**Clinical Study Report Synopsis**

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|---|---|
| Drug Substance | AZD8329 |
| Study Code | D2350C00007 |
| Edition Number | 1 |
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# A Randomised, Open-Label, 3-Way Cross-Over, Phase I Study in Healthy Subjects to Assess the Pharmacokinetics of AZD8329 after Single Doses of the Oral Solid Formulation and the Oral Solution

**Study dates:** First subject enrolled: 16 November 2010
Last subject last visit: 23 December 2010

**Phase of development:** Clinical pharmacology (I)

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

This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

## Publications

None at the time of writing this report

## Objectives and criteria for evaluation

### Table S1 Primary and secondary objectives and outcome variables

| Objectives | Outcome variables | Type |
|---|---|---|
| **Primary** | | |
| To compare the PK of AZD8329 for oral solution and oral solid formulation of AZD8329 | $C_{max}$, AUC, $AUC_{(0-t)}$, $t_{max}$, $t_{1/2\lambda z}$, and CL/F for AZD8329 oral solution and oral tablet (fasting) | Pharmacokinetic |
| **Secondary** | | |
| To explore the effect of food on the PK of AZD8329 for oral solid formulation of AZD8329 | $C_{max}$, AUC, $AUC_{(0-t)}$, $t_{max}$, $t_{1/2\lambda z}$, and CL/F for AZD8329 oral tablet (fasting and fed) | Pharmacokinetic |
| To investigate the safety and tolerability of AZD8329 when administered as 2 different oral formulations | Adverse events, laboratory variables[a], vital signs, electrocardiogram, and physical examination | Safety |
| **Exploratory[b]** | | |
| To collect and store optional blood samples for potential future exploratory genetic research aimed at identifying/exploring the genetic variations that may affect the PK, PD, safety, and tolerability related to AZD8329 | NA | Pharmacogenetic |
| To collect blood samples for mandatory exploratory genetic research aimed at identifying/exploring the genetic variations in CYP3A5 that may affect the PK of AZD8329 | NA | Pharmacogenetic |

a Laboratory variables are listed in Table 3 of the Clinical Study Protocol.
b Reported separate from the Clinical Study Report.

AUC: Area under the plasma concentration-time curve from zero extrapolated to infinite time; $AUC_{(0-t)}$: Area under the plasma concentration-time curve from zero to time of last quantifiable concentration; CL/F: Apparent oral clearance; $C_{max}$: Maximum plasma concentration; CSP: Clinical Study Protocol; CYP: Cytochrome P450; NA: Not applicable; PD: Pharmacodynamics; PK: Pharmacokinetics; $t_{1/2\lambda z}$: Terminal half-life; $t_{max}$: Time to reach maximum plasma concentration.

## Study design

This was a randomised, open-label, 3-way cross-over, Phase I study in 15 healthy male subjects to assess the pharmacokinetics (PK) of AZD8329 after single doses of the oral tablet formulation and the oral solution. The effect of food (Food and Drug Administration [FDA] breakfast) on the PK of the oral tablet formulation was also studied.

The study consisted of 5 visits. Subjects were screened at Visit 1; the investigational product was administered at Visits 2, 3, and 4, and follow-up assessments were performed at Visit 5.

All subjects were to receive single doses of all 3 of the following treatments at Visits 2, 3, and 4 (Periods 1, 2, and 3):

- Treatment A: 200 mg oral tablet (fasting)
- Treatment B: 200 mg oral solution (fasting)
- Treatment C: 200 mg oral tablet (fed)

## Target subject population and sample size

Fifteen healthy male subjects aged ≥18 to ≤45 years with a body mass index (BMI) of between 18 and 30 kg/m$^2$ (both inclusive).

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

**Table S2 Details of investigational product**

| Investigational product | Dosage form, strength, and route of administration | Manufacturer | Lot number | Batch number |
|---|---|---|---|---|
| AZD8329 | Tablet, 200 mg, orally | AstraZeneca | 10-005092AZ | 10-004359AZ |
| AZD8329 | Solution, 20 mg/mL, orally | AstraZeneca | 10-005097AZ | 10-003969AZ |
| | | | 10-005909AZ | 10-003969AZ |

## Duration of treatment

Single 200 mg oral tablet (fasting)

Single 200 mg oral solution (fasting)

Single 200 mg oral tablet (fed)

## Statistical methods

For the primary (ie, the difference between tablet and solution formulations under fasting conditions) and secondary objectives (ie, the difference between fed and fasting conditions for the tablet formulation) estimates of ratios of true geometric means (ie, analysis was performed with a linear mixed-effect analysis of variance [ANOVA] model on log scale and then back transformed) for the outcome variables with 2-sided 90% confidence intervals (CIs) using treatment, period, and sequence as fixed factors; and subject within sequence as random effect are presented.

