AstraZeneca

Revised Clinical Study Protocol

Drug Substance	AZD9291
Study Code	D5160C00013
Edition Number	2
Date	

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

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative

Date

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1			
2			

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1			

AstraZeneca

PROTOCOL SYNOPSIS

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

International Co-ordinating Investigator

Study site(s) and number of patients planned

This study will be conducted at approximately 16 sites across Asia, North America and Western Europe with approximately 38 patients enrolled to achieve at least 30 evaluable patients.

Study period		Phase of development
Estimated date of first patient enrolled	Q3 2014	Clinical pharmacology (I)
Estimated date of last patient completed (Part A)	Q1 2015	
Estimated date of last patient completed (Part B)	Q3 2016	

Study design

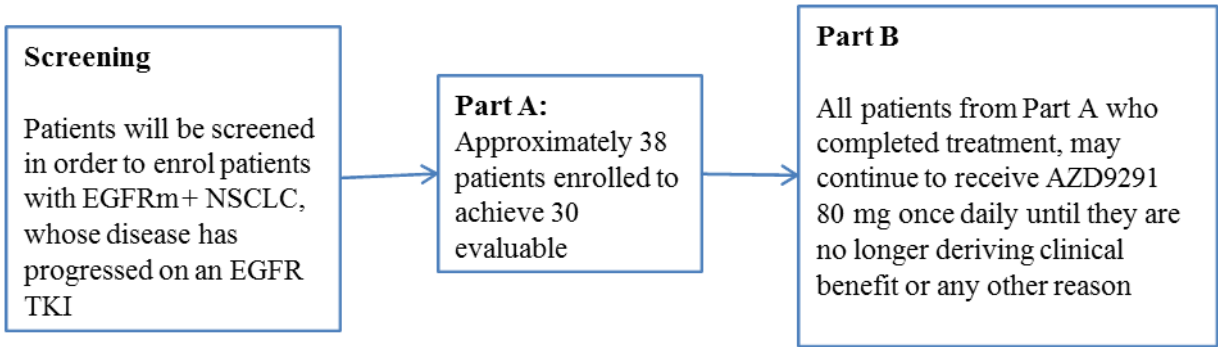
This is a Phase I, open-label, 2-part study in patients with a confirmed diagnosis of epidermal growth factor receptor (EGFR) mutation positive (EGFRm+) non-small cell lung cancer (NSCLC), who have progressed following prior therapy with an approved EGFR tyrosine kinase inhibitor (TKI) agent.

Part A will assess the effect of rifampicin on the 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 will allow patients further access to AZD9291 after the PK phase (Part A) and will provide for additional safety data collection. All patients from Part A who completed

treatment may continue to receive AZD9291 80 mg once daily until they are no longer deriving clinical benefit or they stop taking AZD9291 for any other reason.

Study flow chart



Objectives

Primary Objectives:

Part A: To investigate the effect of multiple oral dosing of rifampicin on the steady-state exposure of AZD9291 ($C_{ss,max}$ and AUC_{tau}), following oral dosing in patients with EGFRm+ NSCLC following progression on a EGFR TKI.

Secondary Objectives:

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.

Safety Objectives:

Part A: To examine the safety and tolerability of AZD9291 in patients with EGFRm+ NSCLC in the presence and absence of co-administered rifampicin.

Part B: To examine the safety and tolerability of AZD9291 following extended administration in patients with EGFRm+ NSCLC.

Exploratory Objectives:

Part A: To assess the induction potential of AZD9291 on cytochrome P450 3A4 (CYP3A4).

Part A: To perform genetic research in the AZD9291 clinical pharmacology development programme to explore how genetic variations may affect the clinical pharmacokinetics of AZD9291.

Part A: To provide data to allow analysis using population PK approaches.

Outcome measures

Analysis: Part A	Outcome Measures:
PK	
Primary AZD9291	• $C_{ss,max}$, and area under the plasma concentration-time curve from time zero to the end of the dosing interval (AUC_{tau}) (alone [Day 28] and in combination with rifampicin [Day 49])
Secondary AZD9291	• AUC_{tau}, 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, and Days 35, 42, and 49 of Period 2, and Days 56, 63, 70, and 77 of Period 3
Secondary AZ5104 and AZ7550	• AUC_{tau}, $C_{ss,max,}$ $t_{ss,max}$, $C_{ss,min}$, and metabolic ratios (AZ5104 to AZD9291 and AZ7550 to AZD9291) $MRAUC_{tau}$ and $MRC_{ss,max}$ in all periods • trough concentrations on Days 7, 14, 21, and 28 of Period 1, and Days 35, 42, and 49 of Period 2, and Days 56, 63, 70, and 77 of Period 3
Secondary rifampicin	• AUC_{tau}, $C_{ss,max,}$ $t_{ss,max}$, $C_{ss,min}$, and CL_{ss}/F
Exploratory 4β-hydroxy-cholesterol	• 4β-hydroxy-cholesterol at baseline and collected throughout the 77-day AZD9291 dosing period

Safety analysis : Part A and B	Outcome Measures :
	• Adverse events (AEs)/SAEs graded by the Common Terminology Criteria for AEs (CTCAE) (version 4) • Vital signs (blood pressure/pulse/temperature/height/weight) • Laboratory parameters (clinical chemistry, haematology, urinalysis) • Physical examination • Standard 12-lead electrocardiograms (ECGs) • Echocardiogram/MUGA

Target patient population

Male and female patients aged 18 years or over with EGFRm+ NSCLC who have progressed following prior therapy with an approved EGFR TKI agent. Patients must have confirmation of histological or cytological NSCLC and Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1.

Duration of treatment

In Part A, each patient will receive AZD9291 80 mg once daily for 77 days (Days 1 to 77). Patients will also receive oral daily doses of rifampicin for 21 days (Day 29 to 49) concurrently with AZD9291.

On completion of Part A, patients may continue to take AZD9291 tablets (Part B) if they and the Investigator agree that this is appropriate. Patients should start Part B immediately (ie, 24 hours) after the last dose received in Part A (Day 78 after the 24-hour sample collection). Patients will have weekly clinic visits for the first 4 weeks; thereafter visits will be every 4 weeks. Safety assessments will be collected and there will be no formal evaluation of efficacy. Patients' medical/oncological care will be according to local clinical practice. Part B will be of approximately 12 months' duration from the date the last patient enters this part of the study (allowing for any scheduled Part B follow-up assessments). Patients who permanently discontinue AZD9291 during Part B will complete a follow-up assessment.

After the end of Part B, patients will be seen as per their normal routine clinical care. No clinical data will be collected for those patients who continue to receive AZD9291 (hereafter referred to as continued access), other than serious adverse events that may be related to AZD9291, outcomes of pregnancy and drug dispensing/accountability. Patients who continue to take AZD9291 after the end of Part B should have their final on treatment visit within 4 weeks prior to the end of Part B.

Investigational product, dosage and mode of administration

Investigational product: AZD9291 80 mg once daily, administered orally as a tablet formulation.

Additional study drug: rifampicin 600 mg once daily, administered orally as a capsule formulation.

In Part A: all treatments (AZD9291 and rifampicin) will be administered fasted from at least 2 hours before dosing to at least 2 hours after dosing. Water is allowed as desired except for 1 hour before and after AZD9291 administration on Days 28, 49, and 77. There are no restrictions for water intake on any other study days.

In Part B and continued access: AZD9291 can be administered with or without food.

Statistical methods

Plasma concentrations of AZD9291, AZ5104, AZ7550, and rifampicin, and the derived PK parameters will be summarised by treatment using descriptive statistics and displayed graphically as appropriate.

For AZD9291 and its metabolites, natural log-transformed AUC_{tau} and $C_{ss,max}$, will be compared between periods using a mixed effects ANOVA with period as a fixed effect and patient as a random effect. Estimates of the mean difference between periods (Period 2

[rifampicin plus AZD9291] versus Period 1 [AZD9291 only, pre-rifampicin], and Period 3 [AZD9291 only, post-rifampicin] versus Period 1) and corresponding 90% CIs will be calculated. The mean differences and the CIs will be 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_{tau} and $C_{ss,max}$ will be estimated and presented. No effect on the PK of AZD9291 after co-administration of rifampicin will be concluded if the lower bound of the 90% CIs for the ratios (Period 2 versus Period 1) of AZD9291 AUC_{tau} and $C_{ss,max}$ are both above 50%.

For AZD9291 and its metabolites, analyses of $t_{ss,max}$ will be 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 will be presented.

In addition to a graphical assessment of the steady state for AZD9291, a statistical evaluation of the steady state will also be made using the trough plasma concentrations collected on Days 7, 14, 21, and 28 (pre-dose and 24 hour). All valid concentrations on the natural-log scale will be analysed using analysis of variance.

As exploratory analyses, the onset of potential induction by rifampicin (AZD9291, AZ5104 and AZ7550 troughs and concentration of 4β-hydroxy-cholesterol after addition relative to before addition of rifampicin) will be explored. Also, the offset of potential induction by rifampicin (AZD9291, AZ5104 and AZ7550 troughs and concentration of 4β-hydroxy-cholesterol after discontinuation of rifampicin relative to before addition of rifampicin) will be explored. An evaluation of potential increase in CYP3A4 enzyme activity, interpreted as the concentration of 4β-hydroxy-cholesterol after dosing relative to before dosing with AZD9291, will be explored. Descriptive statistics (n, arithmetic mean, SD, CV, minimum, median, maximum and geometric mean) will include the ratio of post baseline to baseline concentration with 90% CIs calculated by natural log-transformed data. These results will be back-transformed for presentation.

Steady state of rifampicin will be assessed graphically.

Safety analyses: Safety data will be listed and summarised using descriptive statistics.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
λ_z	Terminal rate constant
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve from zero extrapolated to infinity
AUC_{tau}	Area under the plasma concentration-time curve from zero to the end of the dosing interval
BCRP	Breast cancer receptor protein
CI	Confidence interval
C_{last}	Plasma concentration at the last assessment
CL_{ss}/F	Apparent plasma clearance after multiple dosing
C_{max}	Maximum plasma concentration
CSA	Clinical Study Agreement
$C_{ss,max}$	Maximum plasma concentration after multiple dosing
$C_{ss,min}$	Minimum plasma concentration over the dosing interval
CSR	Clinical Study Report
CTCAE	(National cancer institute) Common Terminology Criteria for Adverse Event
CV	Coefficient of variation
CYP1A2	Cytochrome P450 1A2
CYP2C8	Cytochrome P450 2C8
CYP3A4	Cytochrome P450 3A4
DMP	Data management plan
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram

Abbreviation or special term	Explanation
ECOG	Eastern Cooperative Oncology Group
eCRF	Case Report Form (electronic)
EGFR	Epidermal growth factor receptor
EGFRm+	EGFR mutation positive
GCP	Good Clinical Practice
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methyl-glutaryl coenzyme A
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ILD	Interstitial lung disease
INR	International normalised ratio
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
$MRAUC_{tau}$	Metabolite to parent ratio of AUC_{tau}
$MRC_{ss,max}$	Metabolite to parent ratio for $C_{ss,max}$
MUGA	Multiple Gated Acquisition Scan
NCCN	National Comprehensive Cancer Network
NSCLC	Non small cell lung cancer
OAE	Other Significant Adverse Event
PI	Principal Investigator
PK	Pharmacokinetic
QT	Interval on the electrocardiogram representing the duration of depolarisation and repolarisation of the heart
QTc	The QT interval corrected for heart rate
QTcF	The QT interval corrected for heart rate using Fridericia's correction factor
SAE	Serious adverse event
SAP	Statistical Analysis Plan

Abbreviation or special term	Explanation
SD	Standard deviation
$t_{½}$	Terminal half-life
TKI	Tyrosine Kinase Inhibitor
t_{max}	Time to C_{max}
$t_{ss,max}$	Time to C_{max} after multiple dosing
ULN	Upper limit of normal
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Investigators should be familiar with the current AZD9291 Investigator's Brochure (IB).

Lung cancer has been the most common cancer in the world for several decades, and by 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths (18.2% of the total) (Ferlay et al 2010). Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis approximately 70% of patients with NSCLC already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of early stage NSCLC patients who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer (Pisters and Le Chevalier 2005). Patients presenting with unselected advanced NSCLC have a median overall survival of 10 to 12 months (Bonomi 2010).

Treatment of advanced NSCLC can be guided by the presence of certain molecular drivers such as *EGFR*, anaplastic lymphoma kinase (*AnLK*) and *KRAS* mutations. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are now the established first line therapy in patients with NSCLC known to have activating mutations in *EGFR* (EGFRm+) (NCCN 2012). Patients with EGFRm+ NSCLC who receive EGFR TKIs have a median overall survival of more than 2 years (Heuckmann et al 2012). The incidence of EGFRm+ NSCLC is approximately 10% to 15% and 30% to 40% of patients in the West and Asia, respectively. Second line therapy for EGFRm+ NSCLC is usually a platinum based chemotherapy. There is no global standard of care for third line therapy, but this may include chemotherapy or single agent therapy with an EGFR TKI (Becker et al 2011, Langer et al 2012).

