AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5672
Study Code	D1710C00023
Edition Number	1
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A Double-Blind, Placebo-Controlled, Randomised, Multiple Dose, Phase I Trial to Assess the Safety, Tolerability and Pharmacokinetics of adding AZD5672 at a dose of 100 mg to Oral doses of Methotrexate in Patients with Rheumatoid Arthritis

Study dates: First patient enrolled: 13 August 2007
Last patient completed: 28 April 2008

Phase of development: Clinical pharmacology (I)

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

Study centres

The study was conducted in 11 centres in Hungary and the United Kingdom. The first patient enrolled on the 13 August 2007 and the last patient completed on the 28 April 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to determine the safety and tolerability of AZD5672 when co-administered with oral methotrexate in patients RA.

The secondary objectives of this study were:

1. To investigate the intra-patient pharmacokinetic (PK) plasma profile of methotrexate and its 7-Hydroxy (7-OH) metabolite after oral administration of methotrexate alone and in the presence of AZD5672 (at steady state).

2. To determine the PK plasma and urine profile of AZD5672 after a single dose and at steady state in RA patients on a background of methotrexate.

3. To determine the PK plasma profile of methotrexate and its 7-OH metabolite in RA patients in the presence of placebo AZD5672 formulation.

The exploratory objective of this study was to provide pharmacogenetic data for the AZD5672 project that can be pooled with genetic data from other studies for exploration of the influence of genotype on variability in PK disposition, tolerability and safety of AZD5672 and methotrexate. Results of this exploratory genetic research are not reported in the clinical study report for this study.

Study design

This was a double-blind, placebo-controlled, randomised, multiple dose, phase I study to determine the safety, tolerability and drug-drug interaction potential when AZD5672 was added to methotrexate (MTX).

Target healthy volunteer population and sample size

A total of 24 male and female patients (18 receiving AZD5672; 6 receiving placebo) between the ages of 18 and 70 years with inactive or active rheumatoid arthritis (RA) were required (female patients of child-bearing potential were not permitted in Hungary).

Investigational product and comparator(s): dosage, mode of administration and batch numbers

AZD5672 100 mg (batch numbers 07-011276AZ, 07-012459AZ) or placebo (07-011155AZ, 07-012454AZ), for oral administration, were provided as capsules.

Duration of treatment

All patients received oral MTX every 7 days, as per their normal regimen, followed by either oral AZD5672 (100 mg) once daily for 15 days, or placebo (visually matched to AZD5672), once daily for 15 days.

Criteria for evaluation - safety (main variables)

Adverse events; haematology, clinical chemistry and urinalysis; vital signs; electrocardiograms (ECGs).

Criteria for evaluation - pharmacokinetics (main variables)

- MTX (with/without AZD5672)
  - Area under the plasma-concentration curve from time zero to infinity (AUC), time to reach observed peak or maximum concentration following drug administration (t_{max}), apparent volume of distribution (V_z/F), terminal half-life ($t_{½}$), apparent plasma clearance (CL/F), maximum plasma (peak) drug concentration after single dose administration (C_{max}), area under the plasma-concentration curve from time zero to the time of the last measurable plasma concentration ($AUC_{(0-t)}$), area under the plasma-concentration curve from time zero to 24 hours ($AUC_{(0-24)}$), time to first quantifiable plasma concentration after dosing (t_{lag}), time at which last quantifiable plasma concentration was observed (t_{last}), terminal elimination rate constant (λ_z)
- 7-OH metabolite (with/without AZD5672)
  - AUC, $AUC_{(0-t)}$, $AUC_{(0-24)}$, t_{max}, $t_{½}$, C_{max}, metabolite:parent ratio (%),t_{lag}, t_{last}, λ_z
- AZD5672 single dose (with MTX)
  - $AUC_{(0-24)}$, t_{max}, C_{max}, drug concentration in plasma at 24 hours post-dose (C_{24}), fraction of systemically available drug excreted into urine over the first 24 hours post-dose ($Fe_{(0-24)}$), renal clearance of drug from plasma over the first 24 hours post-dose ($CL_{R(0-24)}$), cumulative amount of unchanged drug excreted into urine over the first 24 hours post-dose ($Ae_{(0-24)}$)
- AZD5672 steady state (with MTX)
  - AUC_{ss}, $C_{ss,min}$, $C_{ss,max}$, t_{max}, V_z/F, $t_{½}$, drug accumulation ratio (R_{ac}), $Fe_{(0-24)}$), λz, apparent plasma clearance following extravascular dosing at steady state (CLss/F), $Ae_{(0-24)}$, $CL_{R(0-24)}$

