AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1981
Study Code	D9831C00005
Edition Number	1
Date	18 March 2009

A Randomised, Placebo Controlled, Double Blind, Phase I Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single and Multiple Oral Doses of AZD1981 in Healthy Male Japanese and Caucasian Subjects

Study dates: First healthy volunteer enrolled: 02 August 2008
Last healthy volunteer completed: 17 October 2008

Phase of development: Clinical pharmacology (1)

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

Study centre

Publications

There were no publications at the time of writing this report.

Objectives

The primary objective of the study was to investigate the safety and tolerability of single and multiple-doses of AZD1981 administered orally to healthy Japanese subjects.

The secondary objectives of the study were to:

1. Investigate the pharmacokinetics (PK) of AZD1981 suspension in plasma and urine in healthy Japanese subjects.

2. Determine the single-dose PK of the AZD1981 tablet formulation in healthy Japanese and Caucasian subjects.

3. Compare the single-dose PK of the AZD1981 250 mg tablet formulation in healthy Japanese and Caucasian subjects.

The exploratory objectives of the study were to:

1. Collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes that may have influenced response, ie, distribution, safety, tolerability and efficacy of AZD1981 treatment.

2. Carry out pharmacodynamic (PD) determination of shape change of eosinophils following ex vivo stimulation by prostaglandin D_2 (PGD_2).

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

Study design

This was a randomised, placebo-controlled, double-blind, single-centre study, comprising a single-dose phase and a multiple-dose phase.

Single-ascending dose study design: Two cohorts of Japanese subjects received AZD1981 suspension or matching placebo on two separate occasions at two different dose-levels (15 mg and 1000 mg [Cohort A] and 75 mg and 2000 mg [Cohort B]). There was a minimum 2-week washout period between the two treatments.

Single-dose, crossover study design: One cohort of Japanese subjects received a single-dose of 250 mg AZD1981 suspension and a single-dose of 250 mg AZD1981 in tablet formulation,

or matching placebo, on two separate occasions (Cohort C). There was a minimum 5-day washout period between the two treatments.

Single-dose, parallel-group design: One cohort of Caucasian subjects received a single-dose of AZD1981 tablet or placebo (Cohort D).

Multiple-dose design: One cohort of Japanese subjects received multiple doses of either AZD1981 tablet or matching placebo twice daily (bid) on Day 1 (one dose only), Days 3 to 9, and on Day 10 (one dose only) (Cohort E).

Target healthy volunteer population and sample size

At least 45 healthy male subjects, comprising 36 Japanese subjects and 9 Caucasian subjects, were to be enrolled in the study.

In total, 47 healthy male subjects, comprising 38 Japanese subjects and 9 Caucasian subjects, were enrolled and analysed in the study.

Investigational product, dosage, mode of administration and batch numbers

In the single-dose phase, AZD1981 was administered as follows: Cohort A, 15 mg and 1000 mg doses of the suspension formulation; Cohort B, 75 mg and 2000 mg doses of the suspension formulation; Cohort C, 250 mg of the tablet and the suspension formulation; and Cohort D, 250 mg of the tablet formulation. AZD1981 was administered orally under fasted conditions. Subjects were served standardised breakfast, lunch and dinner, with a Japanese diet being provided for Japanese subjects.

In the multiple-dose phase, AZD1981 1000 mg bid was administered orally to Cohort E at least 30 minutes prior to consuming a meal. Subjects were served standardised breakfast, lunch and dinner, with a Japanese diet being provided for Japanese subjects.

Batch numbers: 08-013171AZ/DKE 430 (AZD1981 oral suspension 50 mg/g); 08-013149AZ/DKE 431 (placebo for AZD1981 oral suspension); 08-013110AZ/DKB417 (AZD1981 oral tablets 250 mg); 08-013112AZ/DKB418 (placebo for AZD 1981 oral tablets).

Comparator, dosage and mode of administration

The comparator was matching placebo suspension or tablets, and was administered orally.

