Revised Clinical Study Protocol (United Kingdom)

Drug Substance	AZD9291
Study Code	D5160C00009
Edition Number	1

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

Sponsor: AstraZeneca AB Sweden

AstraZeneca Research and Development site representative

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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	

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

AstraZeneca

PROTOCOL SYNOPSIS

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

International Co-ordinating Investigator

Study site(s) and number of patients planned

This study will be conducted at approximately 11 sites across Asia, the United States of America and Western Europe, with approximately 38 patients enrolled and dosed and at least 30 evaluable patients required (evaluable for primary analysis). A maximum of 50% of patients will be recruited from Asia.

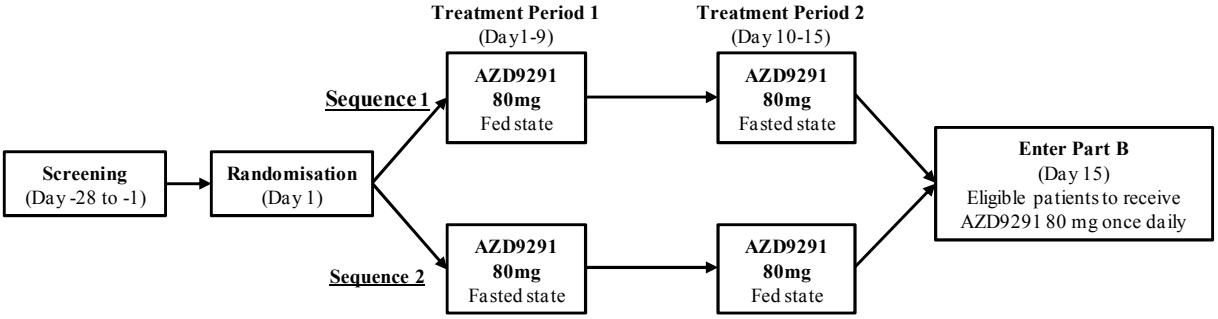
Study period		Phase of development
Estimated date of first patient enrolled	Q3 2014	Clinical pharmacology (I)
Estimated date of last patient completed (Part A)	Q1 2015	
Estimated data of last patient completed (Part B)	Q1 2016	

Study design

This is a 2-part study in patients with epidermal growth factor receptor mutation positive (EGFRm+) non-small cell lung cancer (NSCLC) whose disease has progressed on treatment with an epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI): Part A will determine the effect of food on the pharmacokinetics (PK) of AZD9291; Part B will allow patients further access to AZD9291 and will provide for additional safety data collection. Approximately 38 patients are planned to be enrolled and dosed; at least 30 evaluable patients will be required to complete Part A (ie, the last PK sample in Treatment Period 2 [TP 2] has been collected). Additional patients may be enrolled to allow for at least 30 evaluable patients.

Part A of this study is a randomised, open-label, 2-treatment period crossover study in which patients will each receive a single oral dose of AZD9291 (1 x 80 mg tablet) at breakfast time (approximately 0800) in each of 2 treatment periods (once immediately following a high-fat meal [fed], and once in the fasted state [fasted]), with a washout period of 9 days between doses.

Figure 1 Overall study plan – Part A



Note: Approximately 38 patients are planned to be enrolled; additional patients may be enrolled until 30 evaluable patients have completed Part A. Assessments for pharmacokinetic analyses will be performed in Part A, and for safety assessments in Parts A and B. Patients who withdraw or discontinue will complete a follow-up assessment. Part B will be of 12 months duration from the date the last patient enters this part of the study.

Objectives

Primary objective:
To investigate the effect of food on the exposure of AZD9291 (AUC_{0-72} and C_{max}) following oral dosing of the tablet formulation in patients with EGFRm+ NSCLC following disease progression on an EGFR TKI.
Secondary/exploratory objectives:
To characterise the effect of food on the PK of AZD9291 metabolites (AZ5104 and AZ7550) following oral dosing of the tablet formulation in patients with EGFRm+ NSCLC following disease progression on an EGFR TKI.
To investigate further the safety and tolerability of daily oral doses of AZD9291 in patients with EGFRm+ NSCLC (Part B).
To perform genetic research in the AZD9291 clinical pharmacology development programme to explore how genetic variations may affect the clinical PK of AZD9291.[a]
To provide data to allow analysis using population PK approaches.[a]

a The results of any further analyses will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

Outcome measures:	
Analysis:	**Measures:**
PK – Primary: AZD9291	Maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from zero to 72 hours (AUC_{0-72}).
PK - Secondary: AZD9291	Area under the plasma concentration-time curve from zero to 120 hours (AUC_{0-120}), area under the plasma concentration time curve from zero to the last quantifiable time point (AUC_{0-t}), area under the plasma concentration-time curve from zero to infinity (AUC), time to reach maximum plasma concentration (t_{max}), terminal half-life ($t_{½}$), terminal rate constant (λ_z), apparent plasma clearance (CL/F) and apparent volume of distribution (V_z/F).
PK - Secondary: AZ5104 and AZ7550	C_{max}, AUC_{0-72}, AUC_{0-120} AUC_{0-t}, AUC, t_{max}, $t_{½,}$ and $\lambda_{z,}$.
Safety	Assessment of adverse events, graded by CTCAE (version 4), physical examination, vital signs (blood pressure, pulse rate and body temperature), standard 12-lead electrocardiogram, echocardiogram/Multiple Gated Acquisition Scan (for assessment of left ventricular ejection fraction), and evaluation of laboratory parameters (clinical chemistry, haematology, and urinalysis).

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

On completion of Part A (collection of the 120 hour sample on Day 15), patients may continue to take AZD9291 (Part B), if they and the Investigator agree that it is of clinical benefit, until such time as their disease progresses, the Investigator believes they are no longer deriving clinical benefit, or they stop taking AZD9291 for any other reason. Patients will have weekly clinic/hospital 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 12 months' duration from the date the last patient enters this part of the study.

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, other than serious adverse events and drug dispensing/accountability.

Investigational product, dosage and mode of administration

In Part A, patients will receive a single oral dose of 80 mg AZD9291 in each of 2 treatment periods with 240 mL of water, once in the fasted state and once following a high-fat meal, with a 9 day washout period between doses. Patients will be randomised to one of two treatment sequences: fed:fasted or fasted:fed.

For the fed condition (Treatment A), patients will be fasted for ≥10 hours prior to receiving AZD9291 until 4 hours post-dose, with the exception of a high-fat meal that should be eaten in the 30 minutes prior to AZD9291 being administered. The AZD9291 tablet should be administered 30 minutes after the start of the meal consumption. If the meal is not completed within 30 minutes, AZD9291 may still be administered so long as 75% of the meal has been consumed within 45 minutes of the start of the meal.

In the fasted condition (Treatment B), patients will be fasted for ≥10 hours before AZD9291 dosing, until 4 hours post-dose. Patients may have glucose (sugar tablets) and/or juice (except for grapefruit juices or juices containing grapefruit or Seville oranges) if they have signs or symptoms of hypoglycaemia after they have received AZD9291 in the fasted state.

Water will be restricted from 1 hour pre-dose until 1 hour post-dose for all treatments in Part A, except for the water administered with AZD9291, and any drink provided as part of the meal in the fed portion of the study.

Part B will start immediately after the last PK blood sample has been collected in TP 2 of Part A. Patients will receive daily oral doses of AZD9291 80 mg, given as the tablet formulation, for the duration of their participation. In Part B, patients must fast for ≥1 hour prior to dose to ≥2 hours post-dose. Water is permitted during this fasting period. Restrictions related to fasted administration of AZD9291 may be modified upon PK data emerging from the clinical programme.

