AstraZeneca

**Clinical Study Report Synopsis**

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| Drug Substance | AZD9291 |
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# A Phase I, Open-label, Single-center, Sequential Design Study in Healthy Volunteers to Determine the Relative Bioavailability of Different Oral Formulations of AZD9291 and the Effect of Food

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| **Study dates:** | First subject enrolled: 09 October 2013<br>Last subject last visit: 04 June 2014 |
| **Phase of development:** | Clinical pharmacology Phase I |

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

## Study centre

This study was conducted at 1 study center, in Quintiles Phase I unit, Overland Park, Kansas, United States of America (USA).

## Objectives and criteria for evaluation

**Table S1 Objectives and outcome variables**

| Objective Priority | Type | Description | Outcome Variable Description |
|---|---|---|---|
| Primary | PK | The primary objective of the study is to determine the relative bioavailability of a 20 mg AZD9291 solution formulation and a 20 mg tablet formulation in relation to the 20 mg AZD9291 Phase I capsule formulation (Part A). | AZD9291 and AZ5104 and AZ7550 (AZD9291 metabolites) plasma concentrations were used to assess the following parameters, as applicable: AUC, AUC(0-72), AUC(0-t), Cmax, t1/2,λz, λz, tmax, tlag, CL/F (AZD9291 only), and Vz/F (AZD9291 only), and metabolite to parent ratio (calculated as AZ5104/ AZD9291and AZ7550/ AZD9291for both Cmax and AUC) (Part A and Part B)<br>The primary variables for assessments of relative bioavailability were AZD9291 Cmax, AUC, and/or AUC(0-t) (Part A).<br>The secondary variable for assessment of relative bioavailability was tmax (Part A) |
| Secondary | PK | To investigate the effect of food (high-fat breakfast) on the PK of AZD9291 (Part B). | The primary variables for assessment of food-effect were AZD9291 Cmax, AUC, and/or AUC(0-t) (Part B)<br>The secondary variable for assessment food-effect was tmax (Part B) |
| | | To investigate the safety and tolerability of AZD9291 in healthy volunteers (Part A and Part B). | AEs, vital signs, physical examinations, ophthalmologic examination, ECGs, and clinical laboratory assessments (Part A and Part B). |

AE: Adverse Event; AUC: Area under the concentration-time curve from zero to infinity; $AUC_{(0-t)}$: Area under the concentration-time curve from time zero to the last quantifiable concentration; $AUC_{(0-72)}$: Area under the concentration-time curve from time zero to 72 hours postdose; $C_{max}$: Maximum observed concentration; CSP: Clinical Study protocol; CL/F: Apparent plasma clearance; ECG: Electrocardiogram; PK: Pharmacokinetics; $t_{max}$: Time of maximum concentration; $t_{lag}$: Lag time before observation of quantifiable

analyte concentrations; $t_{1/2,\lambda z}$: Terminal half-life; $\lambda_z$: Terminal rate constant; $V_z/F$: Apparent volume of distribution

## Study design

This Phase 1 study was an open-label, 2-part (Part A and Part B) design.

### Part A

Part A was a 3-period, sequential design conducted in 16 healthy male volunteers aged 18 to 55 years (inclusive), where each volunteer received 20 mg of AZD9291 in the fasted state, in a fixed order as:

- Period 1: 20 mg AZD9291 capsule on Day 1
- Period 2: 20 mg AZD9291 solution on Day 1
- Period 3: 20 mg AZD9291 tablet on Day 1

There was a minimum 21-day washout between each dose.

Part A of the study consisted of 5 visits. The screening visit (Visit 1) was conducted within 28 days of Visit 2. Following fully written informed consent, healthy volunteers were enrolled into the study and screened for eligibility.

Each treatment period was defined as one visit. For all treatment periods (Visits 2, 3, and 4), volunteers reported to the study center on Day -1 (the day prior to dosing) and remained resident until the 48-hour postdose monitoring and evaluations were performed (Day 3). Volunteers returned to the study center for outpatient assessments on Days 4, 6, 8, 10, 15, and 22 (3, 5, 7, 9, 14, and 21 days postdose, respectively) of Visit 2, 3, and 4. A final follow-up visit (Visit 5) was performed 21 to 28 days after the last dose of AZD9291.