Duration of treatment

In the single-dose phase, the total duration of treatment was 2 (1+1) days with a washout period between doses for Cohorts A, B and C, and 1 day for Cohort D. In the multiple-dose phase, the total duration of treatment for Cohort E was 9 days.

Criteria for evaluation - pharmacokinetics (main variables)

Maximum plasma drug concentration (C_{max}), time to maximum plasma drug concentration (t_{max}), area under the plasma drug concentration time curve (AUC) from time zero to 12 hours

post-dosing ($AUC_{[0-12]}$), AUC from time zero to 24 hours post-dosing ($AUC_{[0-24]}$), AUC from time zero to infinity ($AUC_{[0-\infty]}$), terminal half-life of drug in plasma ($t_{½}$), apparent terminal volume of distribution following oral drug administration (V_z/F), observed accumulation ratio (R_{ac}), apparent plasma clearance following oral drug administration (CL/F), renal clearance (CL_R), cumulative amount excreted in urine (A_e), fraction of dose excreted unchanged in the urine (F_e).

Criteria for evaluation – safety and tolerability (main variables)

The main safety variables were adverse events (AEs), clinical chemistry, haematology and coagulation evaluation, urinalysis, vital signs, and electrocardiogram (ECG).

Statistical methods

Descriptive statistics were used to evaluate data from this study.

Subject population

A total of 47 healthy male subjects (38 Japanese and 9 Caucasian subjects) were included in the study. Two Japanese subjects (Cohort C) voluntarily discontinued after completing Period 1. These subjects were replaced and were dosed during Period 2.

Demography and baseline characteristics were in line with the healthy population that was intended to be included in the study. Caucasian subjects had a higher mean age, height and weight compared with Japanese subjects. Japanese subjects in all dose groups were comparable in terms of demographics.

Summary of pharmacokinetic results

In Japanese subjects, following single-doses of 15, 75, 250, 1000 and 2000 mg AZD1981 (via suspension), t_{max} occurred between 2 and 3 hours. This was slightly lower (1 to 2 hours) during the multiple-dose (1000 mg bid AZD1981) phase. There was a reasonably dose-proportional increase in $AUC_{(0-12)}$ and C_{max} up to 250 mg with a less than proportional relationship up to 2000 mg. There was little difference in the exposure to 1000 mg and 2000 mg AZD1981 (suspension). Based on pre-dose trough data, steady state was reached within 2 to 3 days of multiple bid dosing of AZD1981 and accumulation was lower than expected (R_{ac} at Day 10 was 0.79).

A comparison of the pharmacokinetics between Japanese and Caucasians following a single 250 mg dose of AZD1981 (via tablet) indicated that, in most cases, volume of distribution and clearance were slightly lower, and half-life slightly shorter in Japanese compared with Caucasians.

Mean renal clearance of AZD1981 15 mg administered via suspension to the Japanese subjects and AZD1981 250 mg administered via tablet to the Caucasian subjects was similar, 8.47 L/h and 7.74 L/h, respectively. Renal clearance of AZD1981 was lower in all other Japanese dose groups, on average 1.11 - 3.80 L/h after single-dose (75 - 2000 mg) and 1.41 - 1.45 L/h (Days 9 or 10) at steady state.

Summary of safety results

In terms of safety, AZD1981 was well tolerated during single and multiple doses. The incidence of AEs was low (18 AEs overall) and of the 7 AEs the Investigator considered causally related, 5 AEs occurred in subjects dosed with AZD1981 (ie, atrioventricular block second degree [1 AE], ALT increased [2 AEs] and AST increased [2 AEs]). There were no deaths, serious adverse events (SAEs), discontinuations due to an AE (DAEs), or other significant AEs (OAEs).

The clinical laboratory evaluation showed some slight elevations in ALT, fasting glucose and raised AST for some healthy volunteers. These changes were seen both in subjects dosed with AZD1981 and subjects dosed with placebo.

There were no clinically relevant changes in other laboratory parameters, ECG or vital signs data.