Statistical methods

For AZD9291 (primary) and its metabolites (secondary), natural log-transformed $AUC_{0\text{-}72}$ and C_{max}, will be compared between treatments using a mixed effects analysis of variance model. Estimates of the mean difference between treatments and corresponding 90% confidence intervals (CI) 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 and the associated 90% CIs. Additionally, back transformed geometric means together with 95% CIs will be estimated and presented for each food condition. Additional AUCs will be analysed if appropriate. No

effect on the PK of AZD9291 after given with food will be concluded if the 2-sided 90% CIs for the ratios of AZD9291 AUC_{0-72} and C_{max} are both within the range of 70% to 143%.

For AZD9291 and its metabolites, analyses of t_{max} will be performed using the Wilcoxon Signed Rank Test. The Hodges-Lehmann median estimator of the difference in treatments (fed–fasted) and 90% CIs will be presented.

In the event of relevant carry-over exposure across periods, a secondary statistical analysis may be performed including all patients, irrespective of the degree of carry-over. If appropriate, an exploratory analysis on carry-over adjusted concentrations and PK parameters may also be performed.

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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
AnLK	Anaplastic lymphoma kinase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve from zero to infinity
AUC_{0-72}	Area under the plasma concentration time curve from zero to 72 hours
AUC_{0-120}	Area under the plasma concentration time curve from zero to 120 hours
AUC_{0-t}	area under the plasma concentration time curve from zero to the last quantifiable time point
BCRP	Breast cancer resistance protein
BP	Blood pressure
CI	Confidence interval
CL/F	Apparent plasma clearance
C_{max}	Maximum plasma concentration
%CV	Coefficient of variation
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P_{450}
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
Echo	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

Abbreviation or special term	Explanation
EGFR	Epidermal growth factor receptor
EGFRm+	Epidermal growth factor receptor mutation positive
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
%GCV	Geometric coefficient of variation
GMP	Good manufacturing practice
GRand	Global randomisation system
Hb	Haemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HRCT	High-resolution computed tomography
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
LIMS	Laboratory Information Management System
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multiple Gated Acquisition Scan
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
OAE	Other significant adverse event
PGP	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic
QT	Interval on the electrocardiogram representing the duration of depolarisation and repolarisation of the heart

Abbreviation or special term	Explanation
QTc	The QT interval corrected for heart rate
QTcF	Fridericia's correction factor
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
$t_{½}$	Terminal half-life
T790M	An amino acid substitution at position 790 in EGFR, from a Threonine (T) to a Methionine (M)
T790M+	T790M mutation positive
TKI	Tyrosine Kinase Inhibitor
t_{max}	Time to reach maximum plasma concentration
TP 1	Treatment Period 1
TP 2	Treatment Period 2
ULN	Upper limit of normal
USA	United States of America
V_z/F	Apparent volume of distribution
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 NSCLC patients 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 epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (AnLK) and KRAS mutations. Epidermal growth factor receptor-tyrosine kinase inhibitors (TKIs) are now the established first line therapy in patients with NSCLC known to have activating mutations in EGFR (EGFR mutation positive [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 (refer to the latest edition of the IB for further details) (Ranson et al 2013).

Pharmacokinetic (PK) 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 appears to be consistent with the dosing frequency and observed apparent mean (min-max) terminal half-life ($t_{½}$) of 55.18 (29.7 to 146) hours in patients. In healthy volunteers, after a single oral dose of AZD9291 dosed as the capsule, the observed apparent mean (min-max) $t_{½}$ was 52.72 (32.5 to 72.0) hours.

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

1.2 Rationale for study design, doses and control groups

This is a 2-part study in patients with EGFRm+ NSCLC whose disease has progressed following treatment on an EGFR-TKI.

Part A of this study will investigate the effect of food on the PK of AZD9291 (80 mg) given as the tablet formulation in patients with EGFRm+ NSCLC whose disease has progressed on an EGFR TKI. There are currently no robust clinical data on the effect of food on the PK of AZD9291, at the expected therapeutic dose (80 mg), in this patient population. Therefore, the results from this study will help to define what, if any, drug administration guidance related to food intake is needed for future/ongoing studies with AZD9291. As the formulation being used in this study is the likely commercial formulation, it is anticipated that the data generated from this study will support regulatory submissions for AZD9291 in the treatment of patients with NSCLC.

Part A is a 2-period crossover design to allow the investigation of the effect of food within each patient and in a randomised manner. A crossover design is the recommended design for food effect studies to reduce inter-patient variability. Due to the long half-life of the 3 analytes, the primary treatment comparisons will be based on maximum plasma concentration (C_{max}) and area under the plasma concentration time curve from zero to 72 hours (AUC_{0-72}). Period 1 will be 9 days (216 hours) long while Period 2 will be 5 days (120 hours) long. The longer duration for Period 1 will allow for an accurate estimation of the elimination rate constants for AZD9291, AZ5104 and AZ7550, and allow exploratory concentration-adjustment to account for carry-over in Period 2, if required.

Evaluation of exposure (AUC_{0-72} and C_{max}) to AZD9291 will be the primary endpoint in Part A of this study. AZ5104 and AZ7550 are potentially active metabolites of AZD9291; however, they circulate at approximately 10% each of AZD9291. Production and clearance of AZ5104 and AZ7550 are thought to be predominately via Cytochrome P_{450} (CYP)3A4 mediated metabolism, so metabolite to AZD9291 ratios are expected to remain unchanged when AZD9291 is administered after a high-fat meal. 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.

The study will be conducted using the Food and Drug Administration (FDA) standard high-fat meal. In order to optimally manage appropriate fasting and food consumption in this study, patients are asked to check into the clinic the day before each dose administration and remain in the clinic overnight prior to AZD9291 administration.

The tablet dose chosen will deliver exposure that has been previously demonstrated to be tolerated in cancer patients, and is the dose to be used in the pivotal clinical studies for AZD9291. In addition, the mode of action of the drug makes it relevant to use patients with EGFRm+ NSCLC.

Part B will allow patients who have participated in 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 advanced 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 NSCLC. 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 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 investigational product (IP)-related toxicities is provided for all AZD9291 studies (Section 6.7).

All AEs, vital sign, electrocardiogram (ECG) 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 initially gain any benefit from participation in Part A of the study due to the short dosing periods, some 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 tablets until such time as their disease progresses, the Investigator believes they are no longer deriving clinical benefit, or they stop taking the AZD9291 tablets for any other reason.

In addition to their potential effect on CYP3A4, in vitro data suggest that AZD9291 and metabolites AZ5104 and AZ7550 may also have the potential to inhibit CY2C8 and the breast cancer resistance protein (BCRP) transporter or to induce CYP3A4, CYP1A2, CYP2C and/or p-glycoprotein (PGP). Measures have been taken in this protocol to provide appropriate restrictions and/or direction for use of concomitant mediations which are substrates for these metabolizing enzymes or transporters.

The data generated from this study will support a submission for AZD9291 in the treatment of NSCLC. The overall risk for the patients who participate in this study to assess the effect of food on the PK of AZD9291 is acceptable.

Whilst pre-clinical toxicology does not preclude the use of healthy volunteers, ensuring that appropriate limits on the maximum exposure in healthy volunteers are not exceeded, combined with the fact that the effect of food on PK at the anticipated therapeutic dose (80 mg) is unknown, suggests that a patient population is more appropriate for the study.