AZD9291 is a potent irreversible inhibitor of both the single EGFRm+ (TKI sensitivity conferring mutation) and dual EGFRm+/T790M+ (TKI resistance conferring mutation) receptor forms of EGFR with a significant selectivity margin over wild-type EGFR. Therefore AZD9291 has the potential to provide clinical benefit to patients with advanced NSCLC harbouring both the single sensitivity mutations and the resistance mutation following prior therapy with an EGFR TKI. The clinical development programme with AZD9291 will initially assess the safety and efficacy of AZD9291 in patients with advanced NSCLC whose cancers have progressed following an EGFR TKI regimen (with or without additional chemotherapy regimens), as they currently represent a major unmet medical need population. Importantly, preliminary data from an ongoing Phase I study (D5160C00001) in this patient population has demonstrated good evidence of efficacy, while treatment with AZD9291 has been well tolerated across a range of doses (Ranson et al 2013) (refer to the latest edition of the IB for further details).

Pharmacokinetic data show that AZD9291 was slowly absorbed following oral dosing, with patients (D5160C00001) and healthy volunteers (D5160C00005) generally showing a lag time of up to 4 hours in the AZD9291 plasma concentration versus time profile following single dose administration. Following multiple dose administration, AZD9291 steady state appeared to be achieved by 22 days of dosing. The geometric mean accumulation of AZD9291 in the plasma was approximately 4.5 fold after 22 days of dosing. Accumulation of AZD9291 appeared to be consistent with the dosing frequency and observed apparent mean (min-max) terminal half-life ($t_{½}$) of 55.18 (29.7-146) hours in patients. In healthy volunteers after a single oral (capsule) dose of AZD9291 the observed apparent mean (min-max) $t_{½}$ was 52.72 (32.5-72.0) hours.

Both AZ5104 and AZ7550 were slowly produced after a single dose of AZD9291 to patients with time to maximum plasma concentration (t_{max}) ranging from 4 to 72 hours with generally a plateau in concentration observed for 2 to 3 days after dosing. The $t_{½}$ of AZ5104 and AZ7550 was poorly characterised after single dose of AZD9291 but appeared to be longer than that of AZD9291. After a single administration of AZD9291 as capsules to healthy volunteers AZ5104 and AZ7550 were slowly produced with t_{max} ranging from 6 to 72 hours, with a plateau in concentration observed for 3 to 4 days after dosing. The concentration of AZ5104 and AZ7550 then declined mono-exponentially: AZ5104 with similar $t_{½}$ to AZD9291 and AZ7550 displaying a slightly longer half-life. The observed apparent mean (min-max) $t_{½}$ was 48.92 (31.1–65.2) and 73.21 (52.4–105) hours for AZ5104 and AZ7550, respectively.

No human-specific metabolites were found in hepatocytes in *in vitro* metabolism studies. Metabolism was primarily to hydroxylated and dealkylated products with conjugation to a range of glutathione, cysteineglycine, glucuronide and sulphate conjugates. Metabolism of AZD9291 can lead to the formation of potentially pharmacologically active metabolites AZ5104 and AZ5770. CYP3A4 and/or CYP3A5 were the principal P450 isoenzymes responsible for human metabolism of AZD9291, AZ5104 and AZ7550 in recombinant microsomes. Hence the current study has been designed to investigate the effect of a CYP3A4/5 inducer (rifampicin) on the PK of AZD9291.

Pre-clinically, AZD9291 demonstrated induction of CYP3A4 messenger RNA in HepaRG cells with maximal fold induction of 22.5% of the positive control at 18.75 μM. Therefore AZD9291 may have the potential to induce CYP3A4 in a clinical setting. Assessment of 4β-hydroxy-cholesterol after dosing relative to before dosing with AZD9291 has been included to explore potential induction of CYP3A4 metabolism mediated by AZD9291 alone and when combined with a potent CYP3A4 inducer.

1.2 Rationale for study design, doses and control groups

This is a 2-part study in patients with EGFRm+ NSCLC who have progressed on an EGFR TKI. Part A will assess the effect of rifampicin on the PK parameters of AZD9291 and metabolites AZ5104 and AZ7550 following multiple oral dosing of both rifampicin and AZD9291 in a fasted state.

Part B will allow patients who have completed Part A to receive a therapeutic dose of AZD9291 on a continuous basis and therefore possibly gain clinical benefit. Safety and tolerability data collected in Part B will add to the safety database for patients with EGFRm+ NSCLC treated with oral AZD9291.

Rifampicin is a known potent CYP inducer and is therefore a standard compound to use in such drug interaction studies. For the evaluation of the potential effects of rifampicin on AZD9291 and metabolite PK, a 3-period sequential design allows evaluation of onset, and extent of induction effect, following addition of rifampicin to a standard dose of AZD9291 in Period 2 as well as the time course to offset of the potential drug interaction.

The rationale for the doses of study treatments chosen are as follows:

- AZD9291 80 mg once daily will deliver exposure that has been previously demonstrated to be acceptable and tolerated in patients with cancer, and is the dose that has been selected for the Phase II registration trials.

- The recommended daily oral dose of rifampicin is 600 mg. In the current study, the regimen selected for rifampicin will be 600 mg once daily, which is a regimen that is recommended to achieve maximum induction of CYP3A activity. Rifampicin 600 mg will be administered once daily for 21 days (Days 29 to 49) to allow full induction as well as attainment of any adjusted steady-state conditions for AZD9291 and metabolites.

Patients with cancer are required for this study because pre-clinical toxicology data preclude the use of AZD9291 in healthy volunteers after multiple dosing. This study requires AZD9291 to be at steady state. Determining the impact of rifampicin on steady state AZD9291 PK allows full characterisation of the effect of rifampicin on AZD9291 and its metabolites. Evaluation of exposure (area under the plasma-concentration curve [AUC] and maximum plasma concentration [C_{max}]) to AZD9291 will be the primary endpoint to assess the effect of rifampicin on AZD9291 PK in Part A of this study. AZ5104 and AZ7550 are potentially active metabolites of AZD9291 however they circulate at approximately 10% each of AZD9291. Additionally, production and clearance of AZ5104 and AZ7550 are thought to be predominately via CYP3A4 mediated metabolism, so metabolite: AZD9291 ratios are expected to remain approximately constant if CYP3A4 activity is changed. Consequently, changes in metabolites will be assessed as a secondary objective of the protocol and may be further supplemented with a subsequent population PK analysis.

Safety and tolerability data will be collected as per regulatory and ethical guidelines and to expand the safety/tolerability database for patients with EGFRm+ NSCLC treated with oral AZD9291 tablets.

1.3 Benefit/risk and ethical assessment

This study is robustly designed to assess the primary objective while minimising the number of patients exposed to AZD9291. AstraZeneca considers that AZD9291 continues to

demonstrate an overall acceptable benefit-risk balance to support its further clinical development. Pre-clinical and emerging clinical tolerability data from patients indicate that AZD9291 is generally well tolerated by patients with advanced cancer (please refer to the IB for details). Importantly, preliminary data from an ongoing Phase I study (D5160C00001) in this patient population has demonstrated AZD9291 to be well tolerated, with good evidence of efficacy (Ranson et al 2013). Of the 174 patients that received at least a single dose of AZD9291 (data cut off in IB of 19 November 2013), 105/174 (60%) reported any adverse event (AE), with the majority (>55%) being National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Grade 1. The most common AEs were rash (grouped terms), diarrhoea, pruritus and nausea, with no dose-limiting toxicities reported at any dose in escalation cohorts up to 160 mg (refer to the latest edition of the IB for further information including details of discontinuations, dose reductions, deaths and serious adverse events [SAEs]). All trials of AZD9291 exclude patients with clinically significant toxicities related to prior treatments in addition to specifically excluding patients with a history of interstitial lung disease (ILD) or clinically active ILD as this is an uncommon but well documented EGFR-related toxicity. All patients are assessed for possible known EGFR-related toxicities and detailed information on the management of toxicities related to investigational product (IP) is provided for all AZD9291 studies (Section 6.7).

All AEs, vital signs, electrocardiograms (ECGs) and laboratory data will be collected and reviewed by the Principal Investigator (PI) and clinical research staff on an ongoing basis.

Although patients may not benefit from rifampicin there may be some benefit gained from AZD9291. Further benefit may be gained in Part B. If the Investigator believes it is in the patient's interest, the patient may continue treatment with AZD9291 until such time as the Investigator believes they are no longer deriving clinical benefit or they stop taking AZD9291 for any other reason.

In addition to their potential inhibitory effect on CYP3A4, *in vitro* data suggest that AZD9291 and metabolites AZ5104 and AZ7550 may also have the potential to inhibit CYP2C8 and the breast cancer resistance protein (BCRP) transporter or to induce CYP3A4, CYP1A2, CYP2C and/or P-glycoprotein. Measures have been taken in this protocol to provide appropriate restrictions and/or direction for use of concomitant medications which are substrates for these metabolising enzymes or transporters.

The data generated from this study will support submissions for AZD9291 in the treatment of NSCLC. The overall risk for the patients who participate in this study to assess how co-administration of rifampicin affects the PK of AZD9291 is acceptable.

1.4 Study design

This is a Phase I, open-label, non-randomised, two-part study in patients with EGFRm+ NSCLC who have progressed on an EGFR TKI. Part A will assess the effect of rifampicin on the PK parameters of AZD9291 and metabolites AZ5104 and AZ7550 following multiple oral dosing of both rifampicin and AZD9291 in a fasted state.

Part B will allow patients further access to AZD9291 after the PK phase (Part A) and will provide for additional safety data collection.

This study will be conducted at approximately 16 sites across Asia, North America and Western Europe with approximately 38 patients enrolled and dosed to achieve at least 30 evaluable patients. Additional patients may be enrolled to ensure the minimum number of evaluable patients. For a patient to be evaluable the patient must have completed the required PK collections for the primary comparison (AZD9291 and rifampicin combined [Period 2] compared to AZD9291 administered alone [Period 1]).

Part A

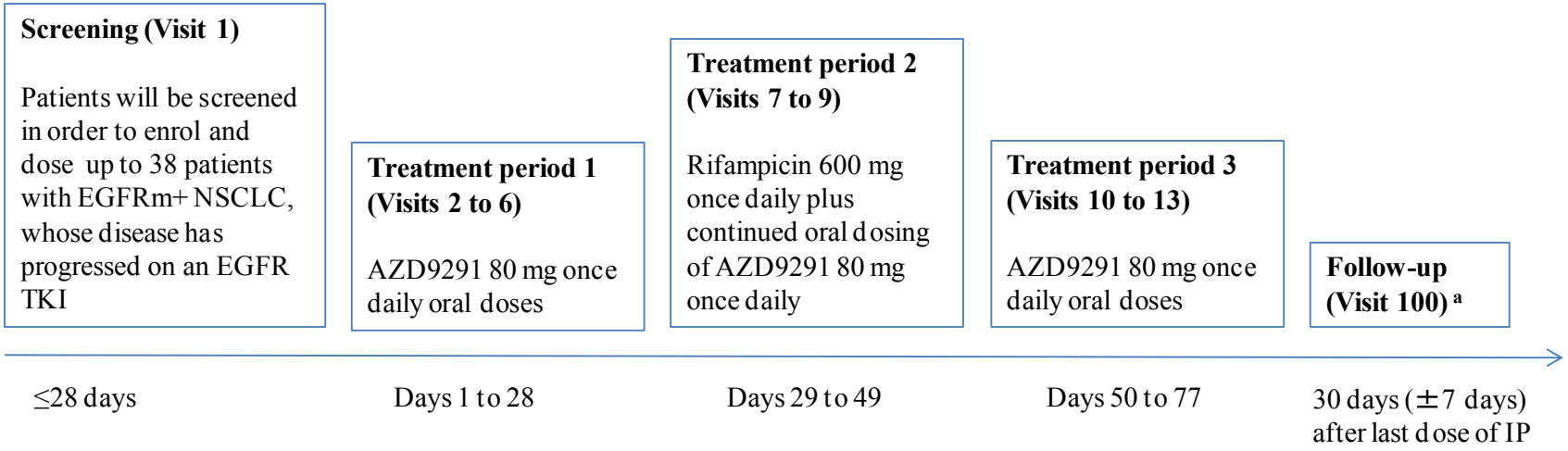
Part A is a non-randomised, open-label, 3-period design. A study flow chart for Part A is presented in Figure 1. Patients will receive AZD9291 80 mg once daily for 77 days (Days 1 to 77). Patients will also receive oral daily doses of rifampicin for 21 days (Days 29 to 49) concurrently with AZD9291.

Part B

On completion of Part A, patients may continue to take AZD9291 tablets (80 mg once daily) in Part B if they and the Investigator agree that this is appropriate. Patients should start Part B immediately (ie, 24 hours) after the last dose received in Part A (Day 78 after the 24-hour sample collection). Patients will have weekly clinic visits for the first 4 weeks; thereafter visits will be every 4 weeks. Safety assessments will be collected and there will be no formal evaluation of efficacy. Patients' medical/oncological care will be according to local clinical practice. Part B will be of approximately 12 months' duration from the date the last patient enters this part of the study (allowing for any scheduled Part B follow-up assessments).

During and after Part B, patients may continue to take AZD9291, if they and the Investigator deem it appropriate, until such time as the Investigator believes they are no longer deriving clinical benefit or they stop taking AZD9291 for any other reason. After the end of Part B (approximately 12 months after the last patient entered Part B), patients will be seen as per their normal routine clinical schedule. No clinical data will be collected for those patients who continue to receive AZD9291 as part of continued access, other than the data specified in Section 7.8.

Figure 1 Study flow chart – Part A



[a] For patients who withdraw from the study prematurely and who do not participate in Part B

2. STUDY OBJECTIVES

2.1 Primary objective

Part A: To investigate the effect of multiple oral dosing of rifampicin on the steady-state exposure of AZD9291 ($C_{ss,max}$ and AUC_{tau}), following oral dosing in patients with EGFRm+ NSCLC following progression on a EGFR TKI.