On Day 1 of Periods 1, 2 and 3 volunteers received a single, oral dose of 20 mg AZD9291 (as described) along with 240 mL water while in an upright position following an overnight fast of 10 hours. Volunteers remained fasted from food until 4 hours postdose. Apart from the water given at dosing, volunteers were fasted from water from 1 hour prior to dosing until 1 hour after dosing.

Blood samples for the determination of AZD9291 and metabolite (AZ5104 and AZ7550) concentrations were collected prior to investigational product administration and serially postdose through Day 22 in each treatment period. The PK profile from 0 to 72 hours postdose were assessed after Periods 1, 2 and 3, and any volunteer with exposures exceeding the PK limits in Period 1 or Period 2 was to be withdrawn and replaced if required to ensure 12 evaluable volunteers to complete the bioavailability assessment.

### Part B

Part B was a fixed-sequence, 2-period, design to assess the effect of food on AZD9291, conducted in 16 healthy male volunteers aged 18 to 55 years (inclusive).

This study consisted of 2 treatment periods during which the following treatments were administered.

- Period 1: A single 20 mg oral AZD9291 dose under fasted conditions on Day 1
- Period 2: A single 20 mg oral AZD9291 dose under fed (high-fat breakfast) conditions on Day 1

The 2 treatment periods were separated by a washout of at least 21 days (from the first AZD9291 administration in Period 1 until the first AZD9291 administration in Period 2).

Based on the bioavailability results from Part A, Part B was conducted with the tablet formulation. All volunteers received a single, oral dose of 20 mg AZD9291 tablet along with 240 mL water while in an upright position following an overnight fast of 10 hours in Period 1, and a single oral dose of 20 mg AZD9291 tablet along with 240 mL water in the fed state (following a high-fat breakfast) in Period 2.

Part B consisted of 4 visits. The screening visit (Visit 1) was conducted within 28 days of Visit 2. Following fully written informed consent, volunteers were enrolled into the study and screened for eligibility.

Each treatment period was defined as one visit. For treatment periods (Visits 2 and 3), volunteers reported to the study center on Day -1 (the day prior to dosing) and remained resident until the 48-hour postdose monitoring and evaluations performed (Day 3). Volunteers returned to the study center for outpatient assessments on Days 4, 6, 8, 10, 15, and 22 (3, 5, 7, 9, 14, and 21 days postdose, respectively) of Visit 2 and 3. A final follow-up visit (Visit 4) was performed 21 to 28 days after the last dose of AZD9291 in Period 2.

On Day 1 of fed period, volunteers began the recommended meal 30 minutes prior to administration of the investigational product. The breakfast was consumed within 30 minutes and volunteers consumed the entire meal. A single dose of 20 mg AZD9291 was administered 30 minutes after the start of the meal along with 240 mL water. No food was allowed for at least 4 hours postdose. Water was withheld from 1 hour before until 1 hour after dosing, apart from the water consumed at investigational product administration.

Apart from the high-fat breakfast on Day 1 of Period 2, volunteers received standardized meals scheduled at the same time during the study.

Blood samples for the determination of AZD9291 and metabolite (AZ5104 and AZ7550) concentrations were collected prior to investigational product and serially postdose. The PK profile from 0 to 72 hours postdose were assessed and any volunteer with exposures exceeding the PK limits was to be withdrawn and replaced if required to ensure 12 evaluable volunteers complete Part B (food-effect).

**Target subject population and sample size**

The target population is healthy male volunteers between the ages of 18 and 55 years, inclusive, with a body mass index between 19.0 and 30.0 kg/$m^2$ and body weight at least 50 kg and no more than 100 kg.

**Part A**:

A total of 16 healthy male volunteers were enrolled in Part A of this study (relative bioavailability). Although 16 healthy volunteers completed the treatments and all the study data being collected for the volunteers, only 14 healthy volunteers completed the study. Two healthy volunteers, Volunteer E0001014 and Volunteer E0001025 were prematurely withdrawn from the study as they were lost to follow-up, though they completed all the required treatments.

**Part B**:

A total of 16 healthy male volunteers were enrolled in Part B of this study (food-effect); however only 14 healthy volunteers completed the treatments and the study. One healthy volunteer, Volunteer E0001049, was discontinued from the investigational product due to an AE and Volunteer E0001057 was lost to follow-up. Both volunteers who were prematurely withdrawn from the study completed the treatment after participating in the fasted period and did not receive treatment in fed period.

