AstraZeneca

**Clinical Study Report Synopsis**

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|---|---|
| Drug Substance | AZD0328 |
| Study Code | D0190C00008 |
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# A phase I, randomised, double-blind, placebo-controlled, parallel-group study to assess the safety, tolerability and pharmacokinetics of AZD0328 in healthy young Japanese and Caucasian male volunteers after oral single and multiple ascending doses

**Study dates:** First healthy volunteer enrolled: 16 June 2008
Last healthy volunteer completed: 13 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

The study was conducted at Richmond Pharmacology Ltd, St George's University of London, Cranmer Terrace, Tooting, London SW17 0RE, UK.

The first healthy volunteer was enrolled on to the study on 23 June 2008.

## Publications

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

## Objectives

### Primary objective

The primary objective was to assess the safety and tolerability of AZD0328 following single and multiple ascending doses of an orally administered solution of AZD0328 in healthy young Caucasian and Japanese male subjects.

### Secondary objectives

The secondary objectives were:

- To investigate PK of AZD0328 following single and multiple dosing of AZD0328 once daily in healthy young Japanese and Caucasian subjects.
- To explore ethnic differences in the PK of AZD0328 between healthy young Japanese and Caucasian subjects by a PK bridging analysis.
- To explore the impact of polymorphic variants of drug metabolising enzymes on pharmacokinetics and safety of AZD0328 in healthy young Japanese and Caucasian subjects.

## Study design

This was a phase I, randomised, double-blind, placebo-controlled, parallel-group single centre study that aimed to assess the safety and tolerability of AZD0328 after oral single and multiple ascending doses.

## Target healthy volunteer population and sample size

Healthy young male Caucasian and first generation Japanese subjects between 20 and 45 years of age were included in the study.

It had been planned to randomise a total of 48 healthy volunteers (24 Japanese and 24 Caucasian) into 3 dose levels with an option to add 2 additional dose levels. During the course of the study, 1 additional dose level was added leading to a total of 64 healthy subjects included in the study (32 Japanese and 32 Caucasian subjects randomised into 4 dose levels).

The study consisted of 4 dose levels for both Japanese and Caucasians (given the same dose) and consisted of 3 visits. A single dose of AZD0328/placebo was administered on Day 1 followed by once daily doses on Day 3-7 (subjects were not dosed on Day 2). The follow-up visit occurred between Days 7-10.

Each dose level consisted of 2 dose panels, one with Japanese and one with Caucasian subjects. Each dose panel included 8 subjects, 6 subjects received active drug and 2 subjects received placebo. Each panel employed a new cohort of subjects and each panel had reserves to compensate for any enrolment failures.

**Investigational product and comparator: dosage, mode of administration and batch numbers´**

AZD0328 was supplied to the study site as bulk supply using a drug in bottle formulation for constitution, 'AZD0328 powder for oral solution'. Each bottle of drug contained 100 mg of AZD0328 powder for oral solution. The AZD0328 was constituted in 0.9% w/v normal saline NaCl solution. Once constituted, the drug was used to dose the multiple subjects within a dose panel.

Batch number - AZD0328 (Powder for oral solution) - 08-013101AZ

Batch number – Placebo (Sodium Chloride) - WKL-141

It was planned that the starting dose for dose level 1 would be 0.075 mg and that the first 3 dose levels would not exceed the GMAD maximum tolerated dose (MTD) of 1.0 mg. Once doses up to the GMAD MTD had been explored and safety and tolerability was confirmed, then doses greater than 1 mg could be explored. The four dose levels investigated during this study were 0.075 mg, 0.23 mg, 1 mg, and 1.35 mg.

**Duration of treatment**

AZD0328 or matching placebo was administered to the subjects in the morning as an oral solution during fasting conditions. A single dose was administered on Day 1 followed by once daily doses on Day 3-7 (subjects are not dosed on Day 2).

**Criteria for evaluation - pharmacokinetics (main variables)**

Single dose profile: $C_{max}$, $t_{max}$, AUC, $AUC_{(0-24)}$, CL/F, $t_{1/2}$, Vz/F, Ae, CLR, $fe_{po}$

Multiple dose profile: $C_{ss,\,max}$, $t_{ss,\,max}$, $AUC_{\tau}$, CL/F, Ae, CLR, $fe_{po}$

The accumulation ratio: ($AUC_{\tau}/AUC_{0-24}$ and $C_{ss,max}/C_{max}$)

Time dependency: $AUC_{\tau,}/AUC$

### Criteria for evaluation - safety (main variables)

Adverse events, vital signs, laboratory variables, STAI, paper ECGs and 12-lead continuous digital ECGs including QT/QTc interval measurements.