2.2 Secondary objective

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.

2.3 Safety objectives

Part A: To examine the safety and tolerability of AZD9291 in patients with EGFRm+ NSCLC in the presence and absence of co-administered rifampicin.

Part B: To examine the safety and tolerability of AZD9291 following extended administration in patients with EGFRm+ NSCLC.

2.4 Exploratory objectives

Part A: To assess the induction potential of AZD9291 on CYP3A4.

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.

Part A: To provide data to allow analysis using population PK approaches.

2.5 Outcome variables

Analysis: Part A	**Outcome Measures:**
PK	
Primary AZD9291	• $C_{ss,max}$ and AUC_{tau} (alone [Day 28] and in combination with rifampicin [Day 49])
Secondary AZD9291	• AUC_{tau}, 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, and Days 35, 42, and 49 of Period 2, and Days 56, 63, 70, and 77 of Period 3
Secondary AZ5104 and AZ7550	• AUC_{tau}, $C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$, and metabolic ratios (AZ5104 to AZD9291 and AZ7550 to AZD9291), $MRAUC_{tau}$ and $MRC_{ss,max}$ in all periods • trough concentrations on Days 7, 14, 21, and 28 of Period 1, and Days 35, 42, and 49 of Period 2, and Days 56, 63, 70, and 77 of Period 3

Secondary rifampicin	• AUC_{tau}, $C_{ss,max,}$ $t_{ss,max}$, $C_{ss,min}$, and CL_{ss}/F
Exploratory 4β-hydroxy-cholesterol	• 4β-hydroxy-cholesterol at baseline and collected throughout the 77-day AZD9291 dosing period

Safety analysis : Part A and B	**Outcome Measures :**
	• AEs/SAEs graded by CTCAE (version 4) • Vital signs (blood pressure/pulse/temperature/height/weight) • Laboratory parameters (clinical chemistry/haematology/urinalysis) • Physical examination • Standard 12-lead ECGs • Echocardiogram/multiple gated acquisition scan (MUGA)

3. PATIENT SELECTION, ENROLMENT, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study patient should fulfil the following criteria:

1. Provision of written informed consent prior to any study-specific procedures. Procedures performed for routine clinical practice before the provision of written consent are acceptable if not intentionally done for study purposes.

2. Male or female, aged at least 18 years.

3. Histological or cytological confirmation diagnosis of NSCLC.

4. Radiological documentation of disease progression while on a previous continuous treatment with an EGFR TKI, eg gefitinib, erlotinib or afatinib. In addition, other lines of therapy may have been given. All patients must have documented radiological progression on the last treatment administered prior to enrolling in the study.

5. Confirmation that the tumour harbours an *EGFR* mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q).

6. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 with no deterioration over the previous 2 weeks (Appendix G).

7. Patients must have a life expectancy of ≥12 weeks as estimated at the time of screening.

8. Females should be using adequate contraceptive measures and must have a negative pregnancy test prior to start of dosing if of child-bearing potential, or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

   – Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments

   – Women under 50 years old would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution

   – Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, but not tubal ligation.

9. Patients are willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.

10. Male patients should be willing to use barrier contraception, ie, condoms, until 6 months after last study drug is taken.

11. For inclusion in **optional genetic research**, patients must provide separate informed consent. If a patient declines to consent to optional genetic research, this does not exclude the patient from participating in any aspect of the study.

12. Contact lens wearers must be prepared to not wear contact lenses and wear glasses for the duration of the rifampicin dosing.

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

2. Previous enrolment and dosing in the present study. Patients who were enrolled, screened but not dosed (ie, withdrew from the study prior to dosing) may be re-enrolled and re-screened if in the opinion of the Investigator, the reason(s) for earlier withdrawal no longer applies.

3. Participation in another clinical study with an IP during the last 14 days (or a longer period depending on the defined characteristics of the agents used).

4. Treatment with any of the following:

   - Treatment with an EGFR TKI (eg, erlotinib or gefitinib) within 8 days or approximately 5 x half-life, whichever is the longer, of the first dose of study treatment

   - Any cytotoxic chemotherapy, investigational agents or other anticancer drugs from a previous treatment regimen or clinical study within 14 days of the first dose of study treatment

   - Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study treatment

   - Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment, with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation which must be completed within 4 weeks of the first dose of study treatment

   - Patients currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be potent inhibitors of CYP3A4 (at least 1 week prior) and potent inducers of CYP3A4 (at least 3 week prior). All patients in Part B and continued access must avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known potent inducer effects on CYP3A4 (Appendix H).

5. Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy.

6. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days of the first administration of the IP until the final PK sample collection on Day 78 of Part A.

7. Spinal cord compression or brain metastases unless asymptomatic, stable and not requiring steroids for at least 4 weeks prior to start of study treatment.

8. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the patient to participate in the study or which would jeopardise compliance with the protocol, or active infection including hepatitis B,

hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required.

9. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:

   - Absolute neutrophil count <1.5 x 10^9/L
   - Platelet count <100 x 10^9/L
   - Haemoglobin <90 g/L
   - Alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases
   - Aspartate aminotransferase (AST) >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases
   - Total bilirubin >1.5 times ULN if no liver metastases or >3 times ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia) or liver metastases
   - Creatinine >1.5 times ULN concurrent with creatinine clearance <50 ml/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN.

10. Any of the following cardiac criteria:

   - Mean resting corrected QT interval corrected for heart rate using Fridericia's correction factor (QTcF) >470 msec obtained from 3 electrocardiograms (ECGs)
   - Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG eg, complete left bundle branch block, third degree heart block, second degree heart block, PR interval >250 msec
   - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age or any concomitant medication known to prolong the QT interval (Appendix H).

11. Patients unable to swallow orally administered medication or patients with gastrointestinal disorders or significant gastrointestinal resection likely to interfere with the absorption of AZD9291.

12. Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.

13. Women who are breastfeeding.

14. Patients with a known hypersensitivity to AZD9291 or any of the excipients of the product.

15. Judgement by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

16. Patients with a known hypersensitivity to rifampicin or any of the excipients of the product.

17. Concomitant medication contraindicated for use with rifampicin (including, but not limited to): cisapride, oral midazolam, nisoldipine, pimozide, quinidine, dofetilide, triazolam, levacetylmethadol (levomethadyl), 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA)-reductase inhibitors metabolised by CYP3A4, such as lovastatin and simvastatin, ergot alkaloids metabolised by CYP3A4, such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine).

In addition, the following is considered a criterion for exclusion from the exploratory genetic research:

18. Previous allogenic bone marrow transplant.

19. Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment

The Principal Investigator(s) or designee will:

1. Obtain signed informed consent from the potential patient before any study-specific procedures are performed.

2. Assign each potential patient a unique enrolment code (E-code) beginning with ‘E#’ after written informed consent has been obtained. The E-code (EWWXXYZZ) will consist of a 2-digit country number (WW), a 2-digit site number (XX), a 1-digit study number (Y) and a 2-digit patient number (ZZ, starting with 01) issued by the study centre in order of informed consent taken.

3. Determine patient eligibility. See Section 3.1 and 3.2.

If a patient withdraws from participation in the study, then his/her enrolment numbers cannot be reused.

Patients who were enrolled, screened but not dosed (ie, withdrew from the study prior to dosing) may be re-enrolled and re-screened if, in the opinion of the Investigator, the reason(s) for earlier withdrawal no longer applies. Such patients will be given a new enrolment code upon re-enrolment. Patients cannot re-enter the study if dosed and subsequently withdrawn from the study. Patients who discontinue their participation in Part A prematurely may still be eligible to continue to take AZD9291 in Part B, if the Investigator believes it is in the patient's interest, ie, discontinuation from Part A may not necessarily result in withdrawal from the study.

3.4 Procedures for handling incorrectly enrolled patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

Where patients who do not meet the selection criteria are enrolled in error or incorrectly started on study treatment, or where patients subsequently fail to meet the study criteria post-initiation, a discussion should occur between the AstraZeneca Physician or his/her representative and the Investigator regarding whether to continue or discontinue the patient from study treatment. Once a decision is made, Investigators need to ensure they comply with all applicable requirements for human patient protection and ethical review.

The AstraZeneca Physician or representative is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study treatment stopped and be withdrawn from the study.

3.5 Methods for assigning treatment groups (not applicable)

3.6 Methods for ensuring blinding (not applicable)

3.7 Methods for unblinding (not applicable)

3.8 Restrictions

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

1. Females of child bearing potential should use reliable methods of contraception (Appendix F) from the time of screening until 6 months after discontinuing study treatment. Acceptable methods of contraception include total sexual abstinence, tubal ligation, hormonal contraceptives that are not prone to drug-drug interactions (IUS Levonorgestrel Intra Uterine System [Mirena], Medroxyprogesterone injections [Depo-Provera]), copper-banded intra-uterine devices and vasectomised partner. All hormonal methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse.

2. Male patients should be asked to use barrier contraceptives (ie, by use of condoms) during sex with all partners during the study and for a washout period of 6 months. Where a sexual partner of a male participant is a woman of child-bearing potential, patients should avoid procreation for 6 months after completion of study treatment. Patients should refrain from donating sperm from the start of dosing until 6 months after discontinuing study treatment. If male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

3. In Part A, patients should not consume any grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days of the first administration of the IP until the final PK sample collection on Day 78.

4. Patients who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE Grade ≤2) while receiving treatment with AZD9291 until at least 1 week after symptoms have resolved. If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE Grade ≥3) ocular events, they must discontinue wearing their contact lenses until at least 1 week after treatment with AZD9291 is permanently discontinued. Patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed by a study doctor, at any time during the study until 1 week after AZD9291 has been permanently discontinued. Patient should consult the clinic/hospital promptly if they have any concerns.

5. Patients should maintain a consistent diet during Part A of the study and should not change their diet between study periods (Periods 1, 2 and 3 of Part A).

Details of restrictions related to concomitant medications can be found in Section 7.7.

3.9 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse event.
- Severe non-compliance with the study protocol.
- Worsened condition.
- Progressive disease.
- Pregnancy.

- Incorrectly enrolled patients.

- The Investigator believes they are no longer deriving clinical benefit (Part B and continued access).

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue IP or withdraw from the study (ie, IP and assessments – see Section 3.10), without prejudice to further treatment. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Section 6); and all study drugs should be returned by the patient.

In Part A and Part B, any patient discontinuing IP should be seen at 30 days (±7 days) after their last dose for the evaluations outlined in the study plan (see Table 1 and Table 2). After discontinuation of study drug, the Investigator will perform the best possible observation(s), test(s), and evaluation(s), as well as give appropriate medication and all possible measures for the safety of the patient. In addition, they will record on the eCRF the date of discontinuation, the reasons, manifestation, and treatment at the time of discontinuation. If patients discontinue IP, the AstraZeneca monitor or its representative must be informed immediately. The patient should return all IP.

After discontinuation of the study drug in Part A or Part B, all ongoing AEs or SAEs must be followed until resolution unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease, or the patient is lost to follow-up (see Sections 6.3.1 and 6.3.2). All new AEs and SAEs occurring during the 30 calendar days after the last dose of study drug must be reported (if SAEs, they must be reported to AstraZeneca or its representative within 24 hours as described in Section 6.4) and followed to resolution as above. Patients should attend for a follow-up visit 30 (±7) days after discontinuing study drug to collect and/or complete adverse event (AE) information and collect IP. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the Investigator assesses as possibly related to the study drug should also be reported as an AE.

At the end of Part B, patients may continue to receive IP as continued access and undergo follow up as part of their normal routine clinical care. After discontinuation of the IP in the continued access phase of the study, patients should be followed for 30 days to follow up any existing SAEs and monitor for any new SAEs that may be related to IP.

If a patient is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be treated. These patients should have the reason for study withdrawal recorded as 'Eligibility Criteria Not Fulfilled' (ie, patient does not meet the required inclusion

criteria or meets exclusion criteria). This reason for study withdrawal is only valid for screen failures.

3.10.2 Withdrawal of the informed consent

Patients are at any time free to withdraw from the study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Patients may withdraw from any aspects of the optional genetics research (see Sections 3.1 and 5.6) at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study.

Patients will always be asked about the reasons and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. Adverse events will be followed up (see Section 6.3.2) and diaries and all study drug should be returned by the patient.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused.

Patients may be withdrawn from the study for the following reasons:

- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment.
- Risk to patients as judged by the Investigator and/or AstraZeneca or its representative.
- Severe non-compliance to protocol as judged by the Investigator and/or AstraZeneca or its representative.
- Incorrectly enrolled patients, ie, the patient does not meet the required inclusion/exclusion criteria for the study.
- The patient becomes pregnant.
- Patient is lost to follow-up.