Additional PK and safety variables are presented by descriptive statistics.

All subjects who received at least 1 dose of randomised investigational product and for whom any post-dose data are available were included in the safety analysis set.

All subjects who received investigational product and who had evaluable PK data appropriate for the comparison of interest (with no major protocol deviations or violations thought to significantly affect the PK of the investigational product) were included in the PK analysis set.

## Subject population

Enrolled: 15 subjects

Randomised: 15 subjects

Completed: 14 subjects

All subjects were male and the age range and BMI range of subjects were in accordance with the inclusion criteria. All 15 subjects were included in both the safety and the PK analysis sets.

## Summary of pharmacokinetic results

The statistical comparison indicated that AUC and area under the plasma concentration-time curve from zero to time of last quantifiable concentration ($AUC_{(0-t)}$) were 11% and 10% higher, respectively, when AZD8329 was given as oral solid formulation compared to when given as oral solution and the maximum plasma concentration ($C_{max}$) was 34% lower for the oral solid formulation (see Table S3). The absorption of AZD8329 was rapid when given as oral solution in fasting state with a median time to reach maximum plasma concentration ($t_{max}$) of 0.67 hours and the absorption was slower when the investigational product was given as the oral solid formulation with a median $t_{max}$ of 2.00 hours.

There was no marked difference in AUC or $AUC_{(0-t)}$ when AZD8329 oral solid formulation was given in fed compared to fasting state but $C_{max}$ was 15% lower during fed state (see Table S3). Absorption was delayed during the fed conditions and the median $t_{max}$ was approximately 4 hours.

Oral plasma clearance was low for all treatments with a geometric mean CL/F of 1.61 L/h for the tablet formulation in both the fed and fasting state and a geometric mean CL/F of 1.78 L/h for the solution. $t_{1/2\lambda z}$ was comparable for all treatments with a geometric mean ranging from 8.96 to 10.2 hours.

Inter-individual variability in the parameter estimates was low (coefficient of variation [CV%]: 13.7% to 22.6%). The extrapolated part of the total AUC was <8% and regression coefficient (Rsq) >0.90.

**Table S3 Statistical comparisons of AUC, $AUC_{(0-t)}$, and $C_{max}$ for each formulation and food condition (PK analysis set)**

| | | | Pairwise comparisons | |
|---|---|---|---|---|
| **Parameter (unit)** | **n** | **Pair** | **Ratio (%)** | **90% CI** |
| AUC (h*umol/L) | | | | |
| | 15 | Tablet, fasting / Solution, fasting | 110.61 | (103.94, 117.70) |
| | 14 | Tablet, fed / Tablet, fasting | 99.80 | (93.62, 106.38) |
| $AUC_{(0-t)}$ (h*umol/L) | | | | |
| | 15 | Tablet, fasting / Solution, fasting | 109.79 | (103.16, 116.84) |
| | 14 | Tablet, fed / Tablet, fasting | 100.43 | (94.21, 107.07) |
| $C_{max}$ (umol/L) | | | | |
| | 15 | Tablet, fasting / Solution, fasting | 66.08 | (59.70, 73.15) |
| | 14 | Tablet, fed / Tablet, fasting | 84.53 | (76.18, 93.81) |

CI: confidence interval.
Results based on a linear mixed model with treatment, period and sequence as fixed effects and subject within sequence as a random effect.

**Summary of safety results**

No deaths, discontinuations due to adverse events (DAEs), or other significant adverse events (OAEs) were reported. One serious adverse event (SAE), psychotic disorder, considered not causally related to the investigational product by the Investigator, was reported. All adverse events (AEs) reported were considered to be mild in intensity, with the exception of 1 moderate AE reported during the Treatment B wash-out period and 1 severe SAE reported during the Treatment C wash-out period. No causally related AEs, as judged by the Investigator, were reported.

Based on the reported AEs, laboratory measurements, vital signs, electrocardiogram (ECG) evaluations, and physical examinations, the 3 treatments administered in this study can be considered safe and well tolerated. No safety concerns were observed in this study.