AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9291
Study Code	D5160C00013
Edition Number	1
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EudraCT Number	2014-001525-32

A Phase I, Open-Label, Non-Randomised, Multicentre Study to Assess the Effect of Rifampicin (a CYP3A4 Inducer) on the Pharmacokinetics of AZD9291 in Patients with EGFRm Positive NSCLC Whose Disease has Progressed on an EGFR TKI

Study dates: First patient enrolled: 04 December 2014
Last patient last visit: 09 July 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 centres

This study was performed at 18 centres across Asia, North America 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 (PK) Part A	To investigate the effect of multiple oral dosing of rifampicin on the steady-state exposure of AZD9291 ($C_{ss,max}$ and AUC_{τ}), following oral dosing in patients with EGFRm+ NSCLC following progression on a EGFR TKI	**AZD9291:** $C_{ss,max}$, and AUC_{τ} (alone [Day 28] and in combination with rifampicin [Day 49])
Secondary (PK) Part A	To characterise the PK of AZD9291 and metabolites (AZ5104 and AZ7550) following oral dosing of the tablet formulation in the presence and absence of rifampicin	**AZD9291:** AUC_{τ}, and $C_{ss,max}$ (Day 77); $t_{ss,max}$, $C_{ss,min}$, and CL_{ss}/F in all periods Trough concentrations on Days 7, 14, 21, and 28 of Period 1, Days 35, 42, and 49 of Period 2, and Days 56, 63, 70, and 77 of Period 3 **AZ5104 and AZ7550:** AUC_{τ}, $C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$, and metabolic ratios (AZ5104 to AZD9291 and AZ7550 to AZD9291) $MRAUC_{\tau}$ and $MRC_{ss,max}$ in all periods C_{trough} on Days 7, 14, 21, and 28 of Period 1, Days 35, 42, and 49 of Period 2, and Days 56, 63, 70, and 77 of Period 3 **Rifampicin:** AUC_{τ}, $AUC_{0\text{-}t}$, $C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$, and CL_{ss}/F in Period 2 C_{trough} on Days 35, 42, and 49 of Period 2
Safety Part A	To examine the safety and tolerability of AZD9291 in patients with EGFRm+ NSCLC in the presence and absence of co-administered rifampicin	Assessment of AEs/SAEs graded by CTCAE (version 4.0); vital signs (including blood pressure, pulse, temperature and weight); laboratory parameters (clinical chemistry, haematology and urinalysis); physical examination; standard 12-lead ECGs; echocardiogram/MUGA; ophthalmology; concomitant medications; and exposure to study treatment
Safety Part B	To examine the safety and tolerability of AZD9291 following extended administration in patients with EGFRm+ NSCLC	
Exploratory (PK) Part A	To assess the induction potential of AZD9291 on CYP3A4	4β-hydroxy-cholesterol at baseline (Day 1) and collected throughout the 77-day AZD9291 dosing period
Exploratory (Pharmaco-genetic) Part A	To perform genetic research in the AZD9291 clinical pharmacology development programme to explore how genetic variations may affect the clinical PK of AZD9291	None defined. The results of any exploratory research will be reported separately and are not included in this CSR
Exploratory (Population PK) Part A	To provide data to allow analysis using population PK approaches	None defined. The results of any exploratory research will be reported separately and are not included in this CSR

AE Adverse event; AUC_{τ} Area under the plasma concentration-time curve from zero to the end of the dosing interval; AUC_{0-t} Area under the plasma concentration-time curve from zero to the last quantifiable concentration; CL_{ss}/F Apparent plasma clearance after multiple dosing; CSR Clinical study report; $C_{ss,max}$ Maximum plasma concentration after multiple dosing; $C_{ss,min}$ Minimum plasma concentration over the dosing interval; CTCAE Common Terminology Criteria for AEs; C_{trough} Trough plasma concentration; CYP3A4 Cytochrome P450 3A4; ECG Electrocardiogram; EGFRm+ Epidermal growth factor receptor mutation positive; EGFR TKI Epidermal growth factor receptor tyrosine kinase inhibitor; $MRAUC_{\tau}$ Metabolite to parent ratio of AUC_{τ}; $MRC_{ss,max}$ Metabolite to parent ratio for $C_{ss,max}$; MUGA Multiple gated acquisition scan; NSCLC Non-small cell lung cancer; PK Pharmacokinetics; SAE Serious adverse event; $t_{ss,max}$ Time to C_{max} after multiple dosing.