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

During each treatment period of Part A, a single dose of 20 mg AZD9291 was administered in the fasted state as either a capsule formulation, as a solution formulation, or as a tablet formulation, with 240 mL of water. During Part B, a single dose of 20 mg AZD9291 tablet formulation was administered in both the fasted and fed state. The selection of the tablet formulation for Part B was based on the relative bioavailability results of Part A.

**Duration of treatment**

**Part A**

The duration of volunteer participation was approximately 14 weeks. This included a 28-day screening period, 3 treatment periods, and a final follow-up visit. There was a minimum of 21-day washout between doses in each treatment period. A final follow-up visit was to take place between 21 and 28 days after the last dose of AZD9291 (up to7 days after completion of Period 3). During the study, each volunteer received single, 20 mg doses of AZD9291 on 3 separate occasions.

**Part B**

The duration of volunteer participation was approximately 11 weeks. This includes a 28-day screening period, 2 treatment periods separated by a minimum of 21-day washout between

doses, and a final follow-up visit. A final follow-up visit was to take place between 21 and 28 days after the last dose of AZD9291 (up to 7 days after completion of Period 2). During the study, each volunteer received a single, 20 mg dose of AZD9291 on 2 separate occasions.

**Statistical methods**

**Part A**

Inferential statistical analyses were performed on the pharmacokinetic data only. The bioavailability of the 20 mg solution and a 20 mg tablet relative to the 20 mg capsule was assessed using the primary pharmacokinetic variables, $C_{max}$, AUC, and/or $AUC_{(0-t)}$, of plasma AZD9291. These endpoints were natural log-transformed and analyzed using a linear mixed effects model. The difference in treatment (formulation) means was determined along with its associated 90% confidence interval and back-transformed to give an estimate of the relative bioavailability. The results of this analysis are presented in terms of geometric means for each treatment, the relative bioavailability (ie, the ratio of the treatment formulation geometric means) and its 90% confidence interval. Similar statistical analyses were performed for AZ5104 and AZ7550. The intent of this inferential analysis was to obtain an estimate of the relative bioavailability of the solution and tablet formulation when compared to the capsule formulation. Although this study was not powered to meet the criteria of a formal bioequivalence study, point estimates and 90% CIs comparing the solution and tablet formulation to the reference capsule formulation were related to the 80.00 to 125.00% bioequivalence criteria for reference purposes throughout this report.

The above treatment comparisons were also performed for $t_{max}$ as the secondary analyses. Nonparametric methods were used to compute median $t_{max}$ for each treatment, median $t_{max}$ difference, and associated 90% confidence interval for the median difference. The data were analyzed by a Wilcoxon Signed-Rank Test. The 90% confidence interval was calculated using the method of Hahn and Meeker.

**Part B**

For the investigation of the effect of food, the primary PK variables AUC and/or $AUC_{(0-t)}$ and $C_{max}$ of plasma AZD9291 were analyzed. These endpoints were natural log-transformed and analyzed using a linear mixed effects model with fixed effect for treatment and random effect for subject. The difference in treatment means was determined along with its associated 90% confidence interval (CI) and back-transformed to give an estimate of the effect of food on the exposure of AZD9291. The results of this analysis were presented in terms of geometric means for both treatments, the effect of food on the exposure of AZD9291 (ie, the ratio of the treatment geometric means) and its 90% confidence interval. Similar statistical analyses were performed for AZ5104 and AZ7550. The intent of this inferential analysis was to obtain an estimate of the effect of food on AZD9291 and metabolite (AZ5104 and AZ7550) exposure. Although this study was not powered to meet the criteria of a formal food effect study, point estimates and 90% CIs comparing the tablet formulation administered with a high fat meal and under fasted conditions were related to the 80.00 to 125.00% bioequivalence criteria for reference purposes throughout this report.

The above treatment comparisons were also performed for $t_{max}$ as the secondary analyses. Nonparametric methods were used to compute median $t_{max}$ for each treatment, median $t_{max}$ difference, and associated 90% confidence interval for the median difference. The data were analyzed by a Wilcoxon Signed-Rank Test. The 90% confidence interval was calculated using the method of Hahn and Meeker.