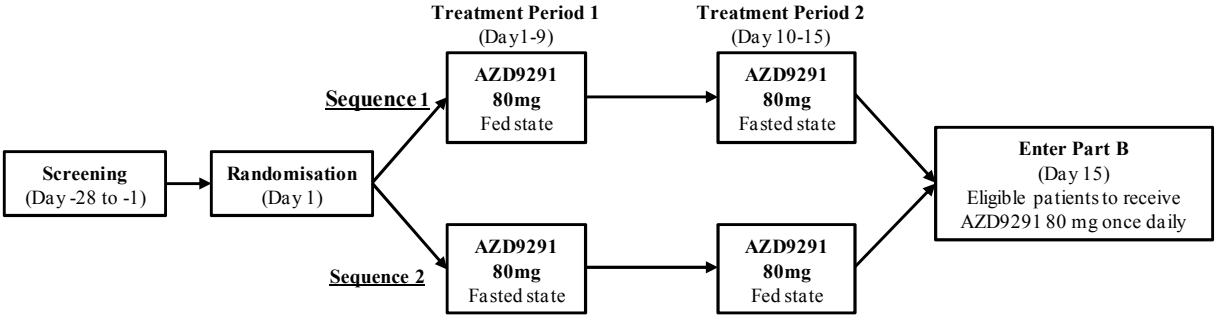
1.4 Study Design

This is a 2-part study in patients with EGFRm+ NSCLC whose disease has progressed following treatment on an EGFR-TKI: Part A will determine the effect of food on the PK of AZD9291; Part B will allow patients further access to AZD9291 after the PK phase and will provide for additional safety data collection. Approximately 38 patients are planned to be enrolled at approximately 11 sites across Asia, the United States of America (USA) and Western Europe; at least 30 evaluable patients will be required to complete Part A of the study. Additional patients may be dosed in the study until such a time as 30 evaluable patients have completed Part A of the study (ie, the last PK sample in Treatment Period 2 [TP 2] has been collected). A maximum of 50% of patients will be recruited from Asia.

On completion of Part A, patients may continue to take AZD9291 (Part B), if they and the Investigator agree that it is of clinical benefit, until such time as their disease progresses, the Investigator believes they are no longer deriving clinical benefit, or they stop taking AZD9291 for any other reason. Safety assessments as detailed in Table 3 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 12 months' duration from the date the last patient enters this part of the study. 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, other than SAEs and drug dispensing/accountability.

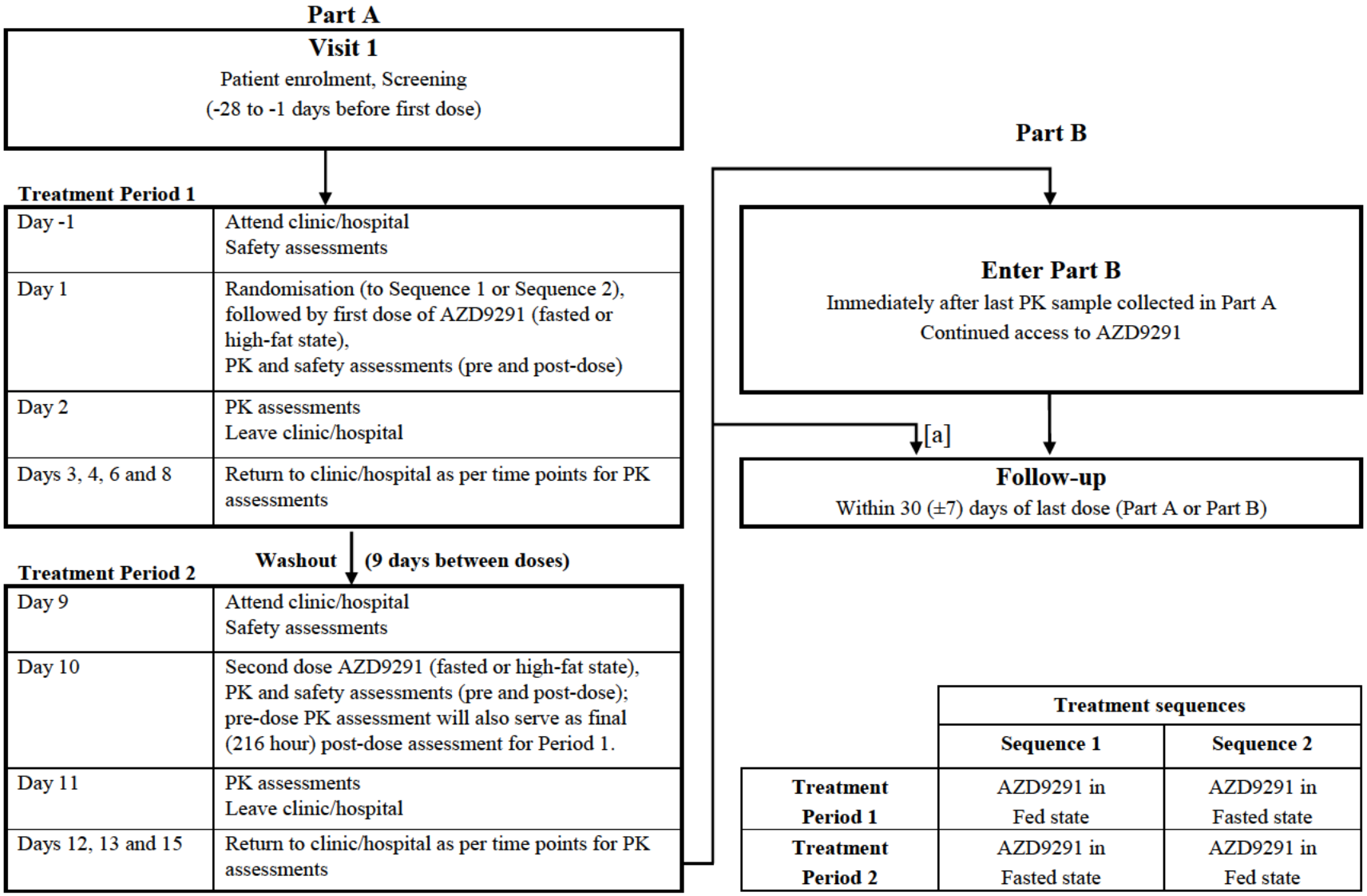
A study plan and flow chart illustrating are provided, respectively, in Figure 1 and Figure 2 for Parts A and B of the study.

Figure 1 Overall study plan



Note: Approximately 38 patients are planned to be enrolled; additional patients may be enrolled until 30 evaluable patients have completed Part A. Assessments for pharmacokinetic analyses will be performed in Part A, and for safety assessments in Parts A and B. Patients who withdraw or discontinue will complete a follow-up assessment. Part B will be of 12 months duration from the date the last patient enters this part of the study.

Figure 2 Overall study flow chart



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

2. STUDY OBJECTIVES

2.1 Primary objective

Primary objective:

To investigate the effect of food on the exposure of AZD9291 (AUC_{0-72} and C_{max}) following oral dosing of the tablet formulation in patients with EGFRm+ NSCLC following disease progression on an EGFR TKI.

2.2 Secondary objectives

Secondary objective:

To characterise the effect of food on the PK of AZD9291 metabolites (AZ5104 and AZ7550) following oral dosing of the tablet formulation in patients with EGFRm+ NSCLC following disease progression on an EGFR TKI.

2.3 Safety objectives

Safety objective:

To investigate further the safety and tolerability of daily oral doses of AZD9291 in patients with EGFRm+ NSCLC (Part B).