Study design

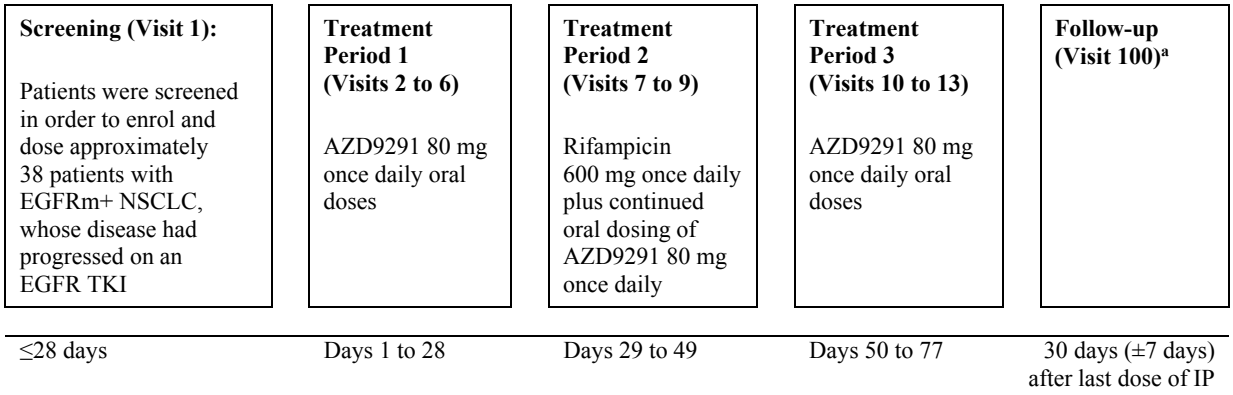
This was a Phase I, open-label, non-randomised, multicentre, 2-part study in patients with a confirmed diagnosis of epidermal growth factor receptor mutation positive (EGFRm+) non-small cell lung cancer (NSCLC), who had progressed following prior therapy with an approved epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) agent.

Part A assessed the effect of rifampicin on the steady state pharmacokinetic (PK) parameters of AZD9291 and metabolites AZ5104 and AZ7550 following multiple oral dosing of both rifampicin and AZD9291 in a fasted state.

Part B allowed patients further access to AZD9291 after the PK phase (Part A) and provided additional safety data. All patients from Part A who completed treatment may continue to receive AZD9291 80 mg once daily until: disease progression; they are no longer deriving clinical benefit; or any other reason.

Figure S1 shows the design of the study (Part A) and the sequence of treatment periods.

Figure S1 Study flow chart - Part A



[a] For patients who withdrew from the study prematurely and did not participate in Part B.
EGFRm+ Epidermal growth factor receptor mutation positive; EGFR TKI Epidermal growth factor receptor tyrosine kinase inhibitor; IP Investigational product; NSCLC Non-small cell lung cancer.

Target patient population and sample size

The target patient population comprised male and female patients aged ≥18 years with EGFRm+ NSCLC, who had progressed following prior therapy with an approved EGFR TKI agent. Patients had to have histological or cytological confirmation diagnosis of NSCLC

which harbours an EGFR mutation known to be associated with EGFR TKI sensitivity, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

The primary objective of Part A of the study was to investigate the effect of rifampicin on the PK of AZD9291 at steady state. In study D5160C00005, a within-patient coefficient of variation of 20% and 23% was observed for both area under plasma concentration-time curve from zero extrapolated to infinity (AUC) and maximum plasma concentration (C_{max}), respectively, in healthy normal subjects. However, since the variability in patients was unknown, it was assumed that the within-patient coefficient of variation for AZD9291 in both AUC and C_{max} was 34%, an approximate 50% increase from that observed in healthy normal subjects. A 33% decrease in the exposure for AZD9291 when given with rifampicin was also assumed. With 30 evaluable patients, the experiment-wide power for the lower bound of the 90% confidence interval (CI) of the geometric mean ratios (AZD9291 + rifampicin/AZD9291 alone) being above 50% was 90% (95% power for each parameter).