Statistical methods

Each safety variable was summarised using standard summary statistics, according to randomised treatment (MTX + AZD5672 or MTX + placebo). Methotrexate pharmacokinetic data were summarised using standard summary statistics, according to the presence or absence of AZD5672. In addition to these standard summary statistics, the plasma MTX PK

parameters of area under the curve and C_{max} were examined using an analysis of variance model fitting for the effects of subject and treatment (presence or absence of AZD5672). Previous experience suggested that these variables are log-normally distributed and they were therefore logarithmically transformed prior to analysis. The results of the analysis were presented in terms of the geometric least squares means for each treatment, the ratio of the geometric least squares means, and the corresponding 90% confidence interval.

Subject population

Forty-eight patients were enrolled for the study, and 24 were randomised as planned (18 to AZD5672, 6 to placebo). All 24 patients received treatment, completed the study, and were included in both the Per Protocol and Safety analysis sets. There were no imbalances between the treatment groups in demographics or any other baseline characteristics, and the baseline characteristics of the study population resembled those in the target population.

Summary of safety results

There were no deaths, serious adverse events (AEs), discontinuations due to AEs or other significant AEs. Twelve patients (50%) reported a total of 37 AEs; 8 patients (44%) receiving AZD5672 100 mg plus MTX reported 23 AEs, and 4 (67%) receiving placebo plus MTX reported 14 AEs. In both treatment groups, AEs most commonly occurred in the 'nervous system disorders' SOC (33% of patients; 6 AZD5672 patients, 2 placebo); these AEs were headaches, dizziness and head discomfort. The most commonly reported AE after dosing with AZD5672/placebo was headache, occurring with equal frequency (33% of patients) in both groups.

There were no notable changes in any laboratory parameter over time, and no patients with treatment-emergent clinically important values that fell outside the pre-defined criteria. With regards to systolic blood pressure (SBP), there were some individual notable drops (>30 mmHg) in patients receiving AZD5672, but overall the mean decrease from baseline in post-dose SBP was greater in the placebo treatment group. Two patients in the AZD5672 treatment group reported AEs of dizziness; one of these patients also had notable drops in SBP during the study but vital signs measurements were not taken at the time of the event so it is not known whether the dizziness was directly associated with any changes in blood pressure. There were no clinically significant ECG abnormalities or physical findings.

Summary of pharmacokinetic results

The 90% CIs for the ratio of Visit 6 to Visit 2 for methotrexate were 0.926 to 1.094 for C_{max} and 1.007 to 1.182 for AUC and for the 7-OH metabolite were 0.807 to 1.068 for C_{max} and 0.842 to 1.090 for AUC. These 90% CIs are all within the FDA bioequivalence limits, 0.8 to 1.25, and thus regarded as not being clinically significant.

The MTX PK data in the placebo group were consistent with those for the patients receiving AZD5672.

The PK profiles of AZD5672 in patients on a background of methotrexate after a single 100 mg dose and at steady state were:

single dose: geometric mean C_{max} 212.2 nmol/L (range 84.7 to 503 nmol/L)
geometric mean $AUC_{(0-24)}$ 743.8 nmol.h/L (range 381 to 1650 nmol.h/L)

steady state: geometric mean $C_{ss,min}$ 21.40 nmol/L (range 4.88 to 67.9 nmol/L)
geometric mean $C_{ss,max}$ 277.6 nmol/L (range 69.1 to 655 nmol/L)
geometric mean AUC_{ss} 1339 nmol.h/L (range 449 to 3230 nmol.h/L)