**Subject population**

**Part A**:

All volunteers were healthy males aged 21 to 53 years (mean age of 32 years) with a mean BMI of 25.95 $kg/m^2$, in accordance with the inclusion criteria. Most of the healthy volunteers were Caucasian in ethnicity (87.5%). Seven volunteers (43.8%) out of the 16 volunteers who were enrolled in the study were of Black or African American in origin.

**Part B**:

All volunteers were healthy males aged 21 to 55 years (mean age of 34 years) with a mean BMI of 26.55 $kg/m^2$, in accordance with the inclusion criteria. Most of the healthy volunteers were Caucasian in ethnicity (87.5%). There were 5 volunteers (31.3%) of Black or African American origin who were enrolled in the study.

**Summary of pharmacokinetic results**

**Part A (Relative bioavailability)**

**AZD9291**

Statistical comparisons of AZD9291 exposure parameters (AUC and $C_{max}$), the primary endpoints for the assessments of relative bioavailability, as well as $t_{max}$ values between formulations are summarized in Table S2.

No difference in AZD9291 AUC and $C_{max}$ was observed when comparing the solution and the tablet to the reference capsule as the 90% confidence intervals of the geometric least squares mean ratios for these parameters were contained within the equivalence limits of 80% to 125%.

Median $t_{max}$ for the solution and tablet were not statistically different compared to the median $t_{max}$ for the reference capsule.

**Table S2 Statistical comparison of key AZD9291 pharmacokinetic parameters by formulation-Part A**

| | | | | Comparisons to Treatment A | | |
|---|---|---|---|---|---|---|
| | **Treatment[a]** | **n** | **Geometric LS Mean** | **Ratio** | **(%)** | **90% CI** |
| AUC | Capsule (Treatment A) | 16 | 1516 | | | |
| (nM*h) | Solution (Treatment B) | 16 | 1481 | B/A | 97.73 | (87.07, 109.70) |
| | Tablet (Treatment C) | 15 | 1584 | C/A | 104.50 | (92.85, 117.61) |
| $C_{max}$ | Capsule (Treatment A) | 16 | 31.64 | | | |
| (nM) | Solution (Treatment B) | 16 | 30.40 | B/A | 96.07 | (84.04, 109.82) |
| | Tablet (Treatment C) | 16 | 31.60 | C/A | 99.88 | (87.37, 114.17) |

| | | | | Comparisons to Treatment A | | | |
|---|---|---|---|---|---|---|---|
| | **Treatment[a]** | **n** | **Median** | **Pair** | **Median Difference** | **90% CI[b]** | **P-value[c]** |
| $t_{max}$ | Capsule (Treatment A) | 16 | 6.00 | | | | |
| (h) | Solution (Treatment B) | 16 | 6.00 | B-A | 0.00 | (-2.00, 0.00) | 0.3750 |
| | Tablet (Treatment C) | 16 | 6.00 | C-A | 0.00 | (0.00, 0.00) | 0.7188 |

CI confidence intervals; LS least-squares

[a] Treatment A: 20 mg AZD9291 capsule; Treatment B: 20 mg AZD9291 solution; Treatment C: 20 mg AZD9291 tablet

[b] Median difference and confidence intervals calculated using the Hahn and Meeker method

[c] P-value for treatment difference in median $t_{max}$ calculated using the Wilcoxon signed rank test

### AZ5104 and AZ7550

Each of the metabolites, AZ5104 and AZ7550, amounted to less than 8% of AZD9291 exposure and were identified as minor circulating species in plasma in Part A.

No difference in AZ5104 AUC and $C_{max}$ was observed when comparing the solution and the tablet to the reference capsule as the 90% confidence intervals of the geometric least squares mean ratios for these parameters were contained within the equivalence limits of 80% to 125%.

For the metabolite AZ7550, the point estimates for the geometric least squares mean ratios for AUC and $C_{max}$ comparing the solution and tablet formulations to the reference capsule fell within the limits of 80% to 125%. For the solution formulation, the 90% confidence intervals for these ratios were not contained within these equivalence limits with the lower bound being approximately 76% and 74% for AUC and $C_{max}$, respectively. For the tablet formulation, the 90% confidence interval for the AUC ratio was contained within these equivalence limits while the lower bound of the 90% CI for $C_{max}$ was approximately 77%.

## Part B (Effect of high-fat meal)

### AZD9291

Statistical comparisons of AZD9291 exposure parameters (AUC and $C_{max}$), the primary endpoints for the assessment of the effect of a high fat meal, as well as associated $t_{max}$ values are summarized in Table S3.