To account for withdrawal of approximately 20% of patients, approximately 38 patients were to be enrolled in order to obtain 30 evaluable patients. Additional patients could be enrolled in order to obtain at least 30 evaluable patients.

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

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

Rifampicin 600 mg oral capsules were sourced centrally only in Korea (Yuhan Corp; batch number: [redacted]) and Taiwan (Remedica-Cyprus; batch number: [redacted]). In all other countries, rifampicin was sourced locally; further information is included in the CSR.

Duration of treatment

In Part A, patients were to receive a once daily 80 mg oral dose of AZD9291, on Days 1 to 77. From Days 29 to 49 each patient received rifampicin 600 mg once daily, taken concomitantly with AZD9291.

In Part B, patients were to receive 80 mg oral AZD9291 once daily, until disease progression or they are no longer deriving clinical benefit.

Statistical methods

For AZD9291 and its metabolites, natural log-transformed area under the plasma concentration-time curve from zero to the end of the dosing interval (AUC_{τ}) and maximum plasma concentration after multiple dosing ($C_{ss,max}$), were compared between periods using a mixed effects analysis of variance (ANOVA) with period as a fixed effect and patient as a random effect. Estimates of the mean difference between periods (Period 2 – Period 1, and Period 3 – Period 1) 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

(Period 2 versus Period 1, and Period 3 versus Period 1) and the associated 90% CIs. Additionally, back-transformed geometric means together with 95% CIs for AUC_{τ} and $C_{ss,max}$ were estimated and presented. No effect on the PK of AZD9291 after co-administration of rifampicin was to be concluded if the lower bound of the 90% CIs for the ratios (Period 2 versus Period 1) of AZD9291 AUC_{τ} and $C_{ss,max}$ were both above 50%.

For AZD9291 and its metabolites, analyses of time to C_{max} after multiple dosing ($t_{ss,max}$) were performed using the Wilcoxon Signed Rank Test. The Hodges-Lehman median estimator of the difference in periods (Period 2 – Period 1, and Period 3 – Period 1) and 90% CIs were presented.

In addition to a graphical assessment of the steady state for AZD9291 and metabolites (AZ5104 and AZ7550), a statistical evaluation of the steady state was also made using the trough plasma concentrations collected on Days 7, 14, 21, 28 (pre-dose), and Day 29 (Day 28, 24 hours). All valid concentrations on the natural-log scale were analysed using mixed effects ANOVA model with day as a fixed repeated effect and repeated variance structure was AR(1). From this model, orthogonal contrasts with 90% CI were formed between the mean concentration at each day and the mean concentrations for all the following days using Helmert contrasts. Precisely, Day 7 was compared to Days 14 through 29 combined; Day 14 was compared to Days 21 through 29 combined; Day 21 was compared to Days 28 through 29 combined; and Day 28 was compared to Day 29.

As exploratory analyses, the onset of potential induction by rifampicin (AZD9291, AZ5104 and AZ7550 trough plasma concentrations after addition relative to before addition of rifampicin) was explored. A repeated-measures linear effects model was fitted to the differences between the log-transformed trough concentrations and the log-transformed trough concentration on Day 29 (on AZD9291 alone), with day as fixed-repeated effect and repeated variance structure was AR(1). For each day, the least-squares (LS) mean together with a 95% CI were estimated. Estimates of the mean differences relative to Day 29 and corresponding 95% CIs were calculated. The 95% CIs of the LS means and the mean differences were back-transformed to the original scale prior to presentation. Additionally, the p-value testing for the ratio equal 1 was presented. To assess the onset, AZD9291, AZ5104 and AZ7550 trough plasma concentrations during Period 2 (Days 35, 42, 49, and 50 [Day 49, 24 hours]) were compared to that on Day 29. To assess the offset, AZD9291, AZ5104 and AZ7550 trough plasma concentrations during Period 3 (Day 56, 63, 70, 77, and 78 [Day 77, 24 hour]) were compared to that on Day 29.

Additionally, an evaluation of potential increase in cytochrome P450 (CYP) 3A4 enzyme activity, as well as onset and offset of induction by rifampicin, interpreted as the concentration of 4β-hydroxy-cholesterol after commencement of AZD9291 administration relative to baseline (Day 1 pre-dose) was performed.

Safety data were listed and summarised using descriptive statistics.

