AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5985
Study Code	D2300C00002
Edition Number	1
Date	17 December 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 AZD5985 in Healthy Male Subjects

Study Dates	First subject enrolled: 26 August 2009 Last subject completed: 12 October 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

AstraZeneca Clinical Pharmacology Unit at Sahlgrenska University Hospital, Gothenburg, Sweden

Publications

None at the time of writing this report.

Objectives

Primary objective

To assess the safety and tolerability of AZD5985 following administration of single ascending doses and to estimate the Maximum Tolerated Dose (MTD) if within the predefined exposure limits.

Secondary objectives

To characterise the pharmacokinetics (PK) of AZD5985 and provisionally assess the dose proportionality of the pharmacokinetics following administration of single ascending doses of AZD5985.

Exploratory objectives

- to obtain material for possible exploratory analyses of metabolites of AZD5985 in urine and plasma
- to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (i.e., distribution, safety, tolerability and efficacy) to AZD5985.

The exploratory data do not form part of the clinical study report.

Study design

This was a Phase I, randomised, double-blind, placebo-controlled, single centre study to assess the safety, tolerability and pharmacokinetics of AZD5985 following single ascending dose administration to healthy male subjects. Up to 9 dose cohorts were planned.

However, the study was terminated after the completion of the first dose cohort due to safety concern (unexplained urinary turbidity observed in 1 subject on AZD5985).

Target healthy volunteer population and sample size

Up to 72 healthy male subjects aged 18-45 years inclusive; 8 subjects per cohort (2 placebo and 6 active drug).

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

AZD5985 (free acid) was provided as a powder for oral suspension for reconstitution (batch no. 09-005240AZ). AZD5985 was administered as a single oral dose of 40 mg. Placebo was provided as oral suspension matching the AZD5985 suspension (batch no. 09-005132AZ).

Duration of treatment

Each healthy volunteer received 1 single dose of AZD5985 or placebo.

Criteria for evaluation - pharmacokinetics (main variables)

$AUC_{(0-t)}$ - area under plasma concentration-time curve from zero to time t, AUC - area under plasma concentration-time curve from zero to infinity, C_{max} - maximum plasma (peak) drug concentration , t_{max} - time to reach peak or maximum concentration following drug administration , $t_{1/2}$- apparent terminal elimination half-life, λ_z - terminal rate constant, CL/F - apparent oral clearance, V_z/F - apparent volume of distribution during terminal phase, MRT - mean residence time, Ae - cumulative amount of unchanged drug excreted into urine and CL_R- renal clearance

Criteria for evaluation - safety (main variables)

Adverse events, physical examinations, vital signs, body temperature, electrocardiograms (ECGs), safety laboratory variables

Statistical methods

All data were graphically illustrated and presented by descriptive statistics for each treatment group. Laboratory safety data were compared between active treatment and placebo. AEs were analysed by means of descriptive statistics and qualitative analyses. The PK parameters were derived using standard non-compartmental methods.

Subject population

A total of 40 subjects were enrolled at 1 study site. Of these, 8 were randomised into first cohort and received a single dose of study drug (AZD5985 or placebo). All randomised subjects completed the study. All 8 subjects were analysed for safety and the 6 subjects who received active treatment were included in the PK analysis set.

Summary of pharmacokinetic results

After administration of 40 mg AZD5985, the compound was rapidly absorbed and reached maximum plasma concentrations between 1 and 1.5 hours post-dose after administration of 40 mg AZD5985. The mean apparent elimination half-life was approximately 14 hours. The mean apparent plasma clearance, CL/F, was approximately 17 L/h after single 40-mg

dose and the mean apparent volume of distribution, Vz/F, was approximately 350 L. Following administration of 40 mg AZD5985, renal clearance constituted about 8% of the oral clearance.

Summary of safety results

There were no serious adverse events or discontinuations due to AEs in the study. AEs (7 events) with onset during or after dosing were reported by 3 subjects on AZD5985 and 1 subject on placebo. Headache was the most frequently reported AE (3 subjects). The majority of AEs were of mild intensity and there were no AEs of severe intensity. There were no clinically relevant findings with respect to safety laboratory variables, vital signs or ECG assessments. However, the Safety Review Committee decided to discontinue the study after the completion of the first dose cohort due to unexplained turbidity of urine observed in one subject 35 hours after administration of AZD5985.