Administration of the tablet with a high fat meal increased AZD9291 AUC and $C_{max}$ approximately 19% and 14%, respectively, compared to fasted conditions. Administration of the tablet with a high fat meal did not affect median $t_{max}$ when compared to fasted conditions.

**Table S3 Statistical comparison of key AZD9291 pharmacokinetic parameters after administration of the AZD9291 20-mg tablet in the fasted and fed state -Part B**

| | | | | Comparison of Fed vs Fasted | |
|---|---|---|---|---|---|
| | **Treatment[a]** | **n** | **Geometric LS Mean** | **Ratio (%)** | **90% CI** |
| AUC | Fasted (Treatment A) | 16 | 1419 | | |
| (nM*h) | Fed (Treatment B) | 14 | 1691 | 119.14 | (110.74, 128.17) |
| $C_{max}$ | Fasted (Treatment A) | 16 | 29.29 | | |
| (nM) | Fed (Treatment B) | 14 | 33.36 | 113.89 | (102.36, 126.71) |

| | | | | Comparison of Fed vs Fasted | | |
|---|---|---|---|---|---|---|
| | **Treatment[a]** | **n** | **Median** | **Median Difference** | **90% CI[b]** | **P-value[c]** |
| $t_{max}$ | Fasted (Treatment A) | 16 | 6.00 | | | |
| (h) | Fed (Treatment B) | 14 | 6.00 | 0.00 | (-2.00, 2.00) | 1.0000 |

CI confidence intervals; LS least-squares

[a] Treatment A = 20-mg AZD9291 tablet (fasted); Treatment B = 20-mg AZD9291 tablet (fed – high-fat meal)

[b] Median difference and confidence intervals calculated using the Hahn and Meeker method

[c] P-value for treatment difference in median $t_{max}$ calculated using the Wilcoxon signed rank test

**AZ5104 and AZ7550**

Administration of the tablet with a high-fat meal had no effect on AZ5104 AUC and $C_{max}$ or AZ7550 AUC compared to fasted conditions. Administration of the tablet with a high-fat meal decreased AZ7550 $C_{max}$ approximately 16% compared to fasted conditions. Exposure to each metabolite, based on metabolite to parent ratios for AUC and $C_{max}$, amounted to less than 10% of exposure to AZD9291 and appeared to be independent of meal conditions.

**Summary of safety results**

**Part A**:

- No deaths, SAEs, or DAEs were reported during Part A of the study
- Overall, no significant trends were observed in the AEs reported across treatments in Part A of the study
- Most of the AEs were considered to be mild in intensity. All AEs were considered not related to the investigational product and most of the AEs resolved
- The highest percentage of AEs reported belonged to the SOC infections and infestations (31.3%). Influenza was reported by 3 healthy volunteers (18.8%)

- No trends were observed over time, in mean or median values in hematology, biochemistry, and urinalysis parameters and vital signs, for any healthy volunteer
- No relevant trends were observed in the 12-lead ECG readings across the treatments and no trends in mean HR, QRS, QTcF, or PR intervals were observed in this study
- Abnormal physical examination findings were reported; however all but 2 (lichen striatus and muscular weakness) abnormal findings were considered to be not clinically significant

**Part B**:

- No deaths or SAEs were reported in this study. Volunteer E0001049 (during fasted period), had an AE of increased ALT, which led to discontinuation of the investigational product. The AE was considered to be mild in intensity and was considered to be related to the investigational product
- Overall, at least 1 AE was reported for 6 volunteers (37.5%) out of 16 volunteers enrolled, across the treatments in Part B of the study
- Most of the AEs were considered to be mild in intensity and All AEs, except 1 (increased ALT), were considered not related to the investigational product. All AEs resolved
- The highest percentage of AEs reported belonged to the SOC infections and infestations (12.5%). Upper respiratory tract infection was reported for 2 healthy volunteers (12.5%), during fasted period
- No trends were observed over time, in mean or median values in hematology, biochemistry, and urinalysis parameters and vital signs, for any healthy volunteer
- No relevant trends were observed in the 12-lead ECG readings across the treatments and no trends in mean HR, QRS, QTcF, or PR intervals were observed in this study
- No clinically significant abnormal physical examination findings were reported