2.4 Exploratory objectives

Exploratory objective:

To perform genetic research in the AZD9291 clinical pharmacology development programme to explore how genetic variations may affect the clinical PK of AZD9291.[a]

To provide data to allow analysis using population PK approaches.[a]

a The results of any further analyses will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

2.5 Outcome measures

Outcome measures:	
Analysis:	**Measures:**[a]
PK – Primary: AZD9291	Maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from zero to 72 hours (AUC_{0-72}).
PK - Secondary: AZD9291	Area under the plasma concentration-time curve from zero to 120 hours (AUC_{0-120}), area under the plasma concentration time curve from zero to the last quantifiable time point (AUC_{0-t}), area under the plasma concentration-time curve from zero to infinity (AUC), time to reach maximum plasma concentration (t_{max}), terminal half-life ($t_{½}$), terminal rate constant (λ_z), apparent plasma clearance (CL/F) and apparent volume of distribution (V_z/F).
PK - Secondary: AZ5104 and AZ7550	C_{max}, AUC_{0-72}, AUC_{0-120} AUC_{0-t}, AUC, t_{max}, $t_{½,}$ and λ_z.
Safety	Assessment of adverse events, graded by CTCAE (version 4), physical examination, vital signs (blood pressure, pulse rate and body temperature), standard 12-lead electrocardiogram, echocardiogram/Multiple Gated Acquisition Scan (for assessment of left ventricular ejection fraction), and evaluation of laboratory parameters (clinical chemistry, haematology, and urinalysis).

a For definition of abbreviations see: Abbreviation or special term

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, 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 patients 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. Able to eat a high-fat meal within a 30-minute period, as provided by the study site (see Appendix I).

4. Histologically or, where appropriate, cytologically confirmed NSCLC.

5. Radiological documentation of disease progression while on a previous continuous treatment on an EGFR-TKI eg, gefitinib or erlotinib. 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.

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

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

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

9. 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 luteinizing hormone and follicle-stimulating hormone 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.

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

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

12. For inclusion in **optional genetic research**, patient 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.

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 AstraZeneca or representative staff, its agents, 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:

   - An approved or experimental EGFR-TKI (eg, erlotinib, 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) (Appendix H). All patients must avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer/inhibitory effects on CYP3A4.

5. 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 end of Part A.

6. 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.

7. Patients unable to fast for up to 14 hours.

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

9. 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. Screening for chronic conditions is not required.

10. Patients with type I diabetes.

11. Patients unable to swallow orally administered medication or patients with gastrointestinal disorders likely to interfere with absorption of AZD9291, and patients who have had previous significant gastrointestinal resection.

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

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

16. 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 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).

17. 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.

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.

For procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment and randomisation

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

The Investigator(s) or designee will:

1. Obtain signed informed consent from the potential subject 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 subject eligibility. See Sections 3.1 and 3.2.

At Visit 2, after the patient is confirmed to be eligible, the PI or suitably trained delegate will:

4. Assign eligible patients a unique randomisation number.

Randomisation numbers will be assigned as described in Section 3.5.

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. Patents 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 or randomised patients

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

Where patients that do not meet the selection criteria are randomised in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation (in either Part A or Part B), a discussion should occur between the AstraZeneca Physician or his/her representative and the Investigator regarding whether to continue or discontinue the patient from 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 his/her representative is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study therapy stopped and be withdrawn from the study.

3.5 Methods for assigning treatment groups

Approximately 38 patients will be enrolled in order to obtain 30 evaluable patients for Part A. Additional patients may be dosed in the study until such a time as 30 evaluable patients have completed Part A of the study (ie, the last PK sample in TP 2 has been collected).

The randomisation scheme will be generated by using the global randomisation system (GRand). The randomisation schedule will be allocated in blocks and will be produced by computer software that incorporates a standard procedure for generating random numbers. A randomisation schedule will be generated for each site. Each site will have unique randomisation numbers. Small block sizes will be used to generate the randomisations to minimize the imbalance across sequence.

Investigational sites will be provided with sealed envelopes with randomisation numbers pre-printed on the cover. The sequence allocated to a specific randomisation number will be contained within the corresponding sealed envelope. A randomisation number which will identify the sequence assigned to an individual patient will be allocated strictly sequentially upon confirmation of eligibility to receive study treatment. Once allocated, the appropriate randomisation code envelope should be opened to identify the sequence that patient will receive. The opened randomisation code envelopes will be stored in the investigator site file.

Patients will be randomised to one of the two sequences as shown in Table 1.

Table 1 Randomisation sequences

Sequence	Treatment Period 1	Treatment Period 2
1	A	B
2	B	A

Treatment A will consist of AZD9291 administered in the fed state.
Treatment B will consist of AZD9291 administered in the fasted state.

3.6 Methods for ensuring blinding (Not applicable)

3.7 Methods for unblinding (Not applicable)

3.8 Restrictions

The following restrictions will apply to patients during Parts A and B of the study, unless otherwise specified:

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

Females of child-bearing potential should be willing to use an acceptable contraceptive method 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 (see Appendix F).

Male patients should be asked to avoid unprotected sex with all sexual partners (by use of condoms) during the study, and for a washout period of 6 months after the last dose of study drug. 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 drug 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.

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 of Part A.

Patients who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE grade $\leq$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 $\geq$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.

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

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

Other restrictions

Part A, Treatment A (fed): Patients will be fasted for ≥10 hours prior to receiving AZD9291, with the exception of a high-fat meal that should be eaten in the 30 minutes prior to AZD9291 being administered. The AZD9291 tablet should be administered 30 minutes after the start of the meal consumption with 240 mL of water, after which patients will fast until 4 hours post-dose. If the meal is not completed within 30 minutes, AZD9291 may still be administered so long as 75% of the meal has been consumed within 45 minutes of the start of the meal. The start and stop date/time of meal consumption along with the percent consumed (in quartiles, ie, 0%, 25%, 50%, 75%, 100%) must be recorded in the electronic Case Report Form (eCRF).

Part A, Treatment B (fasted): Patients will be fasted from at least 10 hours before AZD9291 dosing, until 4 hours post-dose. AZD9291 will be administered with 240 mL of water. Patients may have glucose (sugar tablets) and/or juice (except for grapefruit juices or juices containing grapefruit or Seville oranges) if they have signs or symptoms of hypoglycaemia after they have received AZD9291 in the fasted state. The time and exact nature of any such glucose (sugar tablets/juice) consumed must be recorded in the eCRF.

Water will be restricted from 1 hour pre-dose until 1 hour post-dose for all treatments in Part A, except for the water administered with AZD9291, and any drink provided as part of the meal in the fed portion of the study.

In Part B, patients must fast for ≥1 hour prior to dose to ≥2 hours post-dose. Water is permitted during this fasting period. Restrictions related to fasted administration of AZD9291 may be modified upon PK data emerging from the clinical programme.

For all doses of AZD9291 in parts A and B, tablets should be swallowed whole and not chewed, crushed, or divided.

3.9 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations (applies to Parts A and B):

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance to study protocol
- Worsened condition

- Progressive disease
- The Investigator believes they are no longer deriving clinical benefit (Part B).

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.

Any patient discontinuing IP should be seen at 30 (±7) days after their last dose for the evaluations outlined in the study schedule (see Table 2 and Table 3). After discontinuation of IP, the PI/sub-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 IP at any point in the study, 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 IP 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 IP to collect and/or complete AE information and return IP. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the Investigator assesses as possibly related to the IP should also be reported as an AE.

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 randomised or treated. These patients should have the reason for study withdrawal recorded as 'Eligibility Criteria Not Fulfilled' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).

3.10.2 Withdrawal of the informed consent

Patients are at any time free to withdraw from 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 Sections 6.3.2) and 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.

Reasons for withdrawal from the study include:

- 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 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

A study plan and flow chart illustrating are provided, respectively, in Figure 1 and Figure 2 for Parts A and B of the study. The study plan for Part A (PK evaluation) of the study is provided in Table 2. The study plan for Part B (continued access to AZD9291) of the study is provided in Table 3. The timing of PK blood samples for AZD9291 is detailed in Table 4.