Patient population

In this study, 51 patients were enrolled (consented for screening). Of these, 41 patients were assigned to treatment at 18 centres in 6 countries across Asia, North America and Western Europe: Korea (3 centres), Netherlands (2 centres), Spain (7 centres), Taiwan (2 centres), United Kingdom (2 centres), and USA (2 centres).

Of the 51 patients enrolled, 10 patients failed screening as they met an exclusion criterion. Of the remaining 41 patients assigned to, and who received treatment, 32 patients (78.0%) completed treatment in Part A and continued into Part B. Two patients discontinued treatment during Period 2, and 2 patients discontinued treatment during Period 3 without completing all study assessments, due to worsening of condition under investigation. Three patients completed all study assessments in Part A but withdrew from the study on Day 78 (Period 3), due to worsening of condition under investigation. A further 2 patients did not complete Part A (both withdrew due to an adverse event [AE] which led to discontinuation of rifampicin) but entered Part B directly. A total of 34 patients (82.9%) entered Part B of the study.

Of the 41 patients enrolled and treated (9 males and 32 females), the majority (58.5%) were of White race; the proportion of Asian to non-Asian patients was as a result of the geographical location of participating sites in this study. The mean age of the study population was 62.5 years [redacted], and mean weight was 64.6 kg [redacted]. The majority of patients had never smoked (27 patients [65.9%]).

The safety analysis set included all 41 patients who received at least one dose of AZD9291. The PK analysis set included all 41 patients who received at least 1 dose of study medication and had at least 1 quantifiable plasma concentration collected post-dose without any important deviations or events that would exclude the patient. Forty patients contributed data for AZD9291 and metabolites (AZ5104 and AZ7550), 39 patients contributed data for rifampicin, and 39 patients contributed data for 4β-hydroxy-cholesterol. One patient (E7801302) took AZD9291 less than 18 hours after the previous dose at all PK assessment time points (trough and serial) or did not have records of the dose taken prior to the day of PK sample collection (Period 3, Days 63 through 77) and was excluded from the PK analysis set for AZD9291 and metabolites (AZ5104 and AZ7550).

Summary of pharmacokinetic results

AZD9291

Statistical comparison of AZD9291 steady state exposure parameters ($C_{ss,max}$ and AUC_{τ}) in patients in the analysis set, as well as associated $t_{ss,max}$ values are summarised in Table S2.

Visual inspection and statistical assessment of trough concentrations versus treatment day indicate that AZD9291 plasma concentrations reached steady state by the end of Period 1. Therefore, Day 28 PK parameters in Period 1 were calculated under steady state conditions. Following administration of AZD9291 + rifampicin in Period 2, AZD9291 plasma trough

concentrations decreased over the 21-day dosing period. The decrease was statistically significant as early as 7 days after commencement of rifampicin on Day 35.

Administration of AZD9291 with rifampicin decreased AZD9291 $C_{ss,max}$ and AUC_{τ} approximately 73% and 78%, respectively, compared with administration of AZD9291 alone. The geometric LS mean ratios (90% CI) comparing AZD9291 $C_{ss,max}$ and AUC_{τ} when AZD9291 was administered with rifampicin (Period 2) to AZD9291 administered alone (Period 1) were 27.16% (24.36%, 30.29%) and 21.55% (19.50%, 23.83%), respectively, with both lower bounds falling below 50%. Onset of induction was evident by a significant decrease in AZD9291 plasma trough concentrations as early as 7 days after commencement of rifampicin. The median difference in AZD9291 $t_{ss,max}$ was not statistically significant when comparing AZD9291 administered alone in Period 1 and AZD9291 administered with rifampicin in Period 2.

Within 3 weeks after rifampicin discontinuation, trough AZD9291 plasma concentrations were no longer significantly different from those observed at the end of Period 1. Four weeks after rifampicin discontinuation, the geometric LS mean ratios (90% CI) comparing AZD9291 $C_{ss,max}$ and AUC_{τ} after discontinuation of rifampicin (Period 3) to that prior to rifampicin administration (Period 1) were 95.53% (85.27%, 107.03%) and 95.89% (86.37%, 106.45%), respectively. Based on the geometric LS mean ratios and 90% CIs, $C_{ss,max}$ and AUC_{τ} were similar. The median difference in AZD9291 $t_{ss,max}$ was not statistically significant when comparing AZD9291 administered alone in Period 1 and Period 3.

