistical analysis of the limited observed data. A larger sample size of patients with severe renal impairment and additional data in patients with CLcr between 30 mL/min and 43 mL/min may further clarify the relationship between renal impairment and AZD5672 PK.

Summary of safety results

Fifteen of the 32 subjects (9 healthy volunteers and 6 patients with renal impairment) had at least 1 AE; a total of 21 AEs were reported during the course of the study. There were no serious AEs or other significant AEs and no AEs led to discontinuation of any subject from investigational product. The most common AEs were headache (3 healthy volunteers and 1 patient with moderate renal impairment) and fatigue (3 healthy volunteers). Most AEs were mild in intensity. One healthy volunteer developed a facial pustular rash which coincided with a neutrophilia-driven leukocytosis (all these events resolved, the neutrophilia-driven leukocytosis resolved after study completion). A patient with severe renal impairment showed

a transient increase of serum creatinine above baseline which was found to be within this patient's fluctuation range. None of these AEs raised any safety concern. There were no other clinically relevant changes in laboratory parameters (haematology, clinical chemistry or urinalysis) and there were no clinically relevant findings in ECGs or vital signs during the study.