Table 2 Study plan - Part A

Assessments	**Screening**	**Treatment Period 1[a]**								**Treatment Period 2[a]**					**Follow-up[b]**
Visit Number	**1**	**2**			**3**	**4**	**5**	**6**	**7**			**8**	**9**	**10**	**100**
Day[c]	**-28 to -1 days before dosing**	**-1**	**1**	**2 24 h**	**3 48 h**	**4 72 h**	**6 120 h**	**8 168 h**	**9**	**10**	**11 24 h**	**12 48 h**	**13 72 h**	**15 120 h**	**30 (±7) days after last dose**
Resident in clinic/hospital		<---------->		[d]					<---------->		[d]				
Outpatient visits	X				X	X	X	X				X	X	X	X
Written informed consent	X														
Demography	X														
Medical/surgical history	X														
Inclusion/exclusion criteria	X														
Randomisation[a]			X												
ECOG performance status	X														
Height (cm)[e]	X														
Ophthalmologic examination[f]	X														
Echo/MUGA[g]	X														X
Body weight (kg)[e]	X	X							X						X
Physical examination	X	X							X						X
Vital signs (BP, pulse, body temperature)[h]	X	X	X						X	X					X
Resting standard 12-lead ECG[h]	X	X	X						X	X					X
Haematology/clinical chemistry/Coagulation[i]	X	X							X						X
Urinalysis[j]	X	X							X						X
Serum/urine pregnancy test[k]	X	X													X
Pharmacogenetics blood sample[l]		X													

Table 2 Study plan - Part A

Assessments	**Screening**	**Treatment Period 1[a]**								**Treatment Period 2[a]**					**Follow-up[b]**
Visit Number	**1**	**2**			**3**	**4**	**5**	**6**	**7**		**8**	**9**	**10**		**100**
Day[c]	**-28 to -1 days before dosing**	**-1**	**1**	**2 24 h**	**3 48 h**	**4 72 h**	**6 120 h**	**8 168 h**	**9**	**10**	**11 24 h**	**12 48 h**	**13 72 h**	**15 120 h**	**30 (±7) days after last dose**
AZD9291 administration[m]			X							X[n]					
AZD9291 PK blood sampling[o]			X[p]	X	X	X	X	X		X[p]	X	X	X	X	
Serology Screen (HBV, HCV)	X														
Adverse events[q]	X	X	X	X	X	X	X	X	X	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

a Patients will receive a single oral dose of AZD9291(80 mg) in each of 2 treatment periods in Part A (TP 1 and TP 2), under fasted or fed (high-fat meal) conditions. Patients will be randomised to treatment (fed/fasted condition) on Day 1 of TP 1.

b For patients who withdraw from the study prematurely and do not go on to continuous dosing (Part B).

c There is no Day 0. Day -1 is the day before dosing, and Day 1 is the day of dosing.

d Patients will check into the clinic/hospital on Day -1 for TP 1, and on Day 9 for TP 2. If the patient has completed the laboratory safety assessments within 48 hours prior to dosing in each period there is no requirement to repeat safety laboratory tests.

e For height and weight, indoor clothing may be worn but shoes should be removed. The same weighing scales should be used at each visit.

f 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.

g For the evaluation of the left ventricular ejection fraction. See also Section 5.2.5.

h Supine BP and pulse will be measured 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 time point. On AZD9291 dosing days in Part A, assessments will be performed pre-dose and at 3, 6 and 12 hours post-dose.

i Coagulation (aPTT and INR) will be performed at baseline and if clinically indicated. Patients taking warfarin should be monitored as described and according to local practices (see Section 7.7).

j Protein, blood and glucose; microscopic analysis is to be performed if required.

k 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 prior to their first dose of AZD9291. In the event of a 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.

l 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.

m In the fasted treatment period, patients should be fasted from at least 10 hours prior until 4 hours post-dose unless they have signs or symptoms of hypoglycaemia after they have received AZD9291 in the fasted state (see Section 4.2.1). In the fed treatment period, patients should be fasted from at least 10 hours prior until 4 hours post-dose, except for the consumption of a high-fat meal in the 30 minutes prior to the AZD9291 dose. The AZD9291 should be administered 30 minutes after the start of the meal consumption. If the meal is not completed within 30 minutes, AZD9291 may still be administered so long as 75% of the meal has been consumed within 45 minutes (see Section 7.2). AZD9291 should be swallowed whole with approximately 240 mL of water, and not chewed, crushed, dissolved or divided.

n There will be a 9-day washout period between the first and second dose of AZD9291 in Part A. AZD9291 doses should not be deferred, except in the case for the fed treatment that the patient is unable to eat at least 75% of the meal within 45 minutes. In that case, a second attempt may be made on the next day and an AstraZeneca representative consulted to decide how to proceed in terms of continuation in Part A, and/or eligibility to continue in Part B (see Section 7.2).

o AZD9291 PK samples will be collected on Day 1 (TP 1) and Day 10 (TP 2), at the times specified in Table 4.

p A pre-dose PK sample must be collected on Day 1 of TP 1. The 216 hour PK sample for TP 1 will be used as the pre-dose PK sample for TP 2. If the second dose of AZD9291 is delayed, an additional PK sample should be obtained pre-dose on the day of dosing.

q 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 last dose of study drug. Any existing and any new AEs occurring during the 30-day follow-up period must be recorded and followed to resolution if possible.

AE adverse event; aPTT activated partial thromboplastin time; BP blood pressure; ECG electrocardiogram; Echo echocardiogram; ECOG Eastern Cooperative Oncology Group; HBV hepatitis B virus; HCV hepatitis C virus; INR international normalised ratio; MUGA Multiple Gated Acquisition Scan; PK pharmacokinetics; SAE serious adverse event; TP 1 Treatment Period 1; TP 2 Treatment Period 2.

Table 3 Study plan - Part B (continued access to AZD9291)

Visit Number	**10**[a]	**101**	**102**	**103**	**104**	**Subsequent on-treatment visits every 4 weeks**[b] **Visit 105 onwards**	**Follow-up 30 (±7) days after last dose of study medication**
Day	**15**	**22**	**29**	**36**	**43**	Day 1 of next visit period (equals Day 71 [Week 10] then Day 99 [Week 14], etc)	
Visit window		±3d	±3d	±3d	±3d	±7d	±7d
Physical examination[c]		X	X	X	X	X	X
Vital signs (BP, pulse, body temperature)[d]		X	X	X	X	X	X
Body weight (kg)[e]		X	X	X	X	X	X
Serum/urine pregnancy test[f]	<----------						----------> X
Echo/MUGA[g]					X	<----------	----------> X
Resting standard 12-lead ECG[d]						X	X
Haematology/clinical chemistry		X	X	X	X	X[h]	X
Adverse events		X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X
AZD9291 dispensed/returned	X[i]				X[i]	X[i]	X
Disease status[j]	<----------						----------> [j]

a The last visit in Part A will serve as the first visit in Part B. Assessments listed are additional to those listed for the last visit in Part A (Table 2).
b Visit to take place on Day 1 of a 4 week (28 day) visit period. Visits will continue for 12 months from the date the last patient enters Part B.
c After baseline, it is not necessary to record any physical examination details on the eCRF; any clinically significant changes should be recorded as AEs.
d 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 time point.
e 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 a 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 approximately 4 weeks into Part B (Visit 104), and then subsequently every 12 (± 4) weeks. Echo/MUGA at follow-up is not required if patients have had one in the previous 6 weeks, as long as their cardiac function is stable.
h Additional haematology assessments will be performed on Day 1 of each 4-week visit period in Part B for the first 6 months, at discontinuation, and at the 30 (±7)-day follow-up visit (see Section 5.2.1). Urinalysis and coagulation will only be assessed only if clinically indicated. Patients taking warfarin should be monitored as described in Section 7.7.
i 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.
j During Part B no efficacy data will be collected, therefore patients will be monitored as per their normal routine clinical schedule.

