AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5985
Study Code	D2300C00001
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An Exploratory Phase I, Single centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Pharmacokinetics of Increasing Oral Doses of AZD5985 in Healthy Male Volunteers

Study dates: First healthy volunteer enrolled: 26 November 2008
Last healthy volunteer completed: 23 March 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)

PAREXEL Clinical Pharmacology Research Unit, Northwick Park Hospital, Harrow, Middlesex, United Kingdom.

Publications

None at the time of writing this report.

Objectives

It was the objective of this exploratory clinical study to assess the pharmacokinetics of AZD5985 following administration of single increasing doses.

Study design

This was designed as an exploratory Phase I, first-time-in-man, double-blind, placebo controlled, randomised, single dose study in healthy male volunteers, conducted at a single centre. The study design was to allow a gradual escalation of dose with intensive safety monitoring to ensure the safety of the subjects.

Target healthy volunteer population and sample size

A total of 32 healthy male volunteers, aged 18 to 38 years, with a Body Mass Index of 21.3 to 28.8 kg/m^2. All 32 subjects randomised received investigational product (IP) according to the clinical study protocol, ie 6 subjects each received a single dose of 4 mg, 9 mg, 19 mg or 40 mg AZD5985 and in total 8 subjects received placebo.

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

AZD5985 was provided as a powder for oral suspension for constitution. Single oral doses of AZD5985 4 mg, 9 mg, 19 mg and 40 mg were administered (batch no.: 12.5 mg powder, 08-013691AZ; 250 mg powder, 08-013692AZ). Placebo was provided as oral suspension matching the AZD5985 suspension (batch no.: 08-013654AZ).

Duration of treatment

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

Criteria for evaluation - pharmacokinetics (main variables)

AZD5985 plasma concentrations and calculated pharmacokinetic (PK) parameters such as area under the plasma concentration-time curve from zero to the time t ($AUC_{(0-t)}$) and from zero to infinity (AUC), maximum plasma drug concentration after single dose administration (C_{max}), time to reach peak or maximum concentration following drug administration (t_{max}), apparent terminal elimination half-life ($t_{1/2}$), smallest disposition rate constant (λ_z), apparent oral clearance (CL/F), apparent volume of distribution during terminal phase (V_z/F) and mean residence time (MRT).

Statistical methods

No formal statistical hypothesis testing was performed. The analyses of PK was summarised descriptively including tables, listings and graphs, as appropriate. The AZD5985 plasma concentrations were used to calculate standard PK parameters after oral dosing. The PK parameters were described by dose level to make an initial assessment of dose linearity/proportionality. Data were evaluated by standard summary statistics and additional descriptive methods including individual data listings and plots of individual and group data.

Linear regression analysis was employed to assess dose proportionality over the dose range tested.

Subject population

Thirty-two healthy male volunteers were planned, randomised and completed this study; all 32 subjects were included in the safety analysis set and all 24 subjects who received active treatment were included in the PK analysis set. The healthy male volunteers were well balanced in terms of demographic and baseline characteristics across the treatment groups.

Summary of pharmacokinetic results

The λ_z-dependent PK parameters of the subjects receiving 4 mg AZD5985 were biased and were only derived for 3 out of 6 subjects. Therefore, dose-proportionality analysis was confined to data of the 9 mg, 19 mg and 40 mg dose levels.

The geometric mean plasma concentration-time profiles of AZD5985 (log-linear scale) after dosing of 4 mg to 40 mg are shown in Figure S1.