### Statistical methods

Descriptive statistics were the main statistical technique. Placebo data for all subjects for each group were combined across all AZD0328 dose levels for summarising results. Generally, separate analyses of the two populations (Japanese and Caucasian) were done. However, in some cases data from both populations were modelled together, but then the stratification variable Ethnicity was to be added. The comparison between the Japanese and Caucasian populations were done depending on the statistical method chosen either by comparing the results from the separate analyses or by analysing the impact of the stratification variable Ethnicity.

### Subject population

In total, 64 healthy volunteers (32 Japanese healthy and 32 Caucasian healthy) were randomised into the study (4 dose levels) at a single site. It had been planned to randomise a total of 48 healthy volunteers (24 Japanese and 24 Caucasian) into 3 dose levels with an option to add 2 additional dose levels. Of the 64 enrolled subjects, 48 subjects received study drug and 16 subjects received placebo, in 6 administrations once daily on Day 1 and Days 3 to 7. Overall, both Japanese and Caucasian subjects were well balanced in terms of age. As expected, Caucasian subjects were heavier and had slightly higher BMI values compared to Japanese subjects.

There were 2 discontinuations during the study due to adverse events (DAEs) and both occurred in Caucasian volunteers.

Subject 47 (E0001014) on the 1 mg dose level was discontinued following a severe vasovagal attack on Day 1. Shortly after dosing the subject became pale and unresponsive for 30 seconds and suffered a witnessed vasovagal attack with a sinus arrest of 2 seconds. He recovered fully and spontaneously within 1 minute and his subsequent vital signs were within normal limits. The event was considered not to be related to treatment as judged by the Investigator. Subject 47 was included in both the safety and PK analysis sets.

Subject 64 (E0001155) on the 1.35 mg dose level was discontinued from the study on Day 4 (pre-dose) following repeated vomiting post dose on Day 1 and Day 3. The subject was administered treatment on both Day 1 and Day 3 and on both occasions started vomiting 2-3 minutes after dosing. Following withdrawal on Day 4 (he was not administered drug) the subject did not suffer any further vomiting episodes. The event was considered to be related to treatment as judged by the Investigator. Subject 64 was included in the safety analysis set but not in the PK analysis set.

**Summary of pharmacokinetic results**

Exposure to AZD0328 in terms of $C_{max}$ and $C_{ss,max}$ was considered to be dose proportional in the studied dose range (0.075 mg to 1.35 mg) whereas exposure in terms of AUC and $AUC_{\tau}$ increased somewhat more than in proportion to dose. The estimated increase when the dose is doubled resulted in approximately a 2.2-2.3 fold increase in AUC and $AUC_{\tau}$. When dose proportionality was analysed separately, Japanese subjects showed a similar pattern with $C_{max}$, $C_{ss,max}$ and AUC considered to be dose proportional and $AUC_{\tau}$ to increase slightly more than dose. However, Caucasian subjects were observed to be dose proportional for both $C_{max}$, $C_{ss,max}$ and AUC, $AUC_{\tau}$. Application of a power model demonstrated that there was no relationship between ethnicity and $C_{max}$, $C_{ss,max}$, AUC, and $AUC_{\tau}$.

Following administration of 0.075 mg to 1.35 mg AZD0328 renal excretion was an important route for elimination of AZD0328 in both healthy Japanese and Caucasian subjects. Japanese subjects were found to excrete a slightly greater amount of unchanged drug in urine compared to Caucasian subjects following administration of the 0.075mg and 1.35mg dose levels. Whereas, Caucasian subjects were found to have slightly higher values compared to Japanese subjects after receiving 0.23 mg and 1.00mg. Although all the mean values were below 100% and reflect the data as a whole, there were a few anomalous $fe_{po}$ values in excess of 100% during the course of the study for unexplained reasons. The accumulation of AZD0328 was similar for both Japanese and Caucasian subjects. Steady state was reached within 3 days and accumulation was limited (mean accumulation ratio up to 1.37 in Japanese subjects and 1.34 in Caucasian). There appeared to be an apparent time dependency observed in PK for the Japanese ethnic group.

