AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9291
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An Open-label, Randomised, Phase I Study to Determine the Effect of Food on the Pharmacokinetics of Single Oral Doses of AZD9291 in Patients with EGFRm Positive NSCLC whose Disease has Progressed on an EGFR TKI

Study dates: First patient enrolled: 14 November 2014
Last patient last visit: 23 March 2015 (Part A)

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

This study was performed at 12 sites across Asia and Western Europe.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective		Outcome Variable
Priority	**Description**	**Description**
Primary	To investigate the effect of food on the exposure of AZD9291 (AUC_{0-72} and C_{max}) following oral dosing of the tablet formulation in patients with EGFRm+ NSCLC following disease progression on an EGFR TKI.	Maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from zero to 72 hours (AUC_{0-72}).
Secondary	To characterise the effect of food on the PK of AZD9291 metabolites (AZ5104 and AZ7550) following oral dosing of the tablet formulation in patients with EGFRm+ NSCLC following disease progression on an EGFR TKI.	AZD9291: Area under the plasma concentration-time curve from zero to 120 hours (AUC_{0-120}), area under the plasma concentration-time curve from zero to the last quantifiable time point (AUC_{0-t}), area under the plasma concentration-time curve from zero to infinity (AUC), time to reach maximum plasma concentration (t_{max}), terminal half-life ($t_{1/2\lambda z}$), terminal rate constant (λ_z), apparent plasma clearance (CL/F) and apparent volume of distribution (V_z/F). AZ5104 and AZ7550: C_{max}, AUC_{0-72}, AUC_{0-120} AUC_{0-t}, AUC, t_{max}, $t_{1/2\lambda z}$, and λ_z
Secondary	To investigate further the safety and tolerability of daily oral doses of AZD9291 in patients with EGFRm+ NSCLC (Part B).	Assessment of adverse events, graded by CTCAE, physical examination, vital signs (blood pressure, pulse rate, body temperature), standard 12 lead electrocardiogram, echocardiogram/Multiple Gated Acquisition Scan (for assessment of left ventricular ejection fraction), ophthalmic examination, and evaluation of laboratory parameters (clinical chemistry, haematology, urinalysis)
Exploratory	To perform genetic research in the AZD9291 clinical pharmacology development programme to explore how genetic variations may affect the clinical PK of AZD9291. To provide data to allow analysis using population PK approaches.	None defined. The results of any further analyses will be reported separately and are not included in this Clinical Study Report.

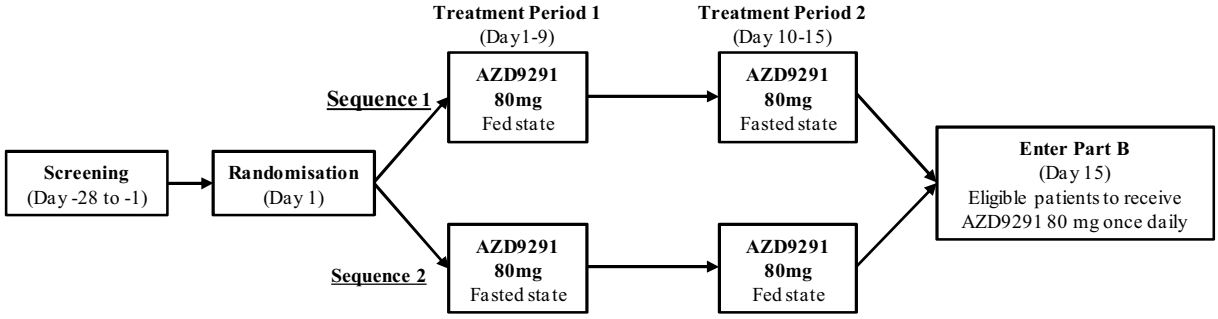
CTCAE Common Terminology Criteria for Adverse Events, EGFR(m+) epidermal growth factor receptor (mutation positive), NSCLC non small cell lung cancer, PK pharmacokinetics, SAP statistical analysis plan, TKI tyrosine kinase inhibitors

Study design

This was a 2-part study (Parts A and B) in patients with epidermal growth factor receptor mutation positive (EGFRm+) non-small cell lung cancer (NSCLC) whose disease had progressed following treatment on an EGFR-Tyrosine kinase inhibitor (TKI). Part A determined the effect of food on the pharmacokinetics (PK) of AZD9291. Part B allows patients further access to AZD9291 after the PK phase and will provide for additional safety data collection. Part B was of 12 months duration from the date the last patient entered this part of the study. Data are presented for Part A of the study only. Data from Part B will be presented in an addendum to the Clinical Study Report.