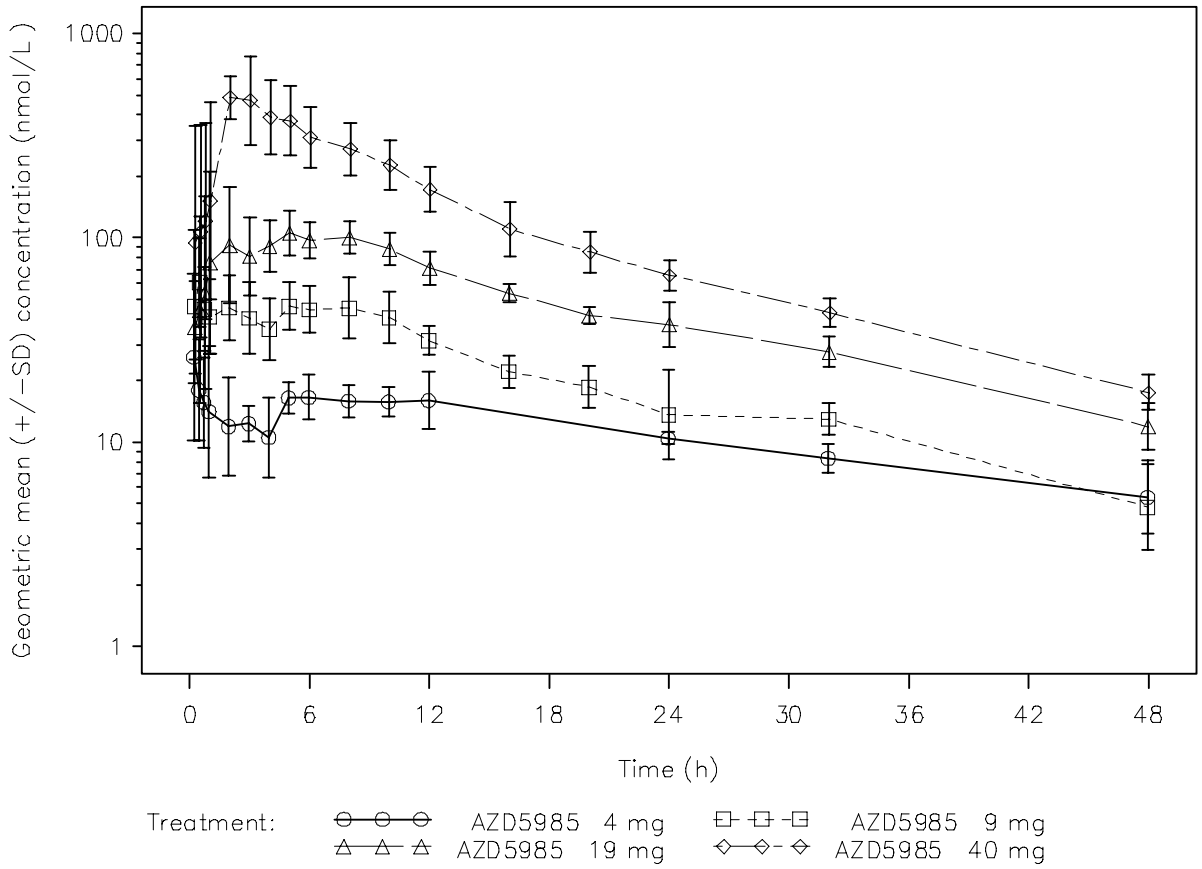
Maximum concentrations of AZD5985 in plasma were achieved at median t_{max} between 0.5 and 2.0 hours post-dose hours after administration of 9, 19 and 40 mg AZD5985. Elimination from plasma proceeded in an apparently mono-exponential fashion with a geometric mean $t_{1/2}$ at about 14 hours.

The maximum mean exposure to AZD5985 was observed after administration of 40 mg AZD5985 with a geometric mean C_{max} of 598.9 nmol/L and AUC of 6413.2 nmol.h/L.

The oral clearance, CL/F, ranged on average between 14.85 and 18.56 L/h and the volume of distribution during the terminal phase, V_z/F, ranged between 286.5 and 380.4 L after administration of 9, 19 or 40 mg AZD5985.

Dose-proportionality analysis showed a slope for the increase in AUC of 1.15 (95% CI: 0.957; 1.340) and for the increase in C_{max} of 1.33 (95% CI: 0.974; 1.678). The 95% CIs for the slopes of AUC and C_{max} both included unity, indicating that systemic exposure of AZD5985 (AUC and C_{max}) increased in a dose-proportional fashion across a dose range of 9 to 40 mg AZD5985.

Figure S1 **Geometric mean (+/- SD) plasma concentrations (nmol/L) of AZD5985 versus time for different treatments – log-linear scale (PK analysis set)**



The geometric mean for the 32 hours post-dose time point could not be directly calculated due to missing samples in the 40 mg treatment group in 5 out of 6 subjects. The depicted geometric mean plasma concentration at 32 hours post-dose is based on interpolated values of 5 subjects and a measured value of 1 subject.

Summary of safety results

Overall, only a few AEs were observed following single dose administration of AZD5985 at 4 to 40 mg. Of 4 AEs reported by 4 subjects across all dose groups, 2 AEs were considered by the Investigator to be related to the IP. These 2 AEs comprised the symptoms fatigue (4 mg AZD5985) and headache (40 mg AZD5985). All AEs were of mild intensity.

Evaluation of safety data including safety laboratory parameter, vital signs, 12-lead ECG recordings and physical examination did not raise any concerns.