AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD4017
Study Code	D2060C00007
Edition Number	1
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A randomized, single-blind, placebo-controlled, single-centre phase I study in healthy Japanese male volunteers to assess the safety, tolerability and pharmacokinetics of AZD4017 after single ascending oral doses

Study dates: First healthy subject enrolled: 20 December 2008
Last healthy subject completed: 30 April 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)

This study was conducted at one study center in Japan.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to assess the safety and tolerability of AZD4017 following administration of single ascending doses.

The secondary objective of this study was to evaluate the pharmacokinetics (PK) of AZD4017 and assess the dose proportionality of the PK following administration of single ascending doses of AZD4017.

Study design

This was a randomized, single-blind, placebo-controlled, single centre, phase I study to assess the safety, tolerability and pharmacokinetics of AZD4017 following single ascending dose administration to healthy male subjects.

Target healthy volunteer population and sample size

In total 56 healthy Japanese male subjects aged 20-45 years were randomized in the study. Each subject participated in one group. 8 subjects participated in each group. Within each group, 6 subjects were randomized to receive AZD4017 and 2 to placebo.

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

AZD4017 (20 mg/mL oral suspension, batch no. 08-013659AZ) and placebo (Matching placebo to AZD4017 oral suspension, batch no. 08-013658AZ) were given as single oral doses starting with a dose of 2 mg. Before proceeding to the next dose level, safety and PK data from the previous dose level(s) were evaluated by a Safety Review Committee (SRC). The planned maximum allowed dose in the study was 1100 mg. The final dose levels were 2 mg, 10 mg, 40 mg, 160 mg, 300 mg, 500 mg and 700 mg.

Duration of treatment

Each subject received a single dose of AZD4017 or placebo.

Criteria for evaluation - pharmacokinetics (main variables)

AZD4017 Plasma concentration and following PK parameters:

Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal half-life ($t_{1/2}$), area under the plasma concentration-time curve from time zero to the time of the last measurable

concentration ($AUC_{(0-t)}$) and from time zero to infinity (AUC) and the apparent oral plasma clearance (CL/F)

Criteria for evaluation - safety (main variables)

Adverse events (AEs), vital signs (blood pressure, pulse rate, body temperature), body weight, ECGs, safety laboratory variables (haematology, chemistry, urinalysis)

Statistical methods

No formal statistical hypothesis testing was performed. The analyses of safety and PK were summarised descriptively including tables, listings and graphs, as appropriate. In addition, dose proportionality of AUC and C_{max} was analysed using an ANOVA model.

Subject population

In total, 56 Japanese male healthy volunteers were randomized into the study at 1 study site, each received 1 administration of study drug during the planned treatment visit. During the study, SRC recommended that dose escalation should be stopped and the study be terminated according to stopping criteria for dose escalation after reviewing safety and PK data at dose level 7 (700 mg). For the decision, SRC considered that AUC in one subject reached exposure limit although there was no safety concern and it was within the allowance of dose escalation. In 56 randomized subjects, 42 received AZD4017 (6 in each group received AZD4017 2 mg, 10 mg, 40 mg, 160 mg, 300 mg, 500 mg and 700 mg, respectively) and 14 received placebo.

All healthy volunteers randomized to treatment completed the study. There were no protocol deviations that led to exclusion of data from the PK or safety analyses.

The safety analysis included all randomized healthy volunteers. Overall, the treatment groups were well balanced/comparable with regards to demographic characteristics.

Summary of pharmacokinetic results

After a single dose of AZD4017, the C_{max} was reached between 1.0 and 4.0 hours post-dose in the dose range 10 to 700 mg. For the 2 mg dose group, AZD4017 plasma concentrations were close to or below the lower limit of quantification at all time points and the estimated t_{max} ranged between 0.3 to 23h. Additionally, the C_{max} of AZD4017 tended to appear earlier with increasing dose.

The plasma concentration versus time profile for AZD4017 seemed to be bi-phasic with a similar profile over the dose range studied, although secondary plasma concentration peaks were occasionally present, making the profile difficult to characterize. In the evaluable subjects, the geometric mean $t_{1/2}$ ranged from 15.4 to 21.9 hours and the geometric mean CL/F ranged from 15.0 to 28.1 L/h within the dose of 10 to 700 mg. The AUC and C_{max} of AZD4017 increased approximately proportionally with dose when overviewing the dose range between 10 and 700 mg.

Summary of safety results

There were no SAEs, DAEs and OAEs in the study. In total, 2 AEs were reported. However these events were of mild intensity and judged to be unrelated to the study drug by the investigator. Overall, no safety or tolerability concerns were identified in this study up to the highest dose given.