AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1305
Study Code	D3191C00001
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A Single-centre, Single-blind, Randomised, Placebo-controlled, Phase I Study to Assess the Safety, Tolerability and Pharmacokinetics after Single Ascending Intravenous Doses of AZD1305 in Healthy Male Japanese Subjects

Study dates: First healthy subject enrolled: 19 July 2008
Last healthy subject completed: 27 October 2008

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)

This study was conducted at one study centre in Japan.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to evaluate the safety and tolerability of AZD1305 after single ascending intravenous doses of AZD1305 in healthy male Japanese subjects by assessment of adverse events (AEs), ECG variables, blood pressure (BP), pulse rate, physical examination, laboratory variables, body temperature and body weight.

The secondary objectives of the study were:

1. to evaluate the pharmacokinetics (PK) of AZD1305 after single ascending intravenous doses of AZD1305 in healthy male Japanese subjects by assessment of plasma and urine concentration of AZD1305 and PK variables of AZD1305.

2. to evaluate the relationship between dose, plasma concentration of AZD1305 and ECG variables.

3. to collect and store DNA samples (from all randomised subjects who give additional informed consent) for potential future exploratory research into genes which may influence drug response (efficacy, disposition, safety and tolerability) of AZD1305 (The data from this exploratory research are not reported in this CSR).

Study design

This was a single-centre, single-blind, randomised, (AZD1305:placebo; 2:1), placebo-controlled, single-dose phase I study where AZD1305 and placebo were administered as a 1 hour continuous iv infusion in escalating doses to healthy male Japanese subjects, aged 20 to 40 years.

Target healthy subject population and sample size

In total 36 healthy male Japanese subjects were randomized in the study. The subjects were divided into 4 different dose groups. In each group, 6 subjects received AZD1305 and 3 subjects received placebo. Each subject only belonged to one of the dose groups. The 9 subjects in each group were further divided into 2 groups of 3-subject group (Group A) and 6-subject group (Group B). On the first dosing day, subjects in Group A received the investigational product (2 subjects received AZD1305 and one subject received placebo). After 48-hour post-dose safety evaluation was completed in the subjects in Group A and they were discharged from the clinic, the subjects in Group B were admitted to the study centre (Day -1) and received the investigational product on the following day (4 subjects received

AZD1305 and 2 subjects received placebo). The dosing interval between subjects had to be at least 3 min.

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

AZD1305 (concentrate for solution for infusion 10 mg/mL, batch no H 1958-01-01-04) and placebo (NaCl 9 mg/mL solution for infusion, batch no H 0732-04-04-12) were given as a 1 h constant intravenous infusion. The final dose levels were 70 mg, 70 mg, 120 mg and 175 mg.

Duration of treatment

Single dose of AZD1305 or placebo

Criteria for evaluation - pharmacokinetics (main variables)

Plasma and urine concentrations of AZD1305, area under the plasma concentration versus time curve from time zero to the last quantifiable plasma concentration ($AUC_{(0-t)}$), area under the plasma concentration versus time curve from time zero to infinity (AUC), maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal half-life ($t_{½}$), total plasma clearance (CL), amount excreted unchanged in urine (Ae), renal clearance (CL_R), volume of distribution at steady state (V_{ss}) and fraction excreted unchanged in urine (fe).

Criteria for evaluation - safety (main variables)

Adverse events, ECG variables (RR, PQ (PR), QRS, QT, QTcF, QTcB and T-wave amplitude), blood pressure (BP), pulse rate, physical examination, laboratory variables, body temperature and body weight.

Statistical methods

All data were descriptively presented. Dose proportionality of AUC and C_{max} was investigated by a power model. The relationship between dose and/or plasma concentration of AZD1305 and ECG variables was exploratively evaluated.

Subject population

In total, 36 Japanese healthy male subjects were randomised into the study at 1 study site, each received 1 administration of study drug during the planned treatment visit. All healthy subjects randomised to treatment completed 1-hour continuous infusions of AZD1305 and the study. There were no protocol deviations that led to exclusion of data from the PK or safety analyses. The safety analysis included all randomised healthy subjects. In the study, no stopping criteria were met. However, QT prolongations, close to QTcF upper limit (550 ms) that was defined as one of the stopping criteria for dose escalation in the Clinical Study Protocol (CSP), were observed in 2 of 6 subjects who received AZD1305 at the 1st dose group (70 mg). The Safety Review Committee (SRC) decided that the same dose level (70 mg) should be given to a new group of subjects in order to further evaluate that dose level. Therefore, 12, 12, 6 and 6 subjects received placebo, 70 mg, 120 mg and 175 mg of AZD1305, respectively. Overall, the treatment groups were comparable with regards to demographic characteristics.

Summary of pharmacokinetic results

Peak plasma concentrations of AZD1305 were observed just before the end of infusion for the majority of subjects. After the end of infusion, the plasma levels of AZ1305 declined multi-exponentially with a mean terminal half-life ranging from 7.7 to 8.8 h across the 70 to 175 mg dose range, with an overall mean half-life of 8.4 h.

Similar mean CL across all doses were seen in the study with a mean CL ranging from 35.8 to 38.0 L/h. There was a tendency of decreasing mean V_{ss} with increasing dose, mean V_{ss} was 171 L for 70 mg and 134 L for 175 mg. The mean CL_R was 5.96 to 6.83 L/h, which means that CL_R accounted only for a small part of the total CL of AZD1305. The mean fraction excreted unchanged in urine after iv infusion of AZD1305 was 15.9 to 19.2%.

The analysis with power model indicated that AUC and C_{max} of AZD1305 increased proportionally with increasing iv doses.

Summary of pharmacokinetic/pharmacodynamic relationships (Not applicable)

Summary of safety results

AZD1305 demonstrated an acceptable safety and tolerability profile when administered as single iv doses of 70 mg to 175 mg to Japanese healthy male volunteers. There were no deaths, other serious adverse events, discontinuations due to AEs or other significant AEs in the study.

A dose-dependent increase in mean QTcF was observed with AZD1305. The maximum of the mean QTcF values were 482, 499 and 529 ms after start of infusion of 70, 120 and 175 mg AZD1305, respectively. These corresponded to mean absolute changes of 106, 137 and 161 ms from baseline, ie, prolongation of QTcF. The mean of the individual maximum QTcF values were 485, 508, and 534 ms after administration of 70, 120, and 175 mg AZD1305, respectively and the mean of the individual maximum increases from baseline were 109, 147 and 166 ms, respectively. The QTcF max occurred around the time point for stop of infusion. However, for some subjects QTcF max was observed 0.5-2 hours later.

Prolongations of PQ and QRS intervals were observed after administration of AZD1305. After administration of 175 mg AZD1305, there were mean relative changes in QRS from baseline (ie, prolongations) of up to 21 ms (at 1 h). The change in QRS increased with increasing doses of AZD1305. However, dose dependency in mean change of PQ was not observed.