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

				Pairwise comparison		
Parameter (unit)	**Treatment[a]**	**n**	**Geometric LS Mean**	**Pair**	**Ratio (%)**	**90% CI**
AUCτ (nM·h)	AZD9291 (1)	38	10730			
	AZD9291 + rifampicin (2)	32	2313	AZD9291 + rifampicin (2)/ AZD9291 (1)	21.55	(19.50, 23.83)
	AZD9291 (3)	28	10290	AZD9291 (3)/ AZD9291 (1)	95.89	(86.37, 106.45)
$C_{ss,max}$ (nM)	AZD9291 (1)	38	572.9			
	AZD9291 + rifampicin (2)	32	155.6	AZD9291 + rifampicin (2)/ AZD9291 (1)	27.16	(24.36, 30.29)
	AZD9291 (3)	28	547.3	AZD9291 (3)/ AZD9291 (1)	95.53	(85.27, 107.03)

					Pairwise Comparison			
Parameter (unit)	**Treatment[a]**	**n**	**Median**	**Pair**	**n**	**Median Difference**	**90% CI[b]**	**p-value[c]**
$t_{ss,max}$ (h)	AZD9291 (1)	38	4.97					
	AZD9291 + rifampicin (2)	32	5.88	AZD9291 + rifampicin (2)/ AZD9291 (1)	30	-0.42	(-1.00, 0.02)	0.2612
	AZD9291 (3)	28	6.00	AZD9291 (3)/ AZD9291 (1)	27	0.08	(-0.05, 1.05)	0.3631

[a] AZD9291 (1): AZD9291 80 mg once daily on Days 1 to 28 (Part A).
AZD9291 + rifampicin (2): AZD9291 80 mg and rifampicin 600 mg once daily on Days 29 to 49 (Part A).
AZD9291 (3): AZD9291 80 mg once daily on Days 50 to 77 (Part A).
[b] Median difference and CIs calculated using the Hodges-Lehmann median estimator.
[c] p-value for treatment difference in median $t_{ss,max}$ calculated using the Wilcoxon signed rank test.
AUC_τ Area under the plasma concentration-time curve from zero to the end of the dosing interval; CI confidence interval; $C_{ss,max}$ Maximum plasma concentration after multiple dosing; LS Least-squares; $t_{ss,max}$ Time of maximum plasma concentration after multiple dosing.

AZ5104

Visual inspection and statistical assessment of trough concentrations versus treatment day indicate that AZ5104 plasma concentrations reached steady state by the end of Period 1. Therefore, Day 28 PK parameters in Period 1 were calculated under steady state conditions. Following administration of AZD9291 + rifampicin in Period 2, AZ5104 plasma trough concentrations decreased over the 21-day dosing period. The decrease was statistically significant as early as 7 days after commencement of rifampicin on Day 35.

Administration of AZD9291 with rifampicin decreased AZ5104 $C_{ss,max}$ and AUC_τ approximately 78% and 81%, respectively, compared with administration of AZD9291 alone. The geometric LS mean ratios (90% CI) comparing AZ5104 $C_{ss,max}$ and AUC_τ when

AZD9291 was administered with rifampicin (Period 2) to AZD9291 administered alone (Period 1) were 21.72% (19.08, 24.72) and 18.76% (16.61, 21.19), respectively. The median difference in AZ5104 $t_{ss,max}$ was not statistically significant when comparing AZD9291 administered alone in Period 1 and AZD9291 administered with rifampicin in Period 2.

After rifampicin discontinuation (Period 3), AZ5104 plasma trough concentrations returned to similar concentrations to that observed by the end of Period 1. On Day 78 (4 weeks after rifampicin discontinuation), the rifampicin-induced difference in trough concentrations was no longer statistically significant.

The geometric LS mean ratios (90% CI) comparing AZD5104 $C_{ss,max}$ and AUC_{τ} after discontinuation of rifampicin (Period 3) to that prior to rifampicin administration (Period 1) were 88.31% (77.17%, 101.07%) and 90.08% (79.34%, 102.27%), respectively. Based on the geometric LS mean ratios and 90% CIs, $C_{ss,max}$ and AUC_{τ} were similar. The median difference in AZ5104 $t_{ss,max}$ was not statistically significant when comparing AZD9291 administered alone in Period 1 and Period 3.