Exposure to AZD0328 in terms of $C_{max}$ and $C_{ss,max}$ was considered to be dose proportional in the studied dose range (0.075 mg to 1.35 mg) whereas exposure in terms of AUC and $AUC_{\tau}$ increased more than in proportion to dose (Table S1). The estimated increase when the dose is doubled resulted in approximately a 2.2-2.3 fold increase in AUC and $AUC_{\tau}$. When dose proportionality was analysed separately, Japanese subjects showed a similar pattern with $C_{max}$, $C_{ss,max}$ and $AUC_{\tau}$ considered to be dose proportional and AUC to increase slightly more than dose. However, Caucasian subjects were observed to be dose proportional for both $C_{max}$, $C_{ss,max}$ and AUC, $AUC_{\tau}$.

Overall, there was little influence of CYP2D6 metabolism on $C_{max}$ and AUC and there was no real clinical significance (Table S2). As expected, UM had the smallest AUC followed by EM, PM and IM.

**Table S1 Slope parameter and dose-doubling factors with 95% CI, for AZD0328 (PK analysis set)**

| | | Beta and its 95% CI | | | When dose is doubled | | |
|---|---|---|---|---|---|---|---|
| **Parameter** | **Ethnicity** | **Estimate** | **Lower** | **Upper** | **Estimate** | **Lower** | **Upper** |
| $C_{max}$ | Japanese | 0.969 | 0.864 | 1.074 | 1.958 | 1.820 | 2.106 |
| $C_{ss,max}$ | Japanese | 1.030 | 0.951 | 1.110 | 2.042 | 1.933 | 2.158 |
| $C_{max}$ | Caucasian | 1.070 | 0.956 | 1.185 | 2.100 | 1.940 | 2.274 |
| $C_{ss,max}$ | Caucasian | 0.988 | -1.090 | 3.067 | 1.984 | 0.470 | 8.379 |
| UC | Japanese | 1.194 | 0.124 | 2.265 | 2.289 | 1.090 | 4.805 |
| $AUC_{\tau}$ | Japanese | 1.147 | 1.094 | 1.200 | 2.215 | 2.134 | 2.298 |
| AUC | Caucasian | 1.091 | 0.999 | 1.183 | 2.130 | 1.998 | 2.270 |
| $AUC_{\tau}$ | Caucasian | 1.074 | 0.988 | 1.161 | 2.106 | 1.983 | 2.236 |

**Table S2 Genotype difference results from the mixed model analysis for AZD0328 (PK analysis set)**

| Parameter | Variable | Geno Type | No | LS Mean | Ratio | Lower | Upper |
|---|---|---|---|---|---|---|---|
| $C_{max}$ (nmol/L) | PHENO | IM | 16 | 10.502 | 1.121 | 0.967 | 1.300 |
| | | PM | 4 | 8.586 | 0.917 | 0.702 | 1.197 |
| | | UM | 2 | 7.907 | 0.844 | 0.573 | 1.244 |
| | | EM | 69 | 9.368 | 1.000 | . | . |
| AUC (nmol*h/L) | PHENO | IM | 16 | 115.129 | 1.214 | 1.097 | 1.344 |
| | | PM | 4 | 114.516 | 1.208 | 1.006 | 1.451 |
| | | UM | 2 | 77.524 | 0.818 | 0.626 | 1.068 |
| | | EM | 69 | 94.803 | 1.000 | . | . |

## Summary of safety results

Overall, there were no major differences between Japanese and Caucasian subjects and the safety and tolerability was acceptable after repeated doses up to 1.35 mg and once daily for 7 days. Dose limiting AEs were not reached. Japanese subjects had higher incidences of gastrointestinal disorders compared to Caucasian subjects on AZD0328. This was most likely to be due to the high level of events reported by the Japanese subjects in the 1 mg group. Caucasian subjects were found to have higher incidences of gastrointestinal disorders compared to Japanese subjects on placebo. For both Japanese and Caucasian subjects the

majority of reported AEs were mild with no reported SAEs or OAEs. Two Caucasian subjects were discontinued from the study due to an adverse event.