If a patient wishes to withdraw their consent to further participation in the study entirely this should be clearly documented in the patient notes and in the clinical study database.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, study patients are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug

- are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation or follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Plan – Part A

Assessments	**Screening**	**Treatment Period 1**						**Treatment Period 2**				**Treatment Period 3**						**Follow-up**[a]
Visits	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10**	**11**	**12**	**13**			**100**
Day[b]	**-28 to -2 days before dosing**	**-1**[b]	**1**	**7 ±1**	**14 ±1**	**21 ±1**	**28 ±1**	**29**	**35 ±1**	**42 ±1**	**49 ±1**	**50**	**56 ±1**	**63 ±1**	**70 ±1**	**77 ±1**	**78**	**30 (±7) days after last dose**
Resident in clinic							<----------> [c]			<----------> [c]					<----------> [c]		
Outpatient visits	X	X	X	X	X	X		X	X			X	X	X			X	
Written informed consent	X																	
Demography and baseline characteristics	X																	
Medical/surgical history	X																	
Inclusion/exclusion criteria	X																	
ECOG performance status	X																	
Height and weight	X		X[d]				X[d]				X[d]					X[d]		
Ophthalmologic examination	X																	
Physical examination	X	X					X[o]				X[o]						X	X
Vital signs (BP/pulse)[e]	X						X				X					X		X
Body temperature	X	X	X				X				X					X		X
Resting standard 12-lead ECG[e]	X						X				X					X		X
Echo/MUGA	X																	X
HBV and HCV Serology	X																	
Haematology/coagulation[f]/ biochemistry	X	X		X	X	X	X		X	X	X		X	X	X		X	X
Urinalysis[g]	X	X		X	X	X	X		X	X	X		X	X	X		X	X
Serum/urine pregnancy test[h]	X		X				X				X					X		X

Assessments	**Screening**	**Treatment Period 1**						**Treatment Period 2**			**Treatment Period 3**						**Follow-up**[a]
Visits	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10**	**11**	**12**	**13**		**100**
Day[b]	**-28 to -2 days before dosing**	**-1**[b]	**1**	**7 ±1**	**14 ±1**	**21 ±1**	**28 ±1**	**29**	**35 ±1**	**42 ±1**	**49 ±1**	**50**	**56 ±1**	**63 ±1**	**70 ±1**	**77 ±1**	**78**	**30 (±7) days after last dose**
Resident in clinic							<----------> [c]			<----------> [c]					<----------> [c]		
Outpatient visits	X	X	X	X	X	X		X	X			X	X	X			X
Pharmacogenetics blood sample[i]		X															
AZD9291 administration[j]			X	X	X	X	X	X	X	X	X	X	X	X	X		
Rifampicin administration[k]								X	X	X	X						
Diary			P	C	C	C	C		C	C	C		C	C	C	C		
AZD9291 PK blood sampling[l]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Rifampicin blood sampling[m]									X	X	X	X						
Blood sample for 4β-hydroxycholesterol			X			X	X				X				X	X		
Prior and concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AZD9291 dispensed/returned			X				X				X					X		

[a] For patients who withdraw from the study prematurely and do not go on to Part B.

[b] Day 1 is the day of dosing; Day -1 is the day before dosing. All Day -1 procedures must be performed on Day -1 or pre-dose on Day 1 provided the results are reviewed before dosing. If the patient has been screened within 48 hours of Day 1, safety laboratory tests (haematology, coagulation, biochemistry and urinalysis) do not need to be repeated.

[c] Patients will check into the clinic on the morning of Day 28, Day 49 and Day 77 and be prepared to stay overnight for 24 hours serial blood collections and safety assessments.

[d] Height to be assessed at Screening only. Weight to be assessed at all timepoints; the same weighing scales should be used at each visit. For height and weight, indoor clothing may be worn but shoes should be removed.

[e] Supine BP and pulse will be measured pre-dose, using a semi automatic BP recording device with an appropriate cuff size after the patient has been resting in bed for 10 minutes. For ECG, patients will rest at least 10 minutes before the start of each ECG recording and they must be in the same supine (maximum 30 degrees flexion in the hip and feet not in contact with the footboard) body position at each recording timepoint. On Days 28, 49 and 77, assessments will be performed pre-dose and at 3, 6 and 12 hours post-dose.

[f] For haematology and clinical chemistry tests, see Table 4. Coagulation (aPTT and INR) will be performed at Screening and if clinically indicated. For patients taking warfarin reference Section 7.7.

[g] Protein, blood and glucose; microscopic analysis is to be performed if required.

[h] Pre-menopausal women of childbearing potential must have a negative urine or serum pregnancy test within 28 days prior to starting treatment and a confirmatory test before treatment at Visit 1. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately. Pregnancy test will be repeated at the follow-up 30 (±7) days after last dose of study medication.

[i] Patients will be invited to participate in optional genetic research. The patient must provide separate informed consent. If the patient declines to consent to the optional genetic research, this will not exclude the patient from participating in any other aspect of the study.

[j] Patients will take AZD9291 80 mg once daily fasted from Day 1 to Day 77. Doses on Day 28, Day 49, and Day 77 will be administered at the clinic by clinic personnel. AZD9291 will be administered fasted from at least 2 hours before dosing to at least 2 hours after dosing. The study treatments should be swallowed whole with approximately 240 mL of water, and not chewed, crushed, dissolved or divided. On Days 28, 49, and 77, water can be allowed as desired except for 1 hour before and after AZD9291 administration. On all other study days there are no water restrictions. The same fasting restrictions apply to self-administered doses.

[k] Patients will take 600 mg rifampicin once daily from Day 29 to Day 49. In Period 2, doses from Day 29 until Day 48 will be self-administered by the patients. The doses on Day 49 (Period 2 Day 21) will be administered at the clinic by clinic personnel. All rifampicin doses should be taken fasted from at least 2 hours before dosing to at least 2 hours after dosing.

[l] AZD9291 PK samples will be collected at the times specified in Table 3.

[m] Rifampicin PK samples will be collected at the times specified in Table 3.

[n] If a patient withdraws for any reason, any ongoing study-related toxicity or SAE at discontinuation must be monitored until resolution. After discontinuation from treatment, patients must be followed up for any new AEs for 30 calendar days after the last dose of study drug. Any existing and any new AEs occurring during the 30-day period must be recorded and followed to resolution if possible.

[o] Brief physical examination (including general appearance, skin, abdomen, cardiovascular system, and lungs).

AE adverse event; aPTT activated partial thromboplastin time BP blood pressure; C check diary; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; HBV Hepatitis B; HCV Hepatitis C virus; INR international normalised ratio; IP investigational product; MUGA multiple gated acquisition scan; P provide diary; PK pharmacokinetics; SAE serious adverse event

Table 2 Study Plan – Part B

Visit Number/Day	Visit 13, Day 77, Part A[a]	Visit 101/ Day 84	Visit 102/ Day 91	Visit 103/ Day 98	Visit 104/ Day 105	Subsequent on-treatment visits every 4 weeks[b] Visit 105 onwards Day 1 of next visit period (Equals Day 133 [Week 19] etc)	Follow-up 30 (±7) days after IP permanently discontinued in Part B[c]
Visit window		±3d	±3d	±3d	±3d	±7d	±7d
Physical examination[d]		X	X	X	X	X	X
Vital signs (BP, pulse, temperature, weight)[e]		X	X	X	X	X	X
Haematology/clinical chemistry		X	X	X	X	X	X
Serum/urine pregnancy test[f]	<----------> [f]						X
Resting standard 12-lead ECG[e]						X	X
Echo/MUGA		X				X[g]	X[g]
Adverse events		X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X
AZD9291 dispensed/returned[h]	X[i]				X[h]	X[h]	
Disease status[j]	<----------> [j]						

[a] The last visit in Part A (Visit 13, Day 77) will serve as the first visit in Part B.

[b] Visit to take place on Day 1 of a 4-week (28-day) visit period. Visits will continue for approximately 12 months from the date the last patient enters Part B. Patients who continue receiving AZD9291 after Part B (continued access) should have their final on-treatment visit within 4 weeks prior to the end of Part B. No further clinical data will be collected in the study database beyond this time (see Section 7.8).

[c] Follow-up assessments will only be performed for patients who permanently discontinue AZD9291 treatment during Part B.

[d] After baseline, it is not necessary to record any physical examination details on the eCRF; any clinically significant changes should be recorded as AEs.

[e] Supine BP and pulse will be measured pre-dose, after the patient has been resting in bed for 10 minutes. For ECG, patients will rest at least 10 minutes before the start of each ECG recording and they must be in the same supine (maximum 30 degrees flexion in the hip and feet not in contact with the footboard) body position at each recording timepoint. For weight assessment, indoor clothing may be worn but shoes must be removed; the same weighing scales should be used at each visit.

[f] In the event of suspected pregnancy during Part B of the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately. Pregnancy test will be repeated at the follow-up 30 (±7) days after last dose of study medication.

[g] Echo/MUGA to be performed at least every 12 weeks ± 4 weeks: at Visit 106 and then subsequently every 12 weeks ± 4 weeks. Echo/MUGA at follow-up or final on-treatment visit is not required if patients have had one in the previous 6 weeks, as long as their cardiac function is stable. However, if their cardiac function has been unstable or they have had signs or symptoms suggestive of cardiac instability, patients should have Echo/MUGA performed at their follow-up or final on-treatment visit prior to the end of Part B.

[h] Sufficient study treatment should be dispensed for at least each treatment period plus overage; however additional treatment can be dispensed to patients to last longer in accordance with local practice.

[i] The return and dispensing of AZD9291 should be on the evening of Visit 13 (Day 77).

j During Part B no efficacy data will be collected, therefore patients will be monitored as per their normal routine clinical schedule.

Note: Urinalysis will be conducted only if clinically indicated.
AE adverse event; BP blood pressure; ECG electrocardiogram; MUGA multiple gated acquisition scan; SAE serious adverse event.

Table 3 Timing of PK samples – Part A

Day	Time (hours)	AZD9291 PK blood	Rifampicin PK blood	4β-hydroxy-cholesterol
Day 1	Pre-dose			+
Day 7	Pre-dose	+		
Day 14	Pre-dose	+		
Day 21	Pre-dose	+		+
Day 28	Pre-dose, 1, 2, 3, 4, 6, 8, 10 and 12	+		+ (pre-dose)
Day 29	24 (pre-dose)	+		
Day 35	Pre-dose	+	+	
Day 42	Pre-dose	+	+	
Day 49	Pre-dose, 1, 2, 3, 4, 6, 8, 10 and 12	+	+	+ (pre-dose)
Day 50	24 (pre-dose)	+	+	
Day 56	Pre-dose	+		
Day 63	Pre-dose	+		
Day 70	Pre-dose	+		+
Day 77	Pre-dose, 1, 2, 3, 4, 6, 8, 10 and 12	+		+ (pre-dose)
Day 78	24 (pre-dose)	+		

Note: AZD9291 80 mg will be administered once daily on Days 1 to 77
Rifampicin 600 mg will be administered on Days 29 to 49.
See Section 4.2 for a description of the sampling windows around the PK samples.

4.1 Enrolment/screening period

Screening procedures will be performed according to the Study Plan for Part A (Table 1).

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

Patients will be considered to be in screening period until all Visit 1 assessments are completed and eligibility is confirmed. Patients will be considered enrolled and in the treatment period once IP has been initiated.

The study procedures carried out during this period include: physical examination, vital signs (blood pressure, pulse rate, body temperature), ECG, Echo/MUGA, weight, height, ophthalmic examination, demographics, concomitant medication, medical/surgical history, smoking history, blood samples for haematology, clinical chemistry and coagulation, hepatitis B and hepatitis C status, urinalysis, pregnancy test, diagnosis and assessment of the disease for which the IP is being tested (ECOG performance status).

4.2 Treatment period

Descriptions of the procedures for this period are included in the Study Plans for Part A (Table 1) and for Part B (Table 2).

The timing of PK blood samples for AZD9291 and rifampicin is detailed in Table 3.

It is important that PK sampling occurs as close as possible to the scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the timepoint. The sequence to be followed at a particular post-dose timepoint is:

1. ECGs
2. Vital signs
3. PK blood sample (at scheduled time)
4. Any other assessments

Pre-dose vital signs assessments should be collected within 60 minutes prior to dosing.

A 30-minute window will be allowed for PK samples taken at pre-dose (sample must be taken prior to dose), a 5-minute window will be allowed for post-dose samples up to 1 hour; a 10-minute window for samples taken at 2 to 10 hours post-dose and a 1-hour window for samples taken from 12 hours post-dose onwards. The window for trough samples is ±1 day; however, on a given day the trough sample must be collected prior to the next dose of IP.

All Day -1 procedures must be performed in the clinic on Day -1 or pre-dose on Day 1; patients may be admitted on Day 1 if the Day -1 activities (see Table 1) can be completed on the same day. If the patient has been screened within 48 hours of Day 1, safety laboratory tests (haematology, coagulation, biochemistry and urinalysis) do not need to be repeated.

Part A

All treatments (AZD9291 and rifampicin) will be administered with the patient fasted from at least 2 hours before dosing to at least 2 hours after dosing. The study treatments should be swallowed whole with approximately 240 mL of water, and not chewed, crushed, dissolved or divided. Water is allowed as desired except for 1 hour before and after AZD9291 administration on Days 28, 49, and 77. There are no restrictions for water intake on any other study days.

Period 1: On Day 1, patients will attend the clinic and receive a single oral dose of AZD9291 80 mg in the morning, having been fasted from at least 2 hours before dosing to 2 hours post-dose. They will continue to take AZD9291 80 mg once daily, fasted, on an outpatient basis from Day 2 to 27. Patients will return to the clinic on an outpatient basis for PK assessments on Days 7, 14 and 21 prior to taking their daily AZD9291 dose. The AZD9291 dose may be taken in the clinic after collection of the pre-dose PK sample. There is a ±1 day

window for the outpatient visits. Patients will check into the clinic on the morning of Day 28 (±1 day) prior to taking their daily AZD9291 regimen. On the morning of Day 28, patients will receive a single oral dose of AZD9291 80 mg, fasted. Patients will remain resident until 24 hours after the dose of AZD9291, during which time PK blood samples and other safety information will be collected.