Part A of this study was a randomised, open-label, 2-treatment period crossover study in which patients each received a single oral dose of AZD9291 (1 x 80 mg tablet) at breakfast time in each of 2 treatment periods (once immediately following a high-fat meal [Fed], and once in the fasted state [Fasted]), with a washout period of 9 days between doses (Figure S1).

Figure S1 Overall study plan



Note: Assessments for pharmacokinetic analyses were performed in Part A, and for safety assessments in Parts A and B. Patients who withdrew or discontinued completed a follow up assessment. Part B was to be of 12 months duration from the date the last patient entered Part B of the study.

Target subject population and sample size

The target population comprised male and female patients aged 18 years or over with EGFRm+ NSCLC that had progressed following prior therapy with an approved EGFR TKI agent. Patients had to have confirmation of histological or cytological NSCLC and Eastern Cooperative Oncology Group Performance Status of 0-1.

In study D5160C00005, a within-subject coefficient of variation (%CV) of 20% and 23% was observed for Area under the plasma concentration time curve (AUC) and maximum plasma concentration (C_{max}), respectively, in healthy normal subjects. As no data was available on the variability of these PK parameters in patients, it was be assumed that the within-patient %CV for AZD9291 in both AUC and C_{max} was 34%, an approximate 50% increase from that observed in healthy normal subjects. A 6% change in the exposure for AZD9291 when given with food was also assumed. With 30 evaluable patients, the experiment-wide power for the 2-sided 90% confidence interval of the geometric mean ratios (Fed/Fasted) being completely contained within 70 to 143% was 90% (95% power for each parameter).

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

AZD9291 40 mg oral tablet [redacted] and AZD9291 80 mg oral tablet [redacted] A 40 mg tablet was provided to support dose reduction in Part B (data to be presented in an addendum to this CSR) and was not used in Part A.

Duration of treatment

In Part A, patients received 2 single doses of AZD9291 (80 mg tablet), 1 tablet in each of 2 treatment periods (Day 1 and Day 10 of Part A). Patients participating in Part B received continuous daily dosing of AZD9291 80 mg (tablet) for the duration of their participation.

Statistical methods

For AZD9291, natural log-transformed AUC from zero to 72 h (AUC_{0-72}) and C_{max}, were compared between treatments using a mixed-effects analysis of variance model with sequence, period, and treatment as fixed effects and patient nested within sequence as a random effect. Estimates of the mean difference between treatments (Fed - Fasted) and corresponding 90% confidence intervals (CIs) were calculated. The mean differences and the CIs were back transformed to the original scale in order to give estimates of the ratios (Fed versus Fasted) and the associated 90% CIs. Additionally, back-transformed geometric means together with 95% CIs for AUC_{0-72} and C_{max} were estimated and presented.

No effect on the PK of AZD9291 after given with food was concluded if the 2-sided 90% CIs for the ratios of AZD9291 AUC_{0-72} and C_{max} were both within the range of 70% to 143%.

AZ5104 and AZ7550, natural log-transformed AUC_{0-72} and C_{max}, were compared between treatments using a fixed-effects analysis of variance model with treatment as fixed effect. Estimates of the mean difference between treatments (Fed - Fasted) and corresponding 90% CIs were calculated. The mean differences and the CIs were back transformed to the original scale in order to give estimates of the ratios (Fed versus Fasted) and the associated 90% CIs. Additionally, back-transformed geometric means together with 95% CIs for AUC_{0-72} and C_{max} were estimated and presented. Only data from Period 1 were utilised in these analyses. Period 2 data were not included because most of the patients had Period 2 pre-dose concentrations that exceeded 10% of C_{max}.