BP blood pressure; eCRF electronic case report form; ECG electrocardiogram; Echo echocardiogram; MUGA Multiple Gated Acquisition Scan.

Table 4 Timing of PK samples – Part A

Study Day	Time (hours)	Study drug	AZD9291 PK blood[a]	
			TP 1	TP 2
Day 1	Pre-dose		X	
	(Dose)	AZD9291 80 mg[b]		
	0.5		X	
	1		X	
	1.5		X	
	2		X	
	3		X	
	4		X	
	6		X	
	8		X	
	10		X	
	12		X	
Day 2	24		X	
Day 3	48		X	
Day 4	72		X	
Day 6	120		X	
Day 8	168		X	
Day 10	216[b]		X[b]	
Day 10	Pre-dose[c]			X[b]
	(Dose)	AZD9291 80 mg[b]		
	0.5			X
	1			X
	1.5			X
	2			X
	3			X
	4			X
	6			X
	8			X
	10			X
	12			X
Day 11	24			X
Day 12	48			X
Day 13	72			X
Day 15	120			X

Note: A 30-minute window will be allowed for samples taken at pre-dose; a 5-minute window for samples taken ≤1 hour; a 15-minute window for samples taken ≥2 to ≤12 hours and a 2-hour window for samples taken from ≥24 hours.

a TP 1 will be 9 days (216 hours) long, while TP 2 will be 5 days (120 hours) long (see Section 1.2).

b In the fasted treatment period, patients should be fasted from at least 10 hours prior until 4 hours post-dose unless they have signs or symptoms of hypoglycaemia after they have received AZD9291 in the fasted state (see Section 4.2.1). For the fed treatment period, patients will follow this same fasting schedule, except for their consumption of a high-fat meal in the 30 minutes prior to dosing.

c The second dose of AZD9291 in Part A will be administered on the morning of Day 10. The 216 h PK sample for TP 1 will be used as the pre-dose PK sample for TP 2. If the second dose of AZD9291 is delayed, an additional PK sample should be obtained pre-dose on the day of dosing.

PK pharmacokinetics; TP 1 Treatment Period 1; TP 2 Treatment Period 2

4.1 Enrolment/screening period

Procedures will be performed according to the Study Plan (Table 2). At screening, consenting patients are assessed to ensure that they meet eligibility criteria (Section 3.1 and 3.2). 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 [BP], pulse rate and body temperature), ECG, echocardiogram (Echo)/Multiple Gated Acquisition Scan (MUGA) for assessment of left ventricular ejection fraction (LVEF), weight, height, ophthalmic examination, demographics, concomitant medication, medical/surgical history, blood samples for haematology, clinical chemistry and coagulation, hepatitis B virus (HBV) and hepatitis B virus (HCV) status, urinalysis, pregnancy test, diagnosis and assessment of the disease for which the IP is being tested (including ECOG performance status).

4.2 Treatment period

Descriptions of the procedures for this period are included in the Study Plans for Part A (Table 2) and for Part B (Table 3). The timing of PK blood samples for AZD9291 (Part A only) is detailed in Table 4.

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 time point. The sequence to be followed at a particular post-dose time point is:

ECGs

Vital signs

PK blood sample (at scheduled time)

Any other assessments

For pre-dose assessments, ECGs and vital signs samples should be collected within 60 minutes prior to dosing; PK samples should be collected within 30 minutes prior to dosing.

A 30-minute window will be allowed for PK samples taken at pre-dose; a 5-minute window will be allowed for samples taken up to and including 1 hour; a 15-minute window for samples taken at 2 to 12 hours and a 2-hour window for samples taken from 24 hours onwards.

4.2.1 Part A

Part A of this study is a randomised, open-label, 2-treatment period crossover study in which patients will each receive a single oral dose of AZD9291 (1 x 80 mg tablet) at breakfast time in each of 2 treatment periods (once immediately following a high-fat meal, and once in the fasted state).

Patients will check into the clinic/hospital on Day -1 for Treatment Period 1 (TP 1), and on Day 9 for TP 2. Patients will remain resident until 24 hours after each dose of AZD9291. Randomisation of each patient to treatment sequences (fed:fasted or fasted:fed) will occur prior to dosing on Day 1 of the first treatment period. Laboratory safety assessment will be completed on the day prior to dosing in TP 1 and TP 2; however, if the patient has completed the safety assessments within 48 hours prior to dosing in each period, there is no requirement to repeat safety laboratory tests.

Patients will receive a single dose of AZD9291 (1 x 80 mg tablet) orally in the morning on Day 1 (TP 1) and Day 10 (TP 2) in the fed (Treatment A) or fasted (Treatment B) state. The study treatments should be swallowed whole with approximately 240 mL of water, and not chewed, crushed, dissolved or divided.

Treatment A (fed): For the fed treatment, patients should be fasted from at least 10 hours prior until 4 hours post-dose, except for the consumption of a high-fat meal in the 30 minutes prior to the AZD9291 dose. Patients should eat the meal within 30 minutes (patients that are unable to eat the meal in 30 minutes will still be considered evaluable as long as they have consumed at least 75% of the meal within 45 minutes). The AZD9291 dose should be administered 30 minutes after the start of the meal consumption. If the meal is not completed within 30 minutes, AZD9291 may still be administered so long as 75% of the meal has been consumed within 45 minutes of the start of the meal. The start and stop date/time of meal consumption along with the percent consumed (in quartiles, ie, 0%, 25%, 50%, 75%, 100%) must be recorded in the eCRF.

Treatment B (fasted): In the fasted treatment period, patients should be fasted from at least 10 hours prior, until 4 hours post-dose. Patients may have glucose (sugar tablets) and/or juice (except for grapefruit juices or juices containing grapefruit or Seville oranges) if they have signs or symptoms of hypoglycaemia after they have received AZD9291 in the fasted state. The time and exact nature of any such glucose (sugar tablets/juice) consumed must be recorded in the eCRF.

Water will be restricted from 1 hour pre-dose until 1 hour post-dose for all treatments in Part A, except for the water administered with AZD9291, and any drink provided as part of the meal in the fed portion of the study.

The window (washout period) between AZD9291 doses in Part A of the study should be 9 days, with the second dose of AZD9291 being administered immediately after the 216 hour post-dose PK sample for TP 1. The 216 hour post-dose PK sample for TP 1 will be used as the pre-dose sample for TP 2. AZD9291 doses must not be deferred, except in the case for the

fed treatment that the patient is unable to eat at least 75% of the meal within 45 minutes. In that case, a second attempt may be made on the next day (all relevant assessments eg, PK sampling and vitals assessments should be deferred accordingly). In such circumstances, an AstraZeneca representative must be consulted to decide how to proceed in terms of the patient's continuation in Part A, and/or eligibility to continue in Part B. If the second dose of AZD9291 is delayed, an additional pre-dose PK sample should be obtained prior to the second dose of AZD9291 being administered.

In TP-1 and TP-2, PK sampling will be conducted whilst patients are resident at the times shown in Table 4. In TP 1, patients will return to the clinic/hospital on an outpatient basis for PK assessments on Days 3 (48 hours), 4 (72 hours), 6 (120 hours) and 8 (168 hours). A PK sample will also be obtained on Day 10 (216 hours) prior to TP 2 dosing, which will also serve as the pre-dose sample for TP 2. In TP 2, outpatient PK assessments will be performed on Days 12 (48 hours), 13 (72 hours) and 15 (120 hours).

For patients who do not enter Part B, after Part A (including follow-up visit) is completed no further data will be collected other than SAEs and drug dispensing/accountability (see Section 6.3.1). During this time, patients will be seen as per their normal routine clinical schedule.