Geometric mean metabolite to parent ratios for AZ5104 $C_{ss,max}$ and AUC_{τ} ranged from approximately 8% to 11% across the three treatments and did not meaningfully change when AZD9291 was administered alone in Period 1 (Day 28), with rifampicin in Period 2 (Day 49), and after discontinuation of rifampicin in Period 3 (Day 77).

AZ7550

Visual inspection and statistical assessment of trough concentrations versus treatment day indicate that AZ7550 plasma concentrations appeared to have approached steady state by the end of Period 1. Therefore, Day 28 PK parameters in Period 1 were calculated under steady state conditions. Following administration of AZD9291 + rifampicin in Period 2, AZ7550 plasma trough concentrations increased over the 21-day dosing period with the maximum increase occurring on Day 35. The increase in AZ7550 was less pronounced on Days 42 through 50. Increases in AZ7550 trough concentrations were statistically significant on all assessments except pre-dose on Day 49.

Administration of AZD9291 with rifampicin increased AZ7550 $C_{ss,max}$ and AUC_{τ} approximately 39% and 30%, respectively, compared with administration of AZD9291 alone. The geometric LS mean ratios (90% CI) comparing AZ7550 $C_{ss,max}$ and AUC_{τ} when AZD9291 was administered with rifampicin (Period 2) to AZD9291 administered alone (Period 1) were 139.32% (127.74%, 151.96%) and 129.81% (119.14%, 141.44%), respectively. The increase in AZ7550 exposure combined with the decrease in AZD9291 exposure resulted in a higher metabolite to parent ratios for AZ7550 $C_{ss,max}$ and AUC_{τ} of approximately 52% and 67%, respectively, compared to approximately 10% and 12%, respectively when AZD9291 was administered alone. The median difference in AZ7550 $t_{ss,max}$ was not statistically significant when comparing AZD9291 administered alone in Period 1 and AZD9291 administered with rifampicin in Period 2.

After rifampicin discontinuation (Period 3), trough AZ7550 plasma concentrations returned to similar concentrations observed by the end of Period 1. On Day 77 (4 weeks after rifampicin discontinuation), the rifampicin-induced difference in trough concentrations was no longer statistically significant.

The geometric LS mean ratios comparing AZ7550 $C_{ss,max}$ and AUC_{τ} after discontinuation of rifampicin (Period 3) to that prior to rifampicin administration (Period 1) were 100.75% (92.04%, 110.29%) and 100.76% (92.15%, 110.19%), respectively. Based on the geometric LS mean ratios and 90% CIs, $C_{ss,max}$ and AUC_{τ} were similar. The median difference in AZ7550 $t_{ss,max}$ was not statistically significant when comparing AZD9291 administered alone in Period 1 and Period 3. After rifampicin discontinuation, metabolite to parent ratios for AZ7550 $C_{ss,max}$ and AUC_{τ} returned to similar levels observed when AZD9291 was administered alone in Period 1.

Rifampicin

Descriptive statistics could not be calculated for trough rifampicin data as the number of patients with values above the limits of quantitation was fewer than half the number of patients in the overall population at each time point. Following 3 weeks of rifampicin administration, the maximum geometric mean rifampicin concentration occurred 2 hours post-dose. Following this time, the plasma concentrations declined mono-exponentially and were generally below the limits of quantitation 24 hours post-dose.

Geometric mean (% geometric coefficient of variation [GCV]) rifampicin $C_{ss,max}$ and AUC_{τ} values were 13810 ng/mL (40.6 %) and 58610 (ng·h/mL) (36.8%) on Day 49, respectively. Median rifampicin $t_{ss,max}$ was 2.00 hours (range 0.83 to 6.07 hours) and the arithmetic mean (±standard deviation apparent plasma clearance after multiple dosing was 10.91 L/h (±4.296 L/h).

Exposure to rifampicin, based on these PK parameters, was of a similar magnitude to that reported in other controlled clinical PK studies utilising this dosing regimen, where significant drug-drug interactions have been demonstrated.