For AZD9291, analyses of t_{max} were performed using the Wilcoxon Signed Rank Test. The Hodges-Lehmann median estimator of the difference in treatments (Fed Fasted) and 90% CIs were presented. AZ5104 and AZ7550 were not analysed due to insufficient data in Period 2.

For AZD9291, AZ5104 and AZ7550, the above mixed-effects analysis of variance model and t_{max} analyses were also performed as supplemental analyses which included data for patients meeting carry-over exclusion criterion in Period 2. For these supplemental analyses, the analysis of variance model defined previously for AZD9291 AUC_{0-72} and C_{max} was used for

all 3 analytes. Similarly, analysis of t_{max} for all 3 analytes followed the methodology described for AZD9291 above.

For AZD9291, AZ5104 and AZ7550, exploratory analyses were carried out utilising data in the PK analysis set in Period 1 and exploratory carry-over adjusted PK parameters from Period 2. Natural log-transformed AUC_{0-72} and C_{max}, were compared between treatments using a mixed-effects analysis of variance model with sequence, period, and treatment as fixed effects and patient nested within sequence as a random effect. Estimates of the mean difference between treatments (Fed - Fasted) and corresponding 90% CIs were calculated. The mean differences and the CIs were back-transformed to the original scale in order to give estimates of the ratios (Fed versus Fasted) and the associated 90% CIs. Additionally, back-transformed geometric means together with 95% CIs for AUC_{0-72} and C_{max} were estimated and presented.

Subject population

In this study, 43 patients were enrolled; of these, 38 were randomised at 12 sites in 4 countries: Spain (4 sites), United Kingdom (3 sites), France (3 sites) and South Korea (2 sites). Overall, patients had a mean age of 62.7 years ([redacted]), mean weight of 66.6 kg ([redacted]) and mean body mass index of 25.29 kg/m^2 ([redacted]). Of the 43 patients enrolled, 3 patients did not fulfil the eligibility criteria, 1 patient had disease progression before dosing commenced, and 1 patient withdrew consent. Of the 38 patients who received treatment, all completed treatment periods and all entered Part B of the study.

The safety analysis set included all 38 patients who received at least one dose of AZD9291. The PK analysis set included 34 patients who received at least one dose of AZD9291 and who had at least 1 quantifiable plasma concentration collected post-dose without any important protocol deviations or events affecting the PK results.

Of the 34 patients in the PK analysis set, 33 and 32 patients for the Fed and Fasted treatments, respectively, had evaluable records without important protocol deviations or events thought to affect PK. Due to the long half-life of AZD9291 and metabolites, quantifiable pre-dose concentrations were observed for Period 2 excluding data for 17, 24 and 30 patients who met the carry-over criteria for AZD9291 (pre-dose >5% of C_{max}), AZ5104 (pre-dose >10% of C_{max}), and AZ7550 (pre-dose >10% of C_{max}), respectively.

Fasted: A total of 10, 11, and 14 patients were considered non-evaluable for the Fasted treatment as they met the carry-over criteria for AZD9291, AZ5104, and AZ7550, respectively. The number of evaluable patients in the PK analysis set for the Fasted treatment for each analyte were: AZD9291 (22 patients), AZ5104 (21 patients), and AZ7550 (18 patients).

Fed: A total of 7, 13 and 16 patients were considered non-evaluable for the Fed treatment as they met the carry-over criteria for AZD9291, AZ5104, and AZ7550, respectively. The

number of evaluable patients in the PK analysis set for the Fasted treatment for each analyte were AZD9291 (26 patients), AZ5104 (20 patients), and AZ7550 (17 patients). As a result:

- Summary and inferential analysis for all patients/data in the PK analysis set could only be performed for AZD9291. For AZ5104 and AZ7550, analyses were performed using a subset (Period 1 data only) of the PK analysis set (n 17). Period 2 data were not included because most of the patients had Period 2 pre-dose concentrations that exceeded 10% of C_{max}.

- A supplemental analysis was performed for all analytes including data for patients meeting the carry-over exclusion criteria.

- An exploratory analysis was performed for all analytes utilising carry-over adjusted concentrations and parameters calculated for Period 2.