4.2.2 Part B

On completion of Part A, patients may continue to take AZD9291 tablets (80 mg Part B), if they and the Investigator agree that it is of clinical benefit, until such time as their disease progresses, the Investigator believes they are no longer deriving clinical benefit, or they stop taking AZD9291 for any other reason. In Part B, patients must fast for ≥1 hour prior to dose to ≥2 hours post dose. Water is permitted during this fasting period. Restrictions related to fasted administration of AZD9291 may be modified upon PK data emerging from the clinical programme.

After the end of Part B (12 months after the last patient entered 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, other than SAEs and drug dispensing/accountability.

Patients should start Part B immediately after the last PK blood sample has been collected in TP 2 of Part A. Patients will have weekly clinic/hospital visits for the first 4 weeks; thereafter visits will be every 4 weeks. Safety assessments as detailed in Table 3 will be collected and there will be no formal evaluation of efficacy. Patients' medical/oncological care will be treated according to local clinical practice. Pharmacokinetic assessments will not be performed in Part B of this study.

After Part B is completed, patients may continue to take AZD9291 tablets (see Section 7.8). During this time, they will be seen as per their normal routine clinical schedule. No further data will be collected other than SAEs and drug dispensing/accountability (see Section 6.3.1).

4.3 Follow-up period

Patients will return to the clinic/hospital for follow-up assessments 30 (±7) days after their last dose (regardless of whether the last dose is in Part A or Part B). Follow-up assessments for Part A are detailed in Table 2; follow-up assessments for Part B are detailed in Table 3.

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 (CSA). 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 parameters will be taken at the times given in the study plans (Table 2 for Part A, and Table 3 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 5 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 virus (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 2. 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 Blood volume

The maximum volume of blood that will be taken for any given patient for the purposes of the study will typically not exceed 190 mL (Table 6).

Table 6 Volume of blood to be drawn from each patient: Parts A and B

Assessment		Expected Sample volume (mL)	Number of samples			Total volume (mL)
			A[a]	B[b]	FU	
Safety	Clinical chemistry	2.7	3	15	1	51.3
	Haematology	2.7	3	15	1	51.3
Coagulation status	aPTT/INR	1.8	3	0	0	5.4
Serology	(HBV, HCV)	1.8	1	0	0	1.8
Pharmacogenetic	AZD9291	10.0	1	0	0	10.0
Pharmacokinetic	AZD9291/ metabolites	2.0	32	0	0	64.0
Total volume (mL)			**97.4**	**81.0**	**5.4**	**183.8**

Note: Table is for guidance. Exact volumes may differ depending on local requirements.
a Includes screening blood volumes and additional pre-dose pharmacokinetic sample.
b Number of samples in Part B is based on a patient being in the study for 12 months.
aPTT activated partial thromboplastin time; FU follow-up; HBV hepatitis B; HCV hepatitis C; INR international normalised ratio.

5.2.3 Physical examination

Physical examinations will be conducted at the times specified in the study plan and any findings recorded on the eCRF (Table 2 for Part A, and Table 3 for Part B). 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 and breast.

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

Performance status will be assessed using the ECOG performance status criteria (see Table 2 and Appendix G).

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 the study plan (Table 2 for Part A, and Table 3 for Part B). On AZD9291 dosing days in Part A, assessments will be performed pre-dose and at 3, 6 and 12 hours post-dose.

For each time point 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 time point 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 patients' 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 Echo or MUGA scan to assess LVEF (%) will be performed at screening, and at the visits indicated in Table 2 and Table 3. The modality of the cardiac function assessments must be consistent within a patient, ie, if an Echo is used for the screening assessment then an Echo 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 measured at the times specified in the study plan (Table 2 for Part A, and Table 3 for Part B); 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 rate and blood pressure

Supine BP and pulse rate will be measured using a semi-automatic BP recording device with an appropriate cuff size after the patient has been at rest for 10 minutes. On AZD9291 dosing days in Part A, assessments will be performed pre-dose and at 3, 6 and 12 hours post dose.

5.2.6.2 Body temperature

Body temperature will be measured using a semi-automatic body temperature recording device at the times specified in the study plan (Table 2 for Part A, and Table 3 for Part B).

5.2.6.3 Weight and height

Height and weight will be assessed at the visits as shown in the Study Plans (Table 2 for Part A, and Table 3 for Part B). 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 Ophthalmologic exam

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 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) will be taken at the time points detailed in the study plan (Table 2) and the PK sampling schedule (Table 4). Every attempt should be made to collect all samples at the times specified in the PK sampling schedule. The actual time and date of collection of

each blood sample must be recorded in the eCRF. Samples will be collected, processed, labelled, and shipped for analysis as detailed in the Laboratory Manual.

A 30-minute window will be allowed for samples taken at pre-dose; a 5-minute window will be allowed for samples taken up to and including 1 hour; a 15-minute window for samples taken at 2 to 12 hours and a 2-hour window for samples taken from 24 hours onwards.

For blood volume see Section 5.2.2.

5.4.2 Determination of drug concentration

Samples for determination of AZD9291 and its metabolites (AZ5104 and AZ7550) will be analysed by on behalf of the Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical methods. Full details of the bioanalytical method used will be described in a separate bioanalytical report. All samples still within the known stability of the analytes of interest (ie, AZD9291 and its metabolites AZ5104 and AZ7550) 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 shipped to AstraZeneca Biobank; see details in the Laboratory Manual).

5.5 Pharmacodynamics (Not applicable)

5.6 Pharmacogenetics

If a patient agrees to participate in the host pharmacogenetics research component of the study a blood sample will be collected (see Table 2). Written consent is mandatory for those patients who agree to participate in the pharmacogenetic research components of the study.

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 single blood sample for genetic research will be obtained from the subjects prior 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 prior to dosing 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.

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. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be 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/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) 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

An 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 including 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 after 12 months. After the final database lock, there may be some patients remaining on study treatment. For these patients who are continuing to receive AZD9291 AstraZeneca will collect information on SAEs, deaths (including those due to disease progression), discontinuation due to AEs/SAEs and drug accountability only.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca or its representative 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 collect for each AE;

- Adverse event (verbatim).
- The date and time when the AE started and stopped.
- Maximum CTCAE grade attained.
- Whether the AE is serious or not.
- Investigator causality rating against the IP (yes or no).
- Action taken with regard to IP.
- Adverse event caused patient's withdrawal from study (yes or no).
- Outcome.

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

- Date AE met criteria for SAE.

- Date Investigator became aware of SAE.
- Adverse event is serious due to [reason].
- Date of hospitalisation.
- Date of discharge.
- Probable cause of death.
- Date of death.
- Autopsy performed.
- Causality assessment in relation to study procedure(s).
- Causality assessment 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 current National Cancer Institute 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 current CTCAE version 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 IP?’.

For SAEs causal relationship will also be assessed for other medication and study procedures. 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 Hb 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 an increase 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, must 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.

- Death 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

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it and report this SAE in the AE 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 AE 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 study protocol. Investigators will be 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 SAEs, standard reporting timelines apply, see Section 6.4. For other overdoses, reporting should be done within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca during the course of the study and within 28 days of the last dose of AZD9291.

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 AE. 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 the last dose should be followed up and documented.

6.7 Management of IP related toxicities

The following text is guidance for Investigators who treat patients with AZD9291 in Part B only.

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 the toxicity resolves or reverts to ≤CTCAE grade 2 within 3 weeks of onset, treatment with AZD9291 may be restarted at the same dose (80 mg) or a lower dose (40 mg) using the rules below for dose modifications (Table 7) and with discussion and agreement with the AstraZeneca or representative Study Team Physician as needed. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption.