4β-hydroxy-cholesterol

Following multiple dose administration of AZD9291 (Day 28), concentrations of 4β-hydroxy-cholesterol increased approximately 10% relative to baseline. The geometric LS mean (90% CI) for the Day 28 to baseline 4β-hydroxy-cholesterol ratio was 1.101 (1.002, 1.210). The addition of rifampicin to AZD9291 (Day 49) increased 4β-hydroxy-cholesterol concentrations approximately 7-fold relative to baseline. The geometric LS mean (90% CI) for the Day 49 to baseline 4β-hydroxy-cholesterol ratio was 6.823 (5.982, 7.782). After discontinuation of rifampicin (Day 77), 4β-hydroxy-cholesterol concentrations decreased but remained approximately 2-fold higher than baseline. The geometric LS mean (90% CI) for the Day 78 to baseline 4β-hydroxy-cholesterol ratio was 2.014 (1.818, 2.231). This residual increase relative to baseline is consistent with the long apparent half-life of 4β-hydroxy-cholesterol (~17 days).

Summary of pharmacogenetic results

The results of any exploratory optional pharmacogenetic research or population PK analysis, if performed, will be reported separately and are not included in this CSR.

Summary of safety results

The number of patients with an AE in any category is summarised in Table S3.

Overall, 39 patients (95.1%) experienced a total of 268 AEs and 34 patients (82.9%) had a total of 113 AEs (42.2%) considered by the Investigator to be possibly causally related to study treatment; of these, 91 AEs (34.0%) were considered possibly causally related to AZD9291 and 15 AEs (5.6%) were considered possibly causally related to both AZD9291 and rifampicin. The most frequently reported AEs were diarrhoea (13 patients [31.7%]), dry skin (10 patients [24.4%]), and fatigue and nausea (8 patients [19.5%] each).

Overall, 10 patients (24.4%) had a total of 17 AEs of maximum Common Toxicity Criteria for AEs (CTCAE) grade 3 or higher; of these, 3 patients (7.3%) had at least one AE that the Investigator considered to be possibly causally related to study treatment.

Table S3 Adverse events in any category - patient level (Safety analysis set)

	Number (%) of patients[a]			
	AZD9291 (1) N=41	**AZD9291 + rifampicin (2)** N=41	**AZD9291 (3)** N=37	**Total** N=41
Any AE	38 (92.7)	30 (73.2)	22 (59.5)	39 (95.1)
Any AE causally related to treatment[b]	24 (58.5)	23 (56.1)	13 (35.1)	34 (82.9)
Any AE causally related to AZD9291[b]	24 (58.5)	17 (41.5)	13 (35.1)	33 (80.5)
Any AE causally related to rifampicin[b]	2 (4.9)	14 (34.1)	2 (5.4)	15 (36.6)
Any AE causally related to both AZD9291 and rifampicin[b]	2 (4.9)	6 (14.6)	2 (5.4)	8 (19.5)
Any AE of CTCAE grade 3 or higher	5 (12.2)	5 (12.2)	4 (10.8)	10 (24.4)
Any AE of CTCAE grade 3 or higher causally related to treatment[b]	0	2 (4.9)	2 (5.4)	3 (7.3)
Any AE of CTCAE grade 3 or higher causally related to AZD9291[b]	0	2 (4.9)	2 (5.4)	3 (7.3)
Any AE of CTCAE grade 3 or higher causally related to rifampicin[b]	0	1 (2.4)	0	1 (2.4)
Any AE of CTCAE grade 3 or higher causally related to both AZD9291 and rifampicin[b]	0	1 (2.4)	0	1 (2.4)
Any AE with outcome = death	0	0	0	0
Any SAE (including events with outcome = death)	3 (7.3)	1 (2.4)	3 (8.1)	7 (17.1)
Any SAE causally related to treatment[b]	0	0	1 (2.7)	1 (2.4)
Any SAE causally related to AZD9291[b]	0	0	1 (2.7)	1 (2.4)
Any SAE causally related to rifampicin[b]	0	0	0	0
Any SAE causing discontinuation of AZD9291	0	0	0	0
Any AE leading to discontinuation of AZD9291	0	0	0	0
Any other significant AE[c]	0	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 one 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 those AEs leading to discontinuation of study treatment, which are of particular clinical importance, are identified and classified as other significant AEs.