Period 2: Treatment Period 2 will start 28 days after the first dose of AZD9291 (Day 29 [±1 day]). On Day 29, patients will commence daily doses of rifampicin (600 mg once daily) and continue daily doses of AZD9291 80 mg once daily for 3 weeks. Rifampicin doses should be taken fasted along with AZD9291. The Day 29 AZD9291 and rifampicin regimen may be taken in the clinic. Patients will then continue to take AZD9291 80 mg once daily and rifampicin 600 mg daily, fasted, on an outpatient basis from Day 30 to 48. Patients will return to the clinic on an outpatient basis for PK assessments on Days 35 and 42 prior to taking their daily AZD9291 and rifampicin dose. The AZD9291 plus rifampicin dose may be taken in the clinic after collection of the pre-dose PK sample. There is a ±1 day window for the outpatient visits. Patients will check into the clinic on the morning of Day 49 (±1 day) prior to taking their daily AZD9291/rifampicin regimen. On the morning of Day 49, patients will receive a single oral dose of AZD9291 80 mg taken concomitantly with rifampicin 600 mg, fasted. They will remain resident until 24 hours after the dose of AZD9291, during which time PK blood samples and safety information will be collected.

Period 3: Treatment Period 3 will start 21 days after the first dose of rifampicin (Day 50). Patients will then continue to take AZD9291 80 mg daily, fasted, on an outpatient basis from Day 50 to 77. The Day 50 AZD9291 regimen may be taken in the clinic. Patients will return to the clinic on an outpatient basis for PK assessments on Days 56, 63 and 70 prior to taking their daily AZD9291 dose. The AZD9291 dose may be taken in the clinic after collection of the pre-dose PK sample. There is a ±1 day window for the outpatient visits. Patients will check into the clinic on the morning of Day 77 (±1 day) prior to taking their daily AZD9291 dose. On the morning of Day 77, patients will receive a single oral dose of AZD9291 80 mg in the morning, fasted. Patients will remain resident until 24 hours after the dose of AZD9291, during which time PK blood samples and other safety information will be collected.

Part B and continued access

AZD9291 can be taken with or without food during Part B and continued access.

On completion of Part A, patients may continue to take AZD9291 tablets (Part B) if they and the Investigator agree that this is appropriate. Patients should start Part B immediately (ie, 24 hours) after the last dose received in Part A (Day 78 after the 24-hour sample collection). Patients will have weekly clinic visits for the first 4 weeks; thereafter visits will be every 4 weeks. Safety assessments as detailed in Table 2 will be collected and there will be no formal evaluation of efficacy. Patients' medical/oncological care will be according to local clinical practice. Part B will be of approximately 12 months' duration from the date the last patient enters this part of the study.

During and after Part B, patients may continue to take AZD9291, if they and the Investigator deem it appropriate, until such time as the Investigator believes they are no longer deriving clinical benefit or they stop taking AZD9291 for any other reason. After the end of Part B (approximately 12 months after the last patient entered Part B), patients will be seen as per their normal routine clinical schedule. After Part B is completed, patients may continue to receive AZD9291 as part of continued access (see Section 7.8). No further data will be recorded, other than the data specified in Section 7.8.

4.3 Follow-up period

Patients will return to the clinic for follow-up assessments 30 days (±7 days) after their last dose, regardless of whether the last dose was in Part A or Part B. Follow-up assessments for Part A are detailed in Table 1; follow-up assessments for Part B are detailed in Table 2.

If the patient's last dose of AZD9291 is in the continued access phase (after Part B), the patient should be contacted 30 days after their last dose of AZD9291 to follow up any existing SAEs and monitor for new SAEs that may be related to IP.

5. STUDY ASSESSMENTS

The Inform Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy assessments (not applicable)

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in the Study Plans (Table 1 for Part A, and Table 2 for Part B). If screening is undertaken with 48 hours of Day 1, safety laboratory tests do not need to be repeated.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The haematology, clinical chemistry, coagulation, and urinalysis will be performed at a local laboratory at or near to the Investigative site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Table 4 Laboratory safety variables

Clinical chemistry (2.7 mL sample)	**Haematology (2.7 mL sample)**
Serum (S)/Plasma (P)-Albumin	Blood (B)-Haemoglobin
S/P-ALT	B-Leukocyte
S/P-AST	B-Haematocrit
S/P-Alkaline phosphatase	B-Red blood cell count
S/P-Bilirubin, total	B-Absolute leukocyte differential count:
S/P-Calcium, total	Neutrophils
S/P-Creatinine	Lymphocytes
S/P-Glucose	Monocytes
S/P-Lactate dehydrogenase	Basophils
S/P-Magnesium	Eosinophils
S/P-Potassium	B-Platelet count
S/P-Sodium	B-Reticulocytes
S/P-Urea nitrogen or Blood urea nitrogen	**Urinalysis (dipstick)[a]**
Coagulation[b] (1.8 mL sample)	U-Glucose
B-Activated partial thromboplastin time	U-Protein
B-International normalised ratio	U-Blood
Serology screen (1.8 mL sample)	**Pregnancy tests**
Hepatitis B and C (HBV, HCV) [c]	Blood or urine

[a] Microscopic analysis should be performed by the hospital's local laboratory if required.
[b] For patients taking warfarin see Section 7.7.
[c] HBV DNA and HCV RNA if required to confirm active disease.
ALT alanine aminotransferase; AST aspartate aminotransferase; HBV hepatitis B virus; HCV hepatitis C virus

Pre-menopausal women of childbearing potential must have a negative urine or serum pregnancy test within 28 days prior to starting study treatment, and a confirmatory test before treatment at Visit 1. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately. The pregnancy test will be repeated at follow-up 30 (±7) days after last dose of study medication (in Part A or Part B as appropriate). Tests will be performed by the hospital's local laboratory. If results are positive, the patient is ineligible/must be discontinued from the study.

Routine urinalysis should be performed if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

NB. In case a patient shows an AST **or** ALT ≥3 x ULN **or** total bilirubin ≥ 2 x ULN please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

5.2.2 Volume of blood

The maximum volumes of blood that will be taken for any given patient for the purposes of the study are as follows:

- Part A: 219.2 mL (see Table 5)
- Part B: 91.8 mL (see Table 6).

Table 5 Blood sample volumes (per patient) – Part A

		Sample Volume (mL)	Number of Samples					Total Volume (mL)
			Screening	Period 1	Period 2	Period 3	FU	
Safety	Clinical chemistry	2.7	1	5	3	4	1	**37.8**
	Haematology	2.7	1	5	3	4	1	**37.8**
Coagulation	aPTT/INR	1.8	1	0	0	0	0	**1.8**
PK	AZD9291 and metabolites	2.0	0	13	12	13	0	**76.0**
	Rifampicin	2.0	0	0	11	1	0	**24.0**
	4β-hydroxy-cholesterol	5.0	0	3	1	2	0	**30.0**
Serology	HBV/HCV	1.8	1	0	0	0	0	**1.8**
PG	Pharmacogenetics sample	10.0	0	1	0	0	0	**10.0**
Total Volume (mL)			**9.0**	**78.0**	**67.2**	**59.6**	**5.4**	**219.2**

Note: Table is for guidance. Exact blood volumes may differ depending on local requirements.
aPTT activated partial thromboplastin time; FU follow-up; HBV hepatitis B; HCV hepatitis C; INR international normalised ratio; PG pharmacogenetics; PK pharmacokinetics

Table 6 Blood sample volumes (per patient) – Part B

		Sample Volume (mL)	Number of Samples			Total Volume (mL)
			Weekly visits	Monthly visits	Follow-up[a]	
Safety	Clinical chemistry	2.7	4	12	1	**29.7**
	Haematology	2.7	4	12	1	**29.7**
Total Volume (mL)			**21.6**	**64.8**	**5.4**	**91.8**

Note: Table is for guidance. Exact blood volumes may differ depending on local requirements. Number of samples is based on a patient being in Part B for 12 months.

[a] Applicable for any patient who permanently discontinues AZD9291 during Part B of the study.

5.2.3 Physical examination

A physical examination will be performed at screening, Day -1 of Part A, at every visit during Part B and at follow-up. Physical examinations conducted during Part B will not be captured on the eCRF.

The physical examination will include a whole body inspection as follows: general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, respiratory, abdomen, neurological, genital/rectal, breast.

If new or aggravated physical findings imply deterioration compared with baseline, the finding should be reported as an AE (Section 6.3.6).

5.2.4 ECG

5.2.4.1 Resting 12-lead ECG

A 12-lead safety ECG (paper ECG printout of 10 seconds for Investigator review) will be taken at the times specified in Table 1 and Table 2.

For each timepoint three ECG recordings should be taken within an approximate 5 minute period. Additional ECGs may be taken at any other time the Investigator deems necessary for safety during the dosing period. The patients will rest for at least 10 minutes before the start of each recording and they must be in the same supine body position (maximum 30 degrees flexion in the hip and feet not in contact with the footboard) at each recording timepoint during all visits.

The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant. The paper copy of each ECG reading will be retained with the patient's completed source documents. Only overall evaluation (normal/abnormal) will be recorded in the eCRF. If there is a clinically significant abnormal ECG findings during the treatment period, this should be recorded on the AE eCRF, according to standard AE collection and reporting processes (see Section 6.3.6).

5.2.5 Echocardiogram/MUGA scan

An echocardiogram or MUGA scan to assess left ventricular ejection fraction (LVEF [%]) will be performed at screening and at the visits indicated in Table 1 and Table 2. The modality of the cardiac function assessments must be consistent within a patient, ie, if an echocardiogram is used for the screening assessment then an echocardiogram should also be used for subsequent scans. The patients should also be examined using the same machine and operator whenever possible. The LVEF value (%) should be recorded on the eCRF.

5.2.6 Vital signs

Vital signs will be performed during Parts A and B, at the times and visits as shown in the Study Plans (see Table 1 and Table 2). However, the Investigator reserves the right to add extra assessments if there are any abnormal findings or for any other reason the Investigator feels meets this requirement.

Deterioration as compared with baseline in protocol-mandated vital signs should only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP, or the Investigator insists the abnormality should be reported as an AE (see Section 6.3.6).

5.2.6.1 Pulse and blood pressure

Supine blood pressure and pulse rate will be measured as show in the Study Plans (see Table 1 and Table 2), using a semi-automatic blood pressure recording device with an appropriate cuff size after the patient has been resting in bed for 10 minutes.

5.2.6.2 Body temperature

Body temperature will be assessed at the visits as shown in the Study Plans (see Table 1 and Table 2), using a semi-automatic body temperature recording device.

5.2.6.3 Weight and height

Height and weight will be assessed at the visits as shown in the Study Plans (see Table 1 and Table 2). Indoor clothing may be worn but shoes should be removed. For weight assessment, the same weighing scales should be used at each visit.

5.2.7 Other safety assessments

5.2.7.1 Ophthalmologic examination

Full ophthalmic assessment, including slit lamp examination, should be performed at Screening and if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Ophthalmology examination results at Screening and for additional ophthalmic assessments during Part B should be collected in the eCRF.

Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs should be performed to record any clinically significant

findings. These photographs should be available for central review by AstraZeneca and AstraZeneca representatives if necessary.

Patients experiencing corneal ulceration will not be permitted to restart study treatment.

5.3 Other assessments (not applicable)

5.4 Pharmacokinetics

5.4.1 Collection of samples

Venous blood samples for determination of concentrations of AZD9291 and its metabolites (AZ5104 and AZ7550), rifampicin and 4β-hydroxy-cholesterol in plasma will be taken at the times presented in the Study Plan (Table 1) and the PK sampling schedule (Table 3). Although every attempt should be made to collect all samples as per the protocol, it is accepted that this will not always be possible and therefore it is essential that the actual time and date of collection of each blood sample (whether collected as per protocol or not) is recorded in the eCRF. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

A 30-minute window will be allowed for samples taken at pre-dose (sample must be taken prior to dose), a 5-minute window will be allowed for post-dose samples up to 1 hour; a 10-minute window for samples taken at 2 to 10 hours post-dose and a 1-hour window for samples taken from 12 hours post-dose onwards. The window for trough samples is ±1 day; however, on a given day the trough sample must be collected prior to the next dose of IP.

For blood volumes see Section 5.2.2.

5.4.2 Determination of drug concentration

Samples for determination of AZD9291, metabolites (AZ5104 and AZ7550), and rifampicin, in plasma will be analysed by on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using appropriate bioanalytical methods. Samples for determination of 4β-hydroxy-cholesterol in plasma will be analysed by on behalf of AstraZeneca R&D, using appropriate bioanalytical methods.

Full details of the analytical method used will be described in separate bioanalytical reports. All samples still within the known stability of the analytes of interest at the time of receipt by the bioanalytical laboratory will be analysed.

In addition, the PK samples may be subjected to further analyses by AstraZeneca in order to further investigate the presence and/or identity of additional AZD9291 metabolites. Any results from such analyses will be reported separately from the Clinical Study Report (CSR).

Details on sample processing, handling, shipment and storage are provided in the Laboratory Manual.

5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

Any residual PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be retained at AstraZeneca or its designee; see details in the Laboratory Manual).

5.5 Pharmacodynamics (not applicable)

5.6 Pharmacogenetics

If a patient agrees to participate in the optional pharmacogenetics research component of the study a blood sample will be collected (see Table 1).

AstraZeneca may perform genetic research in the AZD9291 clinical pharmacology development programme to explore how genetic variations may affect the clinical PK of AZD9291.

For this clinical study pharmacogenetic research will be limited to analysis of genes that may affect AZD9291 PK (for example, but not limited to, drug metabolising enzymes and drug transporters) and will be performed if the results from the clinical study cannot be explained by the current level of drug metabolism and PK understanding or if patients with outlying PK behaviour are observed.