Summary of pharmacokinetic results

AZD9291

Statistical comparisons of AZD9291 exposure parameters (C_{max} and AUC_{0-72}) in patients in the PK analysis set, as well as associated time to maximum plasma concentration (t_{max}) values are summarised below.

The geometric least-squares (LS) mean ratios comparing Fed to Fasted treatments for AZD9291 C_{max} and AUC_{0-72} were 92.75% and 106.05%, respectively. The 90% CIs of these ratios were contained within the predefined equivalence limits of 70% to 143%.

The median difference in AZD9291 t_{max} between the fed and fasted state was -0.04 hours. There was no statistically significant difference in median AZD9291 t_{max} when AZD9291 was administered in the fed and fasted state.

Table S2 Statistical comparison of key AZD9291 pharmacokinetic parameters (Pharmacokinetic analysis set)

Parameter (unit)	Treatment[a]	n	GM LSM	Comparison of Fed vs Fasted	
				Ratio (%)	90% CI
AUC_{0-72} (nM·h)	Fed	26	7847		
	Fasted	22	7399	106.05	(94.82, 118.60)
C_{max} (nM)	Fed	25	208.0		
	Fasted	22	224.3	92.75	(81.40, 105.68)

Parameter (unit)	Treatment[a]	n	Median	Comparison of Fed vs Fasted			
				n	Median Difference	90% CI[b]	p-value[c]
t_{max} (h)	Fed	25	7.97				
	Fasted	22	6.08	13	-0.04	(-1.06, 1.46)	0.8501

Pharmacokinetic analysis set (excludes patients meeting carry-over exclusion criterion in Period 2 defined as Period 2 pre-dose concentration >5% of C_{max} in Period 2)

[a] Fasted: AZD9291 80 mg single oral dose administered in the fasted state
Fed: AZD9291 80 mg single oral dose administered in the fed state

[b] Median difference and confidence intervals calculated using the Hodges-Lehmann median estimator.

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

AUC_{0-72} area under the plasma concentration-time curve from zero to 72 hours; CI confidence interval; C_{max} maximum plasma concentration; GM Geometric; LSM Least squares mean; t_{max} time of maximum concentration.

In the supplemental and exploratory analyses, the geometric LS mean ratios for AZD9291 C_{max} and AUC_{0-72} comparing Fed to Fasted AZD9291 treatments were similar to the results based on the PK analysis set. The 90% CIs for these ratios were contained within the predefined equivalence limits of 70% to 143% for both analyses.

AZ5104

Statistical comparisons of AZ5104 exposure parameters (C_{max} and AUC_{0-72}) in patients in the PK analysis excluded Period 2 parameters as the majority of patients had Period 2 pre-dose concentrations that exceeded 10% of C_{max} in Period 2. The geometric LS mean ratios for AZ5104 C_{max} and AUC_{0-72} comparing Fed to fasted AZD9291 treatments were 76.68% and 81.15%, respectively.

In the supplemental and exploratory analyses, the geometric LS mean ratios for AZ5104 C_{max} and AUC_{0-72} comparing Fed to Fasted AZD9291 treatments were similar to the analysis based on the PK analysis set.

Treatment comparisons for median AZ5104 t_{max} were not made based on the PK analysis set due to insufficient data in Period 2. Based on the supplemental analysis, administration of AZD9291 in a fed state delayed median AZ5104 t_{max} approximately 10 hours compared to administration in a fasted state.

AZ7550

Statistical comparisons of AZ7550 exposure parameters (C_{max} and AUC_{0-72}) in patients in the PK analysis set excluded Period 2 data as a majority of patients had Period 2 pre-dose concentrations that exceeded 10% of C_{max} in Period 2. The geometric LS mean ratios for AZ7550 C_{max} and AUC_{0-72} comparing Fed to Fasted AZD9291 treatments were 82.92% and 88.21%, respectively.

In the supplemental and exploratory analyses, the geometric LS mean ratios for AZ7550 C_{max} and AUC_{0-72} comparing Fed to Fasted AZD9291 treatments were similar to the analysis based on the PK analysis set.

Treatment comparisons for median AZ7550 t_{max} were not made based on the PK analysis set due to insufficient data in Period 2. Based on the supplemental analysis, the median difference between the fed and fasted state was approximately 2 hours. There was no statistically significant difference in median AZ7550 t_{max} when AZD9291 was administered in the fed or fasted state.

