AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5672
Study Code	D1710C00018
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A Phase I Study to Assess Absolute Bioavailability of AZD5672 at Steady-state in Healthy Volunteers

Study dates:	First subject: 27 August 2008 Last subject: 8 January 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 the United Kingdom (UK). The principal investigator was Dr Tania Hugo, PAREXEL Clinical Pharmacology Research Unit, Northwick Park Hospital, Harrow, Middlesex, HA1 3UJ, UK.

The first healthy subject was enrolled into this study on 27 August 2008 and the last subject completed all study procedures on 8 January 2009.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to estimate the absolute oral bioavailability at steady-state of 2 doses of AZD5672 (50 mg and 150 mg administered orally once-daily).

The secondary objectives of this study were:

- To define the pharmacokinetic (PK) parameters of AZD5672 following intravenous (IV) administration.
- To investigate the linearity of the kinetics following IV infusions.
- To investigate intra- and inter-subject variability of AZD5672 following oral dosing at steady-state.
- To further examine the safety and tolerability of AZD5672.

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 and safety of AZD5672. Any genetic data generated are to be reported separately.

Study design

This study included 26 healthy subjects in total. Cohort 1 included 8 subjects. Cohort 2 and Cohort 3 each included 9 subjects.

Cohort 1

Cohort 1 was a within-subject ascending IV dose cohort. Cohort 1 was used to assess the safety and tolerability of IV AZD5672, and to define appropriate IV doses to be selected for Cohort 2 and Cohort 3.

All subjects in Cohort 1 completed 3 double-blind investigational periods, separated by a washout interval of at least 14 days between the start of the IV infusion in each period; each single IV dose was to be administered as a 1-hour infusion. Six subjects were randomised to

receive the AZD5672 IV infusion. Two subjects were randomised to receive the matching placebo IV infusion; the same 2 subjects received placebo in each of the 3 periods.

For safety reasons, only 4 subjects were dosed (3 with AZD5672 and 1 with placebo) on the first day of each IV dosing period. There was a 1-hour interval between the administration of the single IV dose to each subject.

Cohort 2 and Cohort 3

Subjects in Cohort 2 and Cohort 3 were to complete 2 investigational periods. A single IV dose of AZD5672 was administered as a 1-hour infusion in Investigational Period 1, followed by a 14-day washout period and then oral dosing with AZD5762 once-daily for 12 days in Investigational Period 2. For Cohort 2 and Cohort 3, 24-hour PK sampling for the assessment of AZD5672 steady-state occurred on Day 10 and Day 12.

Target healthy volunteer population and sample size

A total of 26 healthy female (of non-childbearing potential) and male subjects aged 18- to 55-years-old (inclusive).

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

AZD5672 IV

A stock solution of AZD5672 5 mg/mL was diluted with sodium chloride 0.9% weight/volume to give a total dose in 48 mL administered over 60 minutes (ie, 0.8 mL/min). For the starting dose of 7 mg this was 0.146 mg/mL. The batch number used was 08-013435AZ

Cohort 1, Period 1: Subjects received a single 7 mg IV dose. The doses of AZD5672 to be used in Period 2 and Period 3 were selected following review of Period 1 data by an unblinded AstraZeneca Safety Review Committee.

Cohort 1, Period 2: Subjects received a single 21 mg IV dose. Cohort 1, Period 3: Subjects received a single 50 mg IV dose.

Cohorts 2 and 3, Period 1: Subjects received a single 24 mg IV dose (Cohort 2) or 50 mg IV dose (Cohort 3); these doses were determined after ongoing safety review of data from Cohort 1.

AZD5672 tablets for oral use

Cohort 2, Period 2: AZD5672 50 mg (1 x 50 mg tablet); batch number 08-013001AZ.

Cohort 3, Period 2: AZD5672 150 mg (3 x 50 mg tablets); batch number 08-013001AZ.

Duration of treatment

Single IV doses were given as 1-hour infusions. Oral doses were taken once daily for 12 days. There was at least a 14-day washout interval between the start of each investigational period.

Criteria for evaluation - pharmacokinetics (primary variables)

The primary outcome variable of absolute oral bioavailability was based upon area under plasma concentration-time curve from zero to infinity (AUC) following IV dosing and area under plasma concentration-time curve during a dosing interval at steady-state (AUC_{ss}) following oral dosing.

Secondary PK outcome variables:

To define the PK parameters of AZD5672 following IV administration the following were assessed: maximum plasma (peak) drug concentration (C_{max}), time to reach peak or maximum concentration following drug administration (t_{max}), total clearance of drug from plasma (CL), AUC, area under plasma concentration-time curve from zero to time of the last quantifiable plasma concentration, area under plasma concentration-time curve from zero to 25 hours ($AUC_{(0-25)}$), area under plasma concentration-time curve from 1 hour to 25 hours ($AUC_{(1-25)}$), terminal elimination half-life ($t_{1/2}$) and the volume of distribution (apparent) during terminal (λ_z) phase (V_z).

Linearity of the kinetics following IV infusions (ie, dose proportionality) was assessed through calculation of: C_{max}, AUC, $AUC_{(0-25)}$, and $AUC_{(1-25)}$.

Intra- and inter-subject variability of AZD5672 following oral dosing at steady-state was assessed using: maximum plasma (peak) steady-state drug concentration in plasma during dosing interval ($C_{ss,max}$) and AUC_{ss} on Day 10 and Day 12.