The results of this pharmacogenetic research will be reported separately and will not form part of the CSR.

5.6.1 Collection of pharmacogenetic samples

The patient's consent to participate in the pharmacogenetic research components of the study is mandatory.

The single blood sample for genetic research will be obtained from the patients at Visit 2 (Day -1 or Day 1) prior 1 to the first administration of AZD9291 in the study. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Day -1, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

5.6.2 Storage, re-use and destruction of pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. Deoxyribonucleic acid (DNA) is a finite resource that may be used up during analyses. The results of any further analyses will be reported separately in a scientific report or publication.

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA).

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment code and the DNA number will be maintained and stored in a secure environment, with restricted access within the relevant tracking system at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

5.7 Biomarker analysis (not applicable)

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from the time of signature of informed consent, throughout the Part A treatment periods, Part B, and the follow-up period.

All SAEs will be recorded from the time of informed consent.

Patients entering Part B will be able to continue taking AZD9291 for as long as they are receiving clinical benefit; however study assessments will cease approximately 12 months after the last patient enters Part B. After Part B, there may be some patients remaining on study treatment via the continued access part of this protocol. For these patients who are continuing to receive AZD9291 and being followed as part of routine clinical care, AstraZeneca will collect limited information only (see Section 7.8).

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment or other assessment/visit as appropriate in the study will be followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

If an Investigator learns of any SAEs, including death, at any time and he/she considers there is a reasonable possibility that the event is related to AZD9291, the Investigator should notify AstraZeneca.

6.3.3 Variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- Changes in CTCAE grade (for skin reactions and diarrhoea only); maximum CTCAE grade for all other AEs
- Whether the AE is serious or not
- Investigator causality rating against the IP and other study drug (ie, rifampicin) (yes or no)
- Action taken with regard to IP
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality in relation to other medication
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

The grading scales found in the revised CTCAE version 4 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE version 4 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

6.3.4 Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'.

For SAEs causal relationship will also be assessed for other medication and study procedures and additional study drug (rifampicin). Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated parameters should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP, unless clearly due to progression of disease under study (see Section 6.3.8).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator

uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.7 Hy's law

Cases where a patient shows an AST or ALT ≥3 x ULN or total bilirubin ≥2 x ULN may need to be reported as SAEs. Prompt reporting of cases meeting Hy's law criteria (via the SAE expedited reporting system) is required for compliance with regulatory guidelines. The Investigator is responsible for, without delay, determining whether a patient meets potential Hy's law criteria.

Details of identification of potential Hy's law cases and actions to take are detailed in Appendix E.

6.3.8 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE.

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.3.9 New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

6.3.10 Handling of deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of IP, should be reported as follows:

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the eCRF module, but should not be reported as a SAE during the study

- Where death is not clearly due to disease progression of the disease under study, the AE causing the death should be reported by entering into the WBDC system as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes

- Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes.

6.4 Reporting of serious adverse events

During Part A and Part B, all SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s), and should be recorded in the eCRF. During continued access after the end of Part B, SAEs that may be related to IP have to be reported and will be collected on paper SAE forms (see Section 7.8).

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it and report this SAE in the Adverse Event eCRF.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it and updates the information into the Adverse Event eCRF.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness is the IB for the AstraZeneca drug.

6.5 Overdose

There are no data on overdosing with AZD9291. An overdose of AZD9291 is defined as any dose greater than the highest daily dose included in the clinical trial protocol. Investigators are advised that any patient who receives a higher dose than intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

Such overdoses should be recorded as follows:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

During continued access, only overdoses associated with a SAE must be reported.

6.6 Pregnancy

The outcome of any pregnancy occurring from the date of the first dose until 6 months after dosing with AZD9291 should be followed up and documented.

Please refer to Section 6.6.1 and Section 6.6.2 for further details.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) from the date of the first dose until 6 months after dosing should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 6 months following the last dose.

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented. To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. The outcome of any conception occurring from the date of the first dose until 6 months after dosing should be followed up and documented.

6.7 Management of IP-related toxicities

Patients who have IP-related toxicities requiring dose interruption or dose reduction may be discontinued from Part A and entered into Part B following discussion with an AstraZeneca representative.

The following text is guidance for investigators who treat patients with AZD9291 in Part B and during continued access.

If a patient experiences a CTCAE Grade 3 or higher and/or unacceptable toxicity (any grade) not attributable to the disease or disease-related processes under investigation, where the Investigator considers the AE of concern to be specifically associated with AZD9291, dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines.

If dose reduction is necessary, then the dose of AZD9291 should be reduced to 40 mg taken once daily. Patients who reduce to the 40 mg dose must remain on the 40 mg dose for the remainder of the study.

Dose interruption and reduction guidelines are provided in Table 7.

Table 7 AZD9291 dose adjustment information for adverse reactions

Target organ	Adverse reaction	Dose modification
Pulmonary	ILD/pneumonitis	Permanently discontinue AZD9291
Ocular	Corneal ulceration	Permanently discontinue AZD9291
Cardiac	QTc interval >500 msec on at least 2 separate ECGs	Withhold AZD9291 until QTc interval is <481 msec or recovery to baseline if baseline QTc is ≥481 msec, then restart at the reduced dose (40 mg)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue AZD9291
Other	Grade 3 or higher adverse reaction	Withhold AZD9291 for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding AZD9291 for up to 3 weeks	AZD9291 may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding AZD9291 for up to 3 weeks	Permanently discontinue AZD9291

6.7.1 Skin reactions

Recommendations for appropriate management of skin reactions, including guidance on dose-adjustments for clinically significant and/or intolerable skin reactions that are considered by the Investigator to be causally related to AZD9291 will be provided to Investigators.

The following is applicable to Part B only:

Skin reactions are to be reported as AEs in the eCRF, with additional details captured in the "SKNREAC" eCRF:

- Changes in the characteristics of skin reactions will be collected in the "SKNREAC" eCRF.
- Changes in the CTCAE grade of skin reactions will be collected in the AE eCRF.

Photographs of skin reactions may be collected and these photographs should be available for central review by AstraZeneca and for external expert dermatological review if required.

Skin biopsies may be taken of skin reactions.

6.7.2 Diarrhoea

Recommendations for appropriate management of diarrhoea, including dose-adjustments for AEs of diarrhoea that are of CTCAE Grade ≥3 or that are clinically significant and/or intolerable and considered by the Investigator to be causally related to AZD9291, will be provided to Investigators. During Part B, changes in CTCAE grade of diarrhoea will be captured in the AE eCRF.

6.7.3 Worsening pulmonary symptoms

If new or worsening pulmonary symptoms (eg, dyspnoea) or a radiological abnormality suggestive of ILD/pneumonitis is observed, an interruption in study treatment dosing is recommended. A questionnaire regarding the results of the full diagnostic workup (including high-resolution computed tomography, blood and sputum culture, haematological parameters) will be sent to Investigators. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema, or pulmonary haemorrhage. In the presence of confirmatory high-resolution computed tomography scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD/pneumonitis should be considered and study treatment permanently discontinued (per Table 7 above).

In the absence of a diagnosis of ILD/pneumonitis, study treatment may be restarted.

An AstraZeneca or representative study team physician may be contacted if required.

6.7.4 QTc prolongation

Refer to Table 7 above.

6.7.5 Corneal ulceration

Any patient developing corneal ulceration will be permanently discontinued from study treatment (per Table 7 above) and should be followed regularly until resolution of the event. Corneal ulceration should be treated according to local guidance.

6.8 Study governance and oversight

No Data Monitoring Committee is planned, as this study is an open-label non-randomised Phase I study. In addition the safety profile of AZD9291 from the ongoing Phase I study in a similar NSCLC patient population is modest and predictable. There is therefore no requirement for pre-planned specified expert independent safety reviews in this study.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply AZD9291 to sites.

Investigational product	Dosage form and strength	Manufacturer
AZD9291	40 and 80 mg Tablets	AstraZeneca

7.1.1 Additional study drug

Rifampicin capsules will either be centrally or locally sourced. In the event that rifampicin is locally sourced, the same product (ie, same manufacturer, and, if possible lot number) will be used for the entire 21-day dosing period for a given patient. The manufacturer and lot number for the administered rifampicin will be documented in the patient's eCRF.

The prescribing information supplied with the rifampicin should be followed.

7.2 Dose and treatment regimens

7.2.1 Part A

In Part A, each patient will receive a once daily 80 mg oral dose of AZD9291, on Days 1 to 77. From Days 29 to 49 each patient will receive rifampicin 600 mg once daily. Rifampicin will be taken concomitantly with AZD9291. All treatments (AZD9291 and rifampicin) will be administered fasted from at least 2 hours before dosing to at least 2 hours after dosing. Water is allowed as desired except for 1 hour before and after AZD9291 administration on Days 28, 49, and 77. There are no restrictions for water intake on any other study days. The study treatments should be swallowed whole with approximately 240 mL of water, and not chewed, crushed, dissolved or divided.

On clinic days on which PK samples are scheduled to be taken, the dosing should be delayed until arrival at the clinic and until the pre-dose PK samples have been taken. Patients should not take their IP until instructed to do so by site personnel.

If a patient vomits on Day 28 or Day 49 within approximately 6 hours of dose administration, the AstraZeneca representative should be contacted for advice regarding the evaluability of the patient or whether the patient may return to the clinic on a subsequent day to repeat the treatment. If a patient is discontinued from Part A, the Investigator may contact an AstraZeneca representative to determine if it is appropriate for the patient to proceed into Part B.

If a patient vomits within approximately 6 hours of dose administration on Day 77, PK sample collection may be discontinued after the event but the safety assessments should continue as

per the study schedule. The patient may proceed to Part B after completion of the required safety assessments, if the patient and Investigator agree that this is appropriate.

Doses of AZD9291 should be taken approximately 24 hours apart at the same timepoint each day. Doses should not be missed. The patient should inform the Investigator of any doses missed prior to any of the outpatient visits for PK trough collections. In case the patient misses any doses of AZD9291 during the 7-day period before each scheduled serial sample collection day (Days 28, 49, and 77), please contact the AstraZeneca representative for advice regarding the evaluability of the patient and appropriate timing of the PK assessments. Outside of this timeframe, if a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time.

The patient should record in the Diary the date and time all doses of AZD9291 or rifampicin taken at home, as well as missed doses. Any change from dosing schedule, dose interruptions, and dose reductions should be recorded in the eCRF.

At each dispensing visit, sufficient AZD9291 for each study period, plus overage, will be dispensed. Individual bottles will be dispensed in accordance with local practice.

AZD9291 tablets will be packed in HDPE bottles with child-resistant closures. Bottles will be dispensed to patients in the AstraZeneca packing provided. The packaging includes bottles, caps and a label. Bottle tampers should not be broken prior to dispensing study drug to a patient.

Additional information about the IP may be found in the IB.

7.2.2 Part B and continued access

In Part B and during continued access, patients may receive 80 mg oral AZD9291 once daily, given as the tablet formulation, for the duration of their participation. Based on results from Part A of study D5160C00009, AZD9291 exposure is not affected by a high fat, high calorie meal (AUC and C_{max} changes were within the no effect limit of 70-143%); therefore, in Part B and in continued access, AZD9291 can be taken with or without food.

The study treatments should be swallowed whole with approximately 240 mL of water, and not chewed, crushed, dissolved or divided.

Doses of AZD9291 should be taken approximately 24 hours apart at the same timepoint each day. Doses should not be missed. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their AZD9291, they should not make up for this dose, but should take the next scheduled dose. Any change from dosing schedule, dose interruptions, dose reductions should be recorded in the eCRF during Part B, or per local site practice after the end of Part B (continued access).

Restrictions related to fasted administration of AZD9291 may be modified upon PK data emerging from the clinical programme.

At each dispensing visit, sufficient AZD9291 for each study period, plus overage, will be dispensed. Individual bottles will be dispensed in accordance with local practice.

The initial dose of AZD9291 can be reduced under circumstances described in Section 6.7.

AZD9291 tablets will be packed in HDPE bottles with child-resistant closures. Bottles will be dispensed to patients in the AstraZeneca packing provided. The packaging includes bottles, caps and a label. Bottle tampers should not be broken prior to dispensing study drug to a patient.

Additional information about the IP may be found in the IB.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. The labels will fulfil Good Manufacturing Practice Annex 13 requirements for labelling. Label text will be translated into local language.

Specific dosing instructions will not be included on the label. The site must complete the 'Patient Dispensing Card' with the details of the dosing instructions at the time of dispensing.

The patient emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Dispensing Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage.

7.5 Compliance

The administration of all study drugs should be recorded in the appropriate sections of the eCRF.

Patients will be issued with a Patient Diary Card, which contains clear instructions on how and when to take their study drug, and the date of their next clinic appointment. Patients will need to complete diaries, which will record the date and time of each dose.

For Part A, at the time when patients are at the study site, compliance will be assured by supervised administration of IP by the investigator or his/her delegate. Patients will record in the Patient Diary any self-administered medications for the periods when they are not resident in the clinic.

For Part B and during continued access, ie, when patients self-administer their AZD9291, they should be given clear instructions on how and when to take their study treatment. Patients should aim to take their doses on outpatient days at similar times each day, approximately 24 hours apart.

Study site pharmacy staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the Investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of AZD9291 at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded on the eCRF. Patients must return all bottles and any remaining tablets when they discontinue IP.