AZD9291 (1) = patient had received AZD9291 in treatment Period 1. AE counted if onset was after first dose of AZD9291 and prior to first dose of rifampicin and up to and including 30 days post-last dose of AZD9291 (and prior to enrolment into Part B).
AZD9291 + rifampicin (2) = patient had received AZD9291 and rifampicin in treatment Period 2. AE counted if onset was after first dose of rifampicin and up to and including 30 days post-last dose of rifampicin (and prior to enrolment into Part B).
AZD9291 (3) = patient had received AZD9291 in treatment Period 3. AE counted if onset was after last dose of rifampicin and up to and including 30 days post-last dose of AZD9291 (and prior to enrolment into Part B).
MedDRA version 18.0.

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; SAE serious adverse event.

Adverse events of special interest (AESI) in this study included diarrhoea, skin effects, ocular effects, nail effects, upper gastrointestinal (GI) tract inflammatory events, cardiac effects and interstitial lung disease (ILD). 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. A total of 29 patients (70.7%) reported at least one AESI in Part A, and all AESIs were of CTCAE grade 1 or 2, with the exception of 2 CTCAE grade 3 events in the cardiac effects grouping (in the same patient). Events were reported for the following AESI grouped terms: diarrhoea (13 patients), skin effects (20 patients; subgroups: dry skin, 13 patients; pruritus, 4 patients; rashes and acnes, 7 patients), ocular effects (4 patients), nail effects (2 patients), upper GI tract inflammatory effects (12 patients) and [redacted] (1 patient). No ILD grouped terms were reported during Part A of the study.

There were no clinically significant changes in laboratory parameters, vital signs, electrocardiograms, or physical examination. There were no Hy's law cases in Part A of this study.

Conclusions

- Administration of AZD9291 with rifampicin decreased AZD9291 $C_{ss,max}$ and AUC_{τ} by approximately 73% and 78%, respectively, compared with administration of AZD9291 alone at steady-state prior to rifampicin administration.

- Four weeks after rifampicin discontinuation, AZD9291 $C_{ss,max}$ and AUC_{τ} had returned to similar levels observed prior to rifampicin co-administration.

- Compared to the changes observed for AZD9291, similar changes in $C_{ss,max}$ and AUC_{τ} were seen for AZ5104 across the treatment periods. Geometric mean metabolite to parent ratios for AZ5104 $C_{ss,max}$ and AUC_{τ} ranged from approximately 8% to 11% across the three treatments and did not meaningfully change when AZD9291 was administered alone in Period 1 (Day 28), with rifampicin in Period 2 (Day 49) and after discontinuation of rifampicin in Period 3 (Day 77).

- AZ7550 $C_{ss,max}$ and AUC_{τ} increased during rifampicin co-administration. This increase was reflected in a pronounced increase in metabolite to parent $C_{ss,max}$ and AUC_{τ} ratios for AZ7550 (52% and 67%) compared to those observed when AZD9291 was administered alone (10% and 12%). After discontinuation of rifampicin, AZ7550 $C_{ss,max}$ and AUC_{τ} as well as metabolite to parent exposure ratios returned to levels observed prior to rifampicin co-administration.

- The effect of rifampicin co-administration on AZD9291, AZ5104 and AZ7550 plasma trough concentrations was evident as early as 7 days after commencement of rifampicin administration, reaching steady state at 3 weeks. Three weeks after rifampicin discontinuation, induction appeared to have abated as trough AZD9291,

AZ5104 and AZ7550 plasma concentrations returned to levels observed prior to rifampicin administration.

- The observed exposure of rifampicin was similar to that observed in the literature, which is sufficient to significantly induce CYP3A4 enzyme activity.

- An approximate 10% increase in 4β-hydroxy-cholesterol levels relative to baseline was observed on Day 28 following administration of AZD9291 80 mg once daily for 27 days. The levels of 4β-hydroxy-cholesterol increased approximately 7-fold relative to baseline following the addition of rifampicin and decreased after discontinuation of rifampicin, but remained approximately 2-fold higher than baseline on Day 78 which is consistent with the long half-life of 4β-hydroxy-cholesterol.

- AZD9291 80 mg administered orally as a tablet either alone or concomitantly with rifampicin was well tolerated in patients with EGFRm+ NSCLC following disease progression on an EGFR TKI. No new safety concerns were identified.