Summary of safety results

In the safety analysis set, 70 adverse events (AEs) were reported in 22 patients (57.9%). Gastrointestinal disorders (11 [28.9%] patients), nervous system disorders (6 [15.8%] patients), respiratory disorders (6 [15.8%] patients) and musculoskeletal and connective tissue disorders (6 [15.8%] patients) were the most frequently reported system organ classes. The most commonly reported preferred terms were diarrhoea (5 [13.2%] patients), nausea (5 [13.2%] patients), and vomiting (4 [10.5%] patients).

Nine (23.7%) patients had AEs considered by the investigator to be possibly related to AZD9291, the most common of which were diarrhoea (4 [10.5%]), nausea (3 [7.9%]) and vomiting (4 [10.5%]). Two patients (5.3%) had AEs of Common Terminology Criteria for Adverse Events grade 3 or higher: 1 patient experienced grade 3 dyspnoea during the Fed period, and 1 patient experienced grade 3 hypokalaemia during the Fasted period. Neither of these were assessed by the investigator as related to AZD9291.

There was 1 serious AE (SAE; atrial flutter, which was not considered to be related to AZD9291 by the investigator), no deaths, and no patients discontinued due to AEs. There were no other significant AEs defined in this study. There were no AEs that led to dose modification, reduction or dose interruption.

Table S3 Number of patients with at least one adverse event in any category (Safety analysis set)

AE category	Number (%) of patients[a]		
	Fed (A) N=38	Fasted (A) N=38	Total (A) N=38
Any AE	13 (34.2)	17 (44.7)	22 (57.9)
Any AE causally related to AZD9291[b]	5 (13.2)	6 (15.8)	9 (23.7)
Any AE of CTCAE grade 3 or higher	1 (2.6)	1 (2.6)	2 (5.3)
Any AE with outcome = death	0	0	0
Any SAE (including events with outcome = death)	0	1 (2.6)	1 (2.6)
Any SAE causing discontinuation of AZD9291	0	0	0
Any AE causing discontinuation of AZD9291	0	0	0
Any other significant AE[c]	0	0	0

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than category are counted once in each of those categories.
[b] As assessed by the investigator, and programmatically derived from individual causality assessments for combination studies.
[c] Significant AEs, other than SAEs and DAEs, which are of particular clinical importance, are identified and classified as other significant AEs (OAEs).
AE counted if onset was after first dose of AZD9291 and up to and including 30 days post-last dose (and prior to enrolment into Part B).
AE adverse event; SAE serious adverse event; CTCAE Common Terminology Criteria for Adverse Events (Version 4.0); MedDRA Medical Dictionary for Regulatory Activities.
MedDRA version 17.0

Adverse events of special interest (AESI) in this study included diarrhoea, skin effects, ocular effects, nail effects, upper gastrointestinal tract inflammatory events, interstitial lung disease and cardiac effects. Apart from diarrhoea (single preferred term), each AESI represents the aggregate of a group of relevant AE preferred terms. Overall, no new significant or unexpected safety concerns were identified in AESI in Part A of this study. AESIs in the following categories were reported: diarrhoea (5 patients), skin effects (1 patient), ocular effects (1 patient), nail effects (1 patient), and upper GI tract (5 patients). No action was taken with respect to IP for any of these events and all had resolved at the end of the study, with the exception of 1 patient with oesophagitis and 1 patient with gastritis. All of the AESIs were CTCAE grade 1 or 2 and non-serious. The AESIs of diarrhoea and skin effects were considered by the investigator to be possibly related to treatment with AZD9291.

There were no clinically significant findings in baseline haematology and clinical chemistry variables. There was no Hy's law case in this study. There were no clinically significant ECG findings during the study.

Conclusions

In patients with EGFRm+ NSCLC following disease progression on an EGFR-TKI:

- Administration of AZD9291 80 mg as a tablet following a high fat meal does not affect AZD9291 exposure.

- Single doses of AZD9291 80 mg are well-tolerated in both fed and fasted states. No new safety concerns have been identified.

The data from this study suggest that AZD9291 can be administered in fed or fasted states.