7.6 Accountability

The IP provided for this study is for use only as directed in the study protocol. It is the Investigator/institution's responsibility to establish a system for handling study treatments, including IPs, so as to ensure that:

- Deliveries of such products from AstraZeneca or its representative are correctly received by a responsible person
- Such deliveries are recorded
- Study treatments are handled and stored safely and properly as stated on the label
- Study treatments are only dispensed to study patients in accordance with the protocol

The study personnel will account for all IP dispensed and returned.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the IP was dispensed, the quantity and date of dispensing, and unused IP returned to the investigator. This record is in addition to any IP accountability information recorded on the CRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist, and copies retained in the investigator site file. Dispensing and accountability records will continue to be collected after the end of Part B for as long as patients continue to receive IP.

7.7 Concomitant and other treatments

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study, with reasons for the treatment, will be recorded in the eCRF. Concomitant use of regular medications that may prolong the QT

interval will be restricted whenever feasible, but patients may receive any medication that is clinically indicated for the treatment of AEs. Guidance on medications that are contraindicated or that require close monitoring is given in Appendix H.

If medically feasible, patients taking regular medication, with the exceptions shown in the table below, should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon BCRP and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving AZD9291. A list of medications that should be treated with caution can be found in Appendix H.

Prohibited medication/class of drug:	**Usage:**
Part A: Concomitant medication contraindicated for use with rifampicin (including, but not limited to): cisapride, oral midazolam, nisoldipine, pimozide, quinidine, dofetilide, triazolam, levacetylmethadol (levomethadyl), HMG-CoA-reductase inhibitors (statins) metabolised by CYP3A4, such as lovastatin and simvastatin, ergot alkaloids metabolised by CYP3A4, such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine).	Should not be given while the patient is on study treatment during Part A. They are permitted in Part B. **Note:** some of these drugs may also be contraindicated with AZD9291 or carry warning of possible interactions (Appendix H). Therefore use of any drugs in Part B which are contraindicated for administration with rifampicin in Part A should be carefully evaluated.
Other anticancer agents (including any listed in Appendix H), investigational agents and radiotherapy (ie, radiotherapy specifically for treatment of asymptomatic lesions, irrespective of whether progressing or not)	Should not be given while the patient is on study treatment.

Restricted medication/class of drug:	**Usage:**
Part A: all patients must avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known inducer/inhibitory effects on CYP3A4	Whenever feasible, but patients may receive any medication that is clinically indicated for treatment of AEs. Such drugs must have been discontinued for an appropriate period before they enter screening and until the end of Part A.
Part B and continued access: all patients must avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known potent inducer effects on CYP3A4	Whenever feasible, but patients may receive any medication that is clinically indicated for treatment of AEs. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 months after the last dose of AZD9291.
Part A: Statins	Statins not affected by CYP3A4 can be given while the patient is on treatment in Part A.

Part B and continued access: Statins	Patients taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP-mediated increase in exposure). If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped, and any appropriate further management should be taken.

Rescue/Supportive Medication/Class of drug:	**Usage:**
Anticoagulant therapy: Patients who are taking warfarin may participate in this study; however, it is recommended that prothrombin time (international normalised ratio [INR] and activated partial thromboplastin time [aPTT]) be monitored carefully at least once per week for the first month of daily AZD9291 administration, then monthly if the INR is stable. Subcutaneous heparin is permitted. At least once weekly monitoring of INR and aPTT is also recommend during repeated administration of strong inducers (eg, rifampicin) of CYP3A4 in Part A of this study.	Allowed at any time during the study.
Pre-medication will be allowed after, but not before the first dose of study treatment.	To be administered as directed by the Investigator. This includes management of diarrhoea, nausea and vomiting.
Blood transfusions	Allowed at any time during the study.
Granulocyte colony stimulating factors	Should not be used prophylactically during Part A. Use of prophylactic colony stimulating factors may be considered after Part A following discussion with the AstraZeneca Study Team Physician.
Corticosteroids and/or bisphosphonates	Patients may receive treatment with corticosteroids and/or bisphosphonates for the treatment of bone metastases.
Palliative radiation	Patients may receive radiotherapy for painful bony metastases. In Part B and continued access, the AstraZeneca Study Team Physician should be consulted when considering irradiation to brain or thorax for treatment of symptomatic lesions.
Supportive care and other medications that are considered necessary for the patient's well-being	To be administered as directed by the Investigator.

Patients should be instructed to inform the Investigator if they take any restricted medications.

7.7.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

7.8 Continued access to study treatment after Part B

Patients who have not discontinued AZD9291 at the end of Part B may continue to receive AZD9291 as a single agent, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment (continued access).

After the end of Part B, the clinical study database will be closed. No further data will be recorded during continued access after Part B other than SAEs that may be related to IP and drug dispensing/accountability, until AZD9291 is permanently discontinued. For pregnancy reporting during continued access, see Section 6.6. Investigators will continue to follow up any existing SAEs, and report all SAEs that may be related to IP to AstraZeneca Patient Safety, until 30 days after IP is permanently discontinued, in accordance with Section 6.4 (Reporting of serious adverse events). Investigators should complete paper SAE forms and fax them directly to the AstraZeneca Patient Safety data entry site for entering onto the AstraZeneca Patient Safety database.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

Statistical analyses will be performed by using SAS® Version 9.2 or higher and, where appropriate, additional validated software.

A comprehensive Statistical Analysis Plan (SAP) will be prepared by the biostatistician prior to first patient enrolled and any subsequent amendments will be documented, with final amendments completed prior to database lock.

8.2 Sample size estimate

8.2.1 Part A

The primary objective of this part of the study is to investigate the effect of rifampicin on the PK of AZD9291. In study D5160C00005, a within-patient coefficient of variation of 20% and 23% was observed for both AUC and C_{max}, respectively, in healthy normal subjects.

However, since the variability in patients is unknown, it will be assumed that the within-patient coefficient of variation for AZD9291 in both AUC and C_{max} is 34%, an approximate 50% increase from that observed in healthy normal subjects. A 33% decrease in the exposure for AZD9291 when given with rifampicin is also assumed. With 30 evaluable

patients, the experiment-wide power for the lower bound of the 90% CI of the geometric mean ratios (AZD9291 + rifampicin/AZD9291 alone) being above 50% is 90% (95% power for each parameter).

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

8.3 Definitions of analysis sets

Analysis sets are presented in Table 8.

Table 8 Definition of analysis sets

Analysis Set	Definition
PK analysis set	Dosed patients who have at least 1 quantifiable plasma concentration collected post-dose.
Evaluable for safety	All patients who receive at least 1 dose of AZD9291

The pharmacokineticist will agree the strategy for dealing with data affected by important protocol deviations before any formal statistical analysis is performed.

Important protocol deviations include changes to the procedures that may impact the quality of the data or any circumstances that can alter the evaluation of the PK. Examples include, but may not be limited to, vomiting following oral dosing occurring within the timeframe of 2 times the median t_{max}, sample processing errors that lead to inaccurate bioanalytical results, incomplete dose administered, incomplete PK profile collected, and/or use of disallowed concomitant medication. In the case of an important protocol deviation or event, affected PK data collected will be excluded from the summaries and statistical analyses, but will still be reported in the study result listings. Important deviations will be listed and summarised in the CSR.

8.4 Outcome measures for analyses

The following outcome measures are to be assessed in relation to the study objectives:

Analysis: Part A	**Outcome Measures:**
PK	
Primary AZD9291	• $C_{ss,max}$, and AUC_{tau} (alone [Day 28] and in combination with rifampicin [Day 49])

Secondary AZD9291	• AUC_{tau}, 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
Secondary AZ5104 and AZ7550	• AUC_{tau}, $C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$, and metabolic ratios (AZ5104 to AZD9291 and AZ7550 to AZD9291) $MRAUC_{tau}$ and $MRC_{ss,max}$ in all periods • 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
Secondary rifampicin	• AUC_{tau}, $C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$, and CL_{ss}/F
Exploratory 4β-hydroxy-cholesterol	• 4β-hydroxy-cholesterol at baseline and collected throughout the 77-day AZD9291 dosing period

Safety analysis : Part A and B	**Outcome Measures :**
	• AEs/SAEs graded by CTCAE v4 • Vital signs (blood pressure/pulse/temperature/height/weight) • Laboratory parameters (clinical chemistry, haematology, urinalysis) • Physical examination • Standard 12-lead ECGs • Echocardiogram/MUGA

Pharmacokinetic analysis of the plasma concentration data for AZD9291, AZ5104, AZ7550, and rifampicin will be performed at The actual sampling times will be used in the final PK parameter calculations.

Pharmacokinetic parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 6.3, or higher, (Pharsight Corp., St Louis, Missouri) and/or SAS® Version 9.2, or higher (SAS Institute, Inc., Cary, North Carolina).

Where possible, the following PK parameters will be determined for AZD9291 and its metabolites (AZ5104 and AZ7550) on Day 29, Day 49, and Day 77:

- AUC_{tau}: Area under the plasma concentration-time curve during a dosing interval
- $C_{ss,max}$: Observed maximum concentration at steady state, taken directly from the individual concentration-time curve

- $t_{ss,max}$: Time to reach observed maximum concentration, taken directly from the individual concentration-time curve
- $C_{ss,min}$: Observed minimum concentration over the dosing interval, tau, taken directly from the individual concentration-time curve
- CL_{ss}/F: Apparent clearance estimated as dose divided by AUC_{tau} (AZD9291 only)
- $MRAUC_{tau}$: Ratio of metabolite (AZ5104 and AZ7550) AUC_{tau} to parent AUC_{tau} adjusted for differences in molecular weight (AZD9291 = 499.62; AZ5104 and AZ7550 = 485.59)
- $MRC_{ss,max}$: Ratio of metabolite (AZ5104 and AZ7550) $C_{ss,max}$ to parent $C_{ss,max}$ adjusted for differences in molecular weight (AZD9291 = 499.62; AZ5104 and AZ7550 = 485.59)

Where possible, the following PK parameters will be determined for rifampicin on Day 49:

- AUC_{tau}: Area under the plasma concentration-time curve during a dosing interval
- $C_{ss,max}$: Observed maximum concentration after multiple dosing, taken directly from the individual concentration-time curve
- $t_{ss,max}$: Time to reach observed maximum concentration, taken directly from the individual concentration-time curve
- $C_{ss,min}$: Observed minimum concentration over the dosing interval, tau, taken directly from the individual concentration-time curve
- CL_{ss}/F: Apparent clearance estimated as dose divided by $AUC_{tau.}$

8.5 Methods for statistical analyses

The sample bioanalysis will be performed by The merging of PK concentration data with actual PK sampling times will be performed by . The PK analysis will be the responsibility of the pharmacokineticist at The PK summaries, figures, and data listings as well as the statistical analysis of the PK variables will be the responsibility of the biostatistician.

All concentration data received will be presented in data listings. Pharmacokinetic summaries will be presented for patients in the PK analysis set, as defined in Section 8.3. Data from patients excluded from the PK analysis set will be included in the data listings, but not in the summaries. Extra measurements (such as unscheduled or repeat assessments) will also not be included in summary tables, but will be included in patient listings.

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative

variables will be summarised using descriptive statistics, including n, arithmetic mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum values. Additionally, geometric means and geometric %CV will be reported for PK variables (concentrations and all PK parameters, except for t_{max}).

8.5.1 Part A

For AZD9291 and its metabolites, natural log-transformed AUC_{tau} and $C_{ss,max}$, will be compared between periods using a mixed effects 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 will be calculated. The mean differences and the CIs will be 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_{tau} and $C_{ss,max}$ will be estimated and presented. No effect on the PK of AZD9291 after co-administration of rifampicin will be concluded if the lower bound of the 90% CIs for the ratios (Period 2 versus Period 1) of AZD9291 AUC_{tau} and $C_{ss,max}$ are both above 50%.

For AZD9291 and its metabolites, analyses of $t_{ss,max}$ will be 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 will be presented.

In addition to a graphical assessment of the steady state for AZD9291, a statistical evaluation of the steady state will also be made using the trough plasma concentrations collected on Days 7, 14, 21, and 28 (pre-dose and 24 hour). All valid concentrations on the natural-log scale will be analysed using ANOVA model with day as a fixed repeated effect and subject as a random effect. From this model, orthogonal contrasts with 90% CI will be formed between the mean concentration at each day and the mean concentrations for all the following days using Helmert contrasts. Precisely, Day 7 will be compared to Days 14 through 28 (24 hr) combined; Day 14 will be compared to Days 21 through 28 (24 hr) combined; and so on.

As exploratory analyses, the onset of potential induction by rifampicin (AZD9291, AZ5104, and AZ7550 troughs and concentration of 4β-hydroxy-cholesterol after addition relative to before addition of rifampicin) will be explored. Also, the offset of potential induction by rifampicin (AZD9291, AZ5104 and AZ7550 troughs and concentration of 4β-hydroxy-cholesterol after discontinuation of rifampicin relative to before addition of rifampicin) will be explored.

Additionally, an evaluation of potential increase in CYP3A4 enzyme activity, interpreted as the concentration of 4β-hydroxy-cholesterol after relative to before dosing with AZD9291, will be explored. Specifically, results for 4β-hydroxy-cholesterol, along with the ratio of post-baseline to baseline concentration, will be listed for individual patients and summarised by day and treatment. Descriptive statistics (n, arithmetic mean, SD, CV, minimum, median, maximum and geometric mean) will include the ratio of post-baseline to baseline concentration with 90% CIs calculated by natural log-transformed data. These results will be back-transformed for presentation.

Steady state of rifampicin will be assessed graphically.