If the toxicity does not resolve to ≤CTCAE grade 2 after 3 weeks, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

Table 7 Dose interventions

Intervention	AZD9291 Dose
Starting Dose	80 mg
Reduced Dose	40 mg

On resolution of toxicity within 3 weeks:

- If an AE subsequently requires dose interruption, AZD9291 may restart at the same dose or the reduced dose, on resolution/improvement of the AE at the discretion of the Investigator.

Patients who reduce to the 40 mg dose must remain on the 40 mg dose for the remainder of the study.

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 are given in Appendix J.

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, are given in Appendix J.

6.7.3 Worsening pulmonary symptoms

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of ILD is observed, an interruption in study treatment dosing is recommended, and the AstraZeneca or representative study team should be informed. A questionnaire regarding

the results of the full diagnostic workup (including high-resolution computed tomography [HRCT], 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 edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered and study treatment permanently discontinued. Recommendations for appropriate management of cases of ILD/pneumonitis are given in Appendix J.

In the absence of a diagnosis of ILD study treatment may be restarted following consultation with the AstraZeneca or representative Study Team Physician.

Patients experiencing ILD will not be permitted to restart study treatment.

6.7.4 QTcF prolongation

Patients with QTcF prolongation fulfilling the following criteria (ie, confirmed QTcF prolongation to >500 msec absolute or a >60 msec increase from baseline) should have study treatment interrupted and regular ECGs performed until resolution to baseline. If the toxicity does not resolve to ≤ grade 1 within 3 weeks the patient will be permanently withdrawn from study treatment.

6.7.5 Corneal ulceration

Any patient developing corneal ulceration will be permanently discontinued from study treatment and should be followed regularly until resolution of the event. Corneal ulceration should be treated according to local guidance. Patients experiencing corneal ulceration will not be permitted to restart study treatment.

6.8 Study governance and oversight

6.8.1 Data Monitoring Committee

No Data Monitoring Committee is planned, as this study is an open-label, 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, predictable with no reported life-threatening AEs. 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(s)

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

7.2 Dose and treatment regimens

7.2.1 Part A

In Part A of the study, each patient will receive 1 single dose of 80 mg AZD9291 comprised of 1 x 80 mg tablet in each of 2 treatment periods. Dosing will occur at approximately 0800. The exact date and time of each dose administration will be recorded in the eCRF. The AZD9291 tablets should be swallowed whole with approximately 240 mL of water, and not chewed, crushed, dissolved or divided, with the patient in an upright position. The Investigator or his/her delegate will administer the IP. If vomiting occurs after AZD9291 dosing, the dose should not be re-administered.

If a patient vomits within approximately 6 hours after dosing with AZD9291 in Period 1, all PK sampling may be omitted for that treatment period, but the safety assessments should continue as per the Study Plan. The patient should continue into Period 2 of Part A according to the Study Plan (Table 2).

If a patient vomits within approximately 6 hours after dosing with AZD9291 in Period 2, all PK sampling may be omitted for that treatment period. The patient will be discontinued from Part A and the Investigator may contact an AstraZeneca representative to determine if it is appropriate for the patient to proceed into Part B. All scheduled safety assessments on Day 15 related to entry into Part B must be performed before the patient can be dosed in Part B.

Any changes from dosing schedule should be recorded in the eCRF.

Treatment A (fed): Following an overnight fast of at least 10 hours, patients should consume the recommended meal prior to administration of the AZD9291 tablet. Patients should eat the meal within 30 minutes.

The AZD9291 tablet should be administered 30 minutes after the start of the meal consumption. If the meal is not completed within 30 minutes, AZD9291 may still be administered and they will still be considered evaluable so long as 75% of the meal has been consumed within 45 minutes of the start of the meal. No food should be allowed for at least 4 hours post-dose. Water will be restricted from 1 hour pre-dose until 1 hour post-dose, except for the water administered with AZD9291, and any drink provided as part of the meal. The start and stop date/time of meal consumption along with the percent consumed (in quartiles, ie, 0%, 25%, 50%, 75%, 100%) must be recorded in the eCRF.

If a patient is unable to eat at least 75% of the meal within 45 minutes, they will be non-evaluable for that treatment period and will not be dosed or sampled for PK in that treatment period. However, a second attempt may be made on the next day (all relevant assessments eg, PK sampling and vitals assessments should be deferred accordingly). In such circumstances, an AstraZeneca representative must be consulted (on a case-by-case basis) to decide how to proceed in terms of the patient's continuation in Part A, and eligibility to continue in Part B.

Treatment B (fasted): Patients should be administered the AZD9291 tablet following an overnight fast of at least 10 hours. No food should be allowed for at least 4 hours post-dose. Patients may have glucose (sugar tablets) and/or juice (except for grapefruit juices or juices containing grapefruit or Seville oranges) if they have signs or symptoms of hypoglycaemia after they have received AZD9291 in the fasted state. The time and exact nature of any such glucose (sugar tablets/juice) consumed must be recorded in the eCRF. Water will be restricted from 1 hour pre-dose until 1 hour post-dose, except for the water administered with AZD9291.

In accordance with FDA guidance (Food and Drug Administration 2002), the high-fat meal should have a total calorie content of approximately 800 to 1000 kcal, with approximately 50% of the calorie content made up from fat. The meal should therefore derive approximately 150, 250 and 500 to 600 kcal from protein, carbohydrate and fat respectively. For an example of a high-fat meal, see Appendix I. The composition of the meal supplied to each patient should be documented in the raw data together with the amount eaten and time period over which it was eaten. The same meal should be provided to all patients dosed at each investigational site.

7.2.2 Part B

Patients who are eligible to continue in Part B will receive 80 mg AZD9291 once daily (comprising 1 x 80 mg tablets) for the duration of their participation. At each dispensing visit during Part B, sufficient AZD9291 for 28 days treatment (plus overage) will be dispensed. Restrictions related to fasted administration of AZD9291 may be modified upon PK data emerging from the clinical programme.

During Part B, the initial dose of AZD9291 can be reduced under circumstances described in Section 6.7. Any change from dosing schedule, dose interruptions, dose reductions should be recorded in the eCRF.

Doses should be taken approximately 24 hours apart at the same time point each day. AZD9291 should be taken under fasted conditions. Fasted for Part B is defined as fasted for at ≥1 hour before dosing through at ≥2 hours post-dose. Water is permitted during this fasting period. Restrictions related to fasted administration of AZD9291 may be modified upon PK data emerging from the clinical programme.

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.

AZD9291 tablets will be packed in high-density polyethylene 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 (GMP) and local regulatory guidelines. The labels will fulfil GMP 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.

For Part A, ie, when patients are at the study site, compliance will be assured by supervised administration of IP by the investigator or his/her delegate. Date and time of the dose will be recorded in the eCRF.

For Part B, 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 eCRF. 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 tables below, should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon CYP3A4, CYP2C8 or BRCP 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. Patients taking concomitant medications whose disposition is dependent upon CYP3A4, CYP1A2, CYP2C or PGP and which have a narrow therapeutic index should be closely monitored for reduction in therapeutic activity as a result of the reduced exposure of the concomitant medication whilst receiving AZD9291.

Prohibited Medication/Class of drug:	**Usage:**
Other anticancer agents, investigational agents and radiotherapy	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: all patients must avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known potent 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 for a period of 3 months after the last dose of AZD9291.
Statins:	Up to a 3-fold increase in exposure may occur in statin exposure when coadministered with AZD9291. It is recommended that the starting and maintenance dose of statins should be as low as possible and should be guided by the statin label. Monitoring of low-density lipoprotein cholesterol levels is advised. If the patient experiences any potentially relevant AE suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, the statin should be stopped, creatine kinase levels should be checked, 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 (INR and 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.	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.
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 subject'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 Post Study Access to Study Treatment

Patients receiving AZD9291 at the time of study completion (ie, after final data cut-off