AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8075
Study Code	D3801C00001
Edition Number	1
Date	29 September 2009

A Phase I, Single Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of Single Ascending Oral Doses of AZD8075 in Healthy Male Volunteers

Study dates: First healthy volunteer: 30 October 2008
Last healthy volunteer completed: 30 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)

The study was conducted at Quintiles AB, Uppsala, Sweden,

The first healthy volunteer entered the study on 30 October 2008 and the last healthy volunteer finished the study on 30 January 2009.

The study was terminated after the 5th cohort out of 9 planned due to safety reasons (urinary turbidity).

Publications

None at the time of writing this report.

Objectives

Primary Objective

To assess the safety and tolerability of AZD8075 following administration of single ascending doses and to estimate the maximum tolerated dose

Secondary Objective

To characterise the pharmacokinetics (PK) of AZD8075 and provisionally assess the dose proportionality of the PK following administration of single ascending doses of AZD8075

Exploratory Objectives

To obtain material for possible exploratory analysis of metabolites of AZD8075 in urine and plasma

To assess the stability of selected plasma samples with and without the addition of phosphoric acid

To collect pharmacogenetic samples for possible retrospective exploratory analysis, investigating the influence of genotype on PK (and pharmacodynamic response where appropriate)

Study design

This was a phase I randomised, double-blind, placebo-controlled single centre study to assess the safety, tolerability and PK of AZD8075 following single ascending dose administration to healthy male volunteers. AZD8075 is being developed for oral treatment of patients with respiratory diseases, such as asthma and chronic obstructive pulmonary disease.

Target healthy volunteer population and sample size

A total of 72 healthy male volunteers were to be randomised in the planned 9 cohorts (8 in each cohort). Since dosing was stopped after the 5th cohort, 40 healthy volunteers (8 in each cohort) were randomised into the study and analysed.

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

AZD8075: powder for oral suspension, batch numbers 08-013667AZ and 08-013693AZ, doses administered: 7 mg (Cohort 1), 20 mg (Cohort 2), 60 mg (Cohort 3), 120 mg (Cohort 4) and 240 mg (Cohort 5)

Placebo: oral suspension, batch number 08-013654AZ

Duration of treatment

Single dose.

Criteria for evaluation - pharmacokinetics (main variables)

C_{max}, t_{max}, AUC_{0-t}, AUC, $t_{1/2\lambda z}$, CL/F, V_z/F, MRT, A_e, CL_R

Criteria for evaluation - safety (main variables)

Adverse events (AEs), vital signs, body temperature, weight, electrocardiogram (ECG), laboratory variables

Statistical methods

The analyses of safety and tolerability and PK were summarised descriptively including tables, graphs and listings. Dose proportionality was analysed by using the power model approach.

Subject population

A total of 72 healthy volunteers were to be randomised in the planned 9 cohorts (8 in each cohort). Since dosing was stopped after the 5th cohort, 40 Caucasian male healthy volunteers (8 in each cohort) were randomised into the study. All healthy volunteers randomised to treatment completed the study. The safety and PK analyses included all randomised healthy volunteers. Overall, the treatment groups were well balanced with regards to demographic characteristics.

Summary of pharmacokinetic results

The predefined maximum exposure limits for AUC (1110 h*µmol/L) and C_{max} (141 µmol/L) were not reached during the study period. Following the highest dose (240 mg) the geometric mean AUC and C_{max} were 458 h*µmol/L and 32.2 µmol/L, respectively. The absorption of AZD8075 was fairly rapid and comparable between doses with a median t_{max} of 2.0 to 3.0 h. The geometric mean $t_{1/2\lambda z}$ and arithmetic mean MRT were comparable between doses: 22 to 27 h and 26 to 34 h, respectively. There were no indications of any dose-dependent changes in geometric mean CL/F (0.96 to 1.2 L/h), CL_R (0.15 to 0.24 L/h) or V_z/F (30 to 40 L).

Renal clearance constituted almost 20% of oral clearance, independently of the dose. The estimated renal clearance indicated AZD8075 to be actively eliminated via the kidneys by

tubular secretion, since CL_R (~0.2 L/h) exceeded glomerular filtration rate (GFR)*fraction unbound in plasma (ie, 7.5*0.04=0.03 L/h).

The plasma exposure of AZD8075 was considered compatible with linear kinetics after single oral doses of 7 to 240 mg.

Summary of safety results

There were no serious adverse events or discontinuations due to AEs in the study. The overall frequency in the AZD8075 groups was 60% (ranging between 33% and 100%) compared to 40% in the placebo group. The majority of AEs were of mild intensity and there were no AEs of severe intensity. There were no safety concerns in the study with respect to vital signs, body temperature, weight, physical examination or ECG assessments. Due to findings of turbid urine in 3 out of 6 healthy volunteers receiving 240 mg AZD8075, dosing in the study was stopped. There were no other safety concerns in laboratory variables.