A SAP will be generated to describe these analyses in more detail.

8.5.2 Population analysis of pharmacokinetic variables

The relationship between PK and treatment period and other variables may be assessed, as deemed appropriate. Results will be reported separately from the CSR.

The PK, demographic, treatment, safety and tumour response data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK methods if deemed appropriate. The results of any such analyses will be reported separately from the CSR.

8.5.3 Demographic and safety analyses

Data for Parts A and Part B will be analysed separately.

For qualitative demographic and safety variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarised using descriptive statistics, including n, mean, SD, median, minimum, and maximum values. Where appropriate, assessments will be summarised by visit. All data will be summarised and listed appropriately.

The number of patients screened and included in the safety analysis set will be summarised. Demographic and baseline characteristics will be summarised and listed for the safety analysis set.

Treatment duration will be summarised. Treatment duration is based on the dates of first and last dose of any study treatment.

Study day will be calculated as follows:

- Days prior to first dose: Study day=date – first dose date.
- Days on or after first dose: Study day=date – first dose date+1.

Where day is missing from the date, but is required in the calculation of time to informed consent, day will be imputed as 01, ie, 1st of the month. Otherwise no imputations will be made for any missing data, unless agreed by the study team.

Safety profiles will be assessed in terms of AEs, vital signs (including blood pressure and pulse rate), ECG, laboratory data (clinical chemistry, haematology and urinalysis) and physical examinations.

Appropriate summaries of AEs, laboratory data, vital signs, and ECGs will be produced. Adverse events will be summarised separately for Parts A and B of the study. Laboratory data, vital signs, physical examinations, temperature, and ECGs will be summarised for

Parts A and B. Summaries will be presented for scheduled visits only. Any unscheduled assessments will be listed. The baseline value is defined as the latest result obtained prior to the start of study treatment.

The number of patients experiencing AEs following administration of AZD9291 and rifampicin, as well as the number of AEs experienced, will be summarised. Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) system of nomenclature (preferred term and system organ class). Adverse events reported before administration of AZD9291 will be listed only and be referred to as "pre-treatment". Treatment emergence will be defined for each part of the study (A and B).

For each part (A and B), a treatment-emergent AE will be defined as an AE with the start date and time on or after the first dose date of study treatment and time (Part A) or first dose date (Part B) up to (and including) 30 days after the last dose date. Similarly, the number of patients experiencing SAEs, other significant AEs (OAEs), AEs that led to withdrawal, AEs that led to death, and treatment-related AEs and the number of such events will be summarised by part and period within part, as applicable. Adverse events with a start date and time in Part A that are ongoing at the start of Part B of the study will be summarised separately.

All AE data will be listed for all patients. In addition, SAEs, OAEs, and AEs that led to withdrawal or death, and treatment-related AEs will be listed.

Laboratory data (haematology, clinical chemistry and urinalysis) will be summarised and listed. Shift tables will be provided for select tests, where shift from baseline to the worst value within each part of the study and overall will be summarised. Laboratory data outside the reference ranges should be indicated in the listings.

Concomitant medications will be summarised by the coded terms. The number of patients receiving a medication will be summarised overall and for each part of the study. A medication taken during the course of the study is considered concomitant. A patient is only counted once even if they receive the medication more than once within that Part of the study.

The impact of any important protocol deviations, missing data and the use of rescue or concomitant medication on the robustness of study results will be investigated and any methods employed to deal with these will be documented.

Additional tables, figures, or listings, or combinations of Part A and Part B data may be produced to aid interpretation.

Further details of summaries of the safety data will be given in the SAP.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca designee will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca designee will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Study agreements

The PI at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement (CSA), or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the PI should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'. This will occur when the last patient receiving treatment as continued access has permanently discontinued AZD9291 and had their 30 day safety follow-up contact..

The study is expected to start in Q3 2014 and Part B is expected to end by Q3 2016.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD9291.

9.4 Data management by

Data management will be performed by , according to the Data Management Plan (DMP).

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the DMP. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The DMP will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all patients have completed Part A of the study (or at the request of AstraZeneca), a database lock will be carried out. All Part A data for patients who have completed by the time of the database lock transfer will be cleaned and validated as defined in the DMP. A CSR will be produced reporting the Part A data. On completion of Part B, a further database lock will occur and the Part B data will be reported. Part B will be reported as a CSR addendum.

Data from the continued access phase of the study will only be recorded in the source documents; these data will not be entered into the study database (see also Section 7.8), nor reported as an addendum to the CSR.

Serious Adverse Event Reconciliation

Serious AE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data Management of genotype data

Any genotype data generated in this study will be stored within the relevant sample tracking system at AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples.

The results from this genetic research will be reported separately from the main CSR.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International conference on harmonisation (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The Informed Consent Form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study. The Ethics Committee should approve all advertising used to recruit patients for the study. AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements. If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations. AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities. AstraZeneca will provide Regulatory Authorities, Ethics Committees and PIs with safety updates/reports according to local requirements.

Each PI is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the PIs so that he/she can meet these reporting requirements.

10.4 Informed consent

The PI(s) or sub-investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each patient provides signed and dated ICF before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator, and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to Ethics Committee see Section 10.3.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca and the centre's Ethics Committee are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

11. LIST OF REFERENCES

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Clinical Study Protocol Appendix B

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Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement should be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C

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Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

AstraZeneca

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Appendix D
Pharmacogenetics Research

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AE	Adverse event
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
PGx	Pharmacogenetics

1. BACKGROUND AND RATIONALE

AstraZeneca may perform genetic research in the AZD9291 clinical pharmacology development programme to explore how genetic variations may affect the clinical pharmacokinetics of AZD9291

For this clinical study pharmacogenetic research will be limited to analysis of genes that may affect AZD9291 pharmacokinetics (for example, but not limited to, drug metabolising enzymes and drug transporters) and will be performed if the results from the clinical study cannot be explained by the current level of DMPK understanding or if patients with outlying pharmacokinetic behaviour are observed.

The results of this pharmacogenetic research will be reported separately and will not form part of the CSR.

2. GENETIC RESEARCH OBJECTIVES

The objective is to perform genetic research in the AZD9291 clinical pharmacology development programme to explore how genetic variations may affect the clinical pharmacokinetics of AZD9291.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

3.1.2 Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

3.1.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or the following:

- Previous allogeneic bone marrow transplant

- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection.

3.1.4 Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 3.6 and 3.7 of the main Clinical Study Protocol.

3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Visit 2. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 5.2.2 of the Clinical Study Protocol.

3.3 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access within the relevant sample tracking system at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10 of the main Clinical Study Protocol.

4.1 Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

4.2 Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

5. DATA MANAGEMENT

Any genotype data generated in this study will be stored within the relevant sample tracking system at AstraZeneca and/or third party contracted to work with AstraZeneca to analyse the samples.

The results of this pharmacogenetic research will be reported separately and will not form part of the CSR.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

7. LIST OF REFERENCES

None

AstraZeneca

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Appendix E
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

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1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

A PHL case is defined as a study subject with an increase in serum Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3 x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥2 x ULN irrespective of serum Alkaline Phosphatase (ALP), at any point during the study following the start of study medication.

Hy's Law (HL)

A HL case is defined as a study subject with an increase in serum AST or ALT ≥3 x ULN together with TBL ≥2 x ULN, where no other reason can be found to explain the combination of increases, eg, elevated serum ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL to be met the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data (including scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study) for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 x ULN

- AST ≥3 x ULN
- TBL ≥2 x ULN.

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF.

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases (see Section 6)

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated by conducting repeated testing and observations
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver CRF Modules as information becomes available

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this section should be followed for all cases where PHL criteria were met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  - The 'Medically Important' serious criterion should be used if no other serious criteria apply

  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

6. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to patients who meet PHL criteria on study treatment (including the 30 day follow-up period post discontinuation of study treatment) having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required
  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section 4.2 of this Appendix

[#] A 'significant' change in the patient's condition refers to a subsequent clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, eosinophilia. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment (including the 30-day follow-up period) and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 6?

If No: follow the process described in Section 4.2 of this Appendix

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix.

[#] A 'significant' change in the patient's condition refers to a subsequent clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms, such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, eosinophilia. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

8. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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Clinical Study Protocol Appendix F

Drug Substance	AZD9291
Study Code	D5160C00013
Edition Number	1
Date	

Appendix F
Acceptable Birth Control Methods

ACCEPTABLE BIRTH CONTROL METHODS

AZD9291 is regarded as a compound with medium/high foetal risk.

Patients of childbearing potential and their partners, who are sexually active, must agree to the use of 2 highly effective forms of contraception throughout their participation in the study and for 6 months after last dose of study drug.

Acceptable non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must be for the total duration of the trial and until 6 months after discontinuation of study treatment.
- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion plus male condom with spermicide
- IUD plus male condom + spermicide. Provided coils are copper-banded

Acceptable hormonal methods that are not prone to drug-drug interactions:

- IUS Levonorgestrel Intra Uterine System (Mirena) + male condom with spermicide
- Medroxyprogesterone injections (Depo-provera) + male condom with spermicide.

Clinical Study Protocol Appendix G

Drug Substance	AZD9291
Study Code	D5160C00013
Edition Number	1
Date	

Appendix G
Eastern Cooperative Oncology Group (ECOG) Performance Status

1. ECOG PERFORMANCE STATUS

Patient ability	**Score**
Fully active, able to carry on all pre-disease performance without restriction	**0**
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	**1**
Ambulatory and capable of all self-care, but unable to work. Up and about more than 50% of waking hours	**2**
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	**3**
Completely disabled, unable to carry out any self-care and confined totally to bed or chair	**4**

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Clinical Study Protocol Appendix H

Drug Substance	AZD9291
Study Code	D5160C00013
Edition Number	2
Date	

Appendix H
Guidance Regarding Potential Interactions With Concomitant Medications

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LIST OF TABLES

GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

1. DRUGS INDUCING CYP3A4 METABOLISM THAT ASTRAZENECA STRONGLY RECOMMEND ARE NOT COMBINED WITH AZD9291

AZD9291 is metabolised by CYP3A4 and CYP3A5 enzymes.

A drug-drug interaction study of AZD9291 evaluated in patients showed that there is potential for AZD9291 being a victim when co-administered with strong inducers of CYP3A4 (AZD9291 concentrations are decreased when co-dosed with rifampicin).

The following potent inducers of CYP3A4 must not be used during this study for any patient receiving AZD9291.

Table 1 Drugs inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to AZD9291 start
Carbamazepine, phenobarbital, phenytoin Rifampicin, rifabutin, rifapentin St John's Wort	3 weeks
Phenobarbitone	5 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

2. MEDICINES WHOSE EXPOSURES MAY BE AFFECTED BY AZD9291 THAT ASTRAZENECA CONSIDERS MAY BE ALLOWED WITH CAUTION

AZD9291 may increase the concentration of sensitive BCRP substrates (concentration of the sensitive BCRP substrate, rosuvastatin, is increased).

Table 2 Exposure, pharmacological action and toxicity may be increased by AZD9291

Warning of possible interaction	Advice
Rosuvastatin Sulfasalazine Doxorubicin Daunorubicin Topotecan	Note, some of these medications are not permitted during Part A due to contraindication with rifampicin. Please see Section 4. Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD9291.

3. DRUGS THAT MAY PROLONG QT INTERVAL

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland. Ref: http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm.

3.1 Drugs known to prolong QT interval

The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with AZD9291. Recommended withdrawal periods following cessation of treatment with these agents are provided in the table.

Table 3 Drugs prolonging QT interval

Contraindicated drug	Withdrawal period prior to AZD9291 start
Clarithromycin, droperidol, erythromycin, procainamide	2 days
Cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine	7 days
Bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine	14 days
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide	6 weeks*
Pentamidine	8 weeks
Amiodarone, chloroquine	1 year

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

3.2 Drugs that may possibly prolong QT interval

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated.

Table 4 Drugs that may prolong QT interval

Drug	Minimum treatment period on medication prior to AZD9291 start
Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, foscarnet, galantamine, gemifloxacin, isridipine, ketoconazole, levofloxacin, mexiletine, nicardipine, octreotide, ofloxacin, ondansetron, quetiapine, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine, ziprasidone	2 days
Amantadine, amitriptyline, amoxapine, clozapine, doxepin, felbamate, flecainide, fluconazole, fosphenytoin, gatifloxacin, granisetron, imipramine, indapamide, lithium, moexipril/HCTZ, moxifloxacin, risperidone, roxithromycin, sertraline, trimethoprin-sulfa, trimipramine, voriconazole	7 days
Azithromycin, citalopram, clomipramine, itraconazole, nortriptyline, paroxetine, solifenacin, tacrolimus	14 days
Fluoxetine	5 weeks
Protriptyline	6 weeks
Tamoxifen	8 weeks

4. DRUGS CONTRAINDICATED FOR ADMINISTRATION WITH RIFAMPICIN (PART A)

Concomitant medication contraindicated for use with rifampicin (including, but not limited to): cisapride, oral midazolam, nisoldipine, pimozide, quinidine, dofetilide, triazolam, levacetylmethadol (levomethadyl), 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA)-reductase inhibitors (statins) metabolised by CYP3A4, such as lovastatin and simvastatin, ergot alkaloids metabolised by CYP3A4, such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine).

Note: some of the drugs listed in Section 4 may also be contraindicated with AZD9291 (Table 1; Table 3) or carry warning of possible interactions (Table 2). Therefore use of any drugs in Part B which are contraindicated for administration with rifampicin in Part A should be carefully evaluated.