Criteria for evaluation - safety (main variables)

Safety was assessed by incidence and severity of adverse events (AEs), vital signs, electrocardiogram (ECG) parameters, continuous cardiac monitoring (for IV doses from 1 hour to 4 hours post-infusion), physical examination, clinical chemistry, haematology and urinalysis.

Statistical methods

The absolute oral bioavailability (%) at steady-state (on Days 10 and 12) was estimated using the following method:

$$F = \left(\frac{AUC_{ss\,oral}}{AUC_{iv}}\right) \times \left(\frac{Dose_{iv}}{Dose_{oral}}\right) \times 100$$

An analysis of variance (ANOVA) model was conducted using log-transformed dose-normalised oral AUC_{ss} values on Days 10 and 12 (averaged to reduce variability) and AUC values following the IV infusion within the same subject.

All of the secondary PK parameters were summarized by cohort and AZD5672 dose/administration route, using standard summary statistics. The linearity of PK parameters were assessed using the power law method to analyse dose-dependent PK parameters of AUC, $AUC_{(0-25)}$, $AUC_{(1-25)}$ and C_{max} using all available data. Intra- and inter-subject variability were evaluated based on PK parameters of AUC_{ss} and $C_{ss,max}$, using a mixed effect ANOVA model for the measurements taken on Days 10 and 12, with subject as a random effect.

Subject population

- Twenty-six patients were enrolled in this study. Cohort 1 included 8 subjects (6 subjects received IV AZD5672 and 2 subjects received IV placebo), Cohort 2 included 9 subjects who received IV and oral AZD5672 and Cohort 3 included 9 subjects who received IV and oral AZD5672. A total 24 subjects received AZD5672.

- All the subjects were male and most of the subjects (22 [85%] subjects) were Caucasian. The mean age of subjects was 31 years (range: 19 years to 50 years).

Summary of pharmacokinetic results

Primary objective

The observed absolute oral bioavailability was greater for AZD5672 150 mg at steady-state (approximately 81%; 90% confidence interval [CI]: 69% to 95%) compared with AZD5672 50 mg at steady-state (approximately 31%; 90% CI: 27% to 34%), reflecting the observed non-dose proportionality in AZD5672 AUC_{ss} following oral dosing.

Secondary objectives

Estimation of PK parameters following IV administration of AZD5672 indicated that AZD5672 was cleared rapidly from the body (66.9 L/h for AZD5672 7 mg; 56.7 L/h to 64.7 L/h for AZD5672 21 mg to 50 mg) and had a large V_z (1623.1 L for AZD5672 7 mg; 2297.8 L to 2533.6 L for AZD5672 21 mg to 50 mg). Mean $t_{1/2}$ was shorter following the AZD5672 7 mg IV dose (17.0 hours) than that for IV doses between 21 mg and 50 mg (mean $t_{1/2}$ of 25 hours to 31 hours). This was due to plasma concentrations falling below the lower limit of quantification for the 7 mg IV dose after 25 hours to 48 hours, resulting in the inability to estimate the terminal elimination phase that occurred later for the higher doses of AZD5672.

Over the dose range studied of AZD5672 7 mg to 50 mg, C_{max}, $AUC_{(0-25)}$ and AUC increased dose proportionally in the dose range of 21 mg to 50 mg; the 90% CI spanned 1.0 for each PK parameter (AUC: 0.89 to 1.10; $AUC_{(0-25)}$: 0.91 to 1.13; C_{max}: 0.82 to 1.28). Exposure increased slightly greater than proportionally for these parameters in the dose range of 7 mg to

50 mg; the 90% CI for all 3 PK parameters were all greater than 1 (AUC: 1.04 to 1.14; $AUC_{(0-25)}$: 1.03 to 1.10; C_{max}: 1.02 to 1.18).

Intra-subject variability for both $C_{ss,max}$ (approximately 12%) and AUC_{ss} (about 10%) on the steady-state sampling days (Day 10 and Day 12) was low, signifying reproducible exposure at steady-state. Inter-subject variability for AZD5672 50 mg and 150 mg was moderate; 21% and 31% for AUC_{ss}, and 34% and 36% for $C_{ss,max}$, respectively, which is consistent with previous data for AZD5672.

Summary of safety results

- The majority of subjects (19 of the 24 subjects) receiving AZD5672 had at least 1 AE. A total of 53 AEs were reported in subjects who received AZD5672 during the study. There was no relationship between the number of AEs reported and the dose of AZD5672 or whether AZD5672 was administered IV or orally. There were no SAEs or other significant AEs and no AEs led to discontinuation of any subject from investigational product.

- The most common AEs reported in subjects who received AZD5672 were: abdominal discomfort in Cohort 1 (2 subjects, AZD5672 7 mg and AZD5672 50 mg by IV), toothache in Cohort 2 (2 subjects, AZD5672 24 mg by IV), and flatulence (3 subjects, AZD5672 150 mg), diarrhoea (2 subjects, AZD5672 150 mg), headache (2 subjects, AZD5672 150 mg), rhinitis (2 subjects, AZD5672 150 mg), and viral infection (2 subjects, AZD5672 150 mg) in Cohort 3. Most AEs in all 3 cohorts were mild in intensity.

- There were no clinically relevant changes in haematology, clinical chemistry or urinalysis parameters, vital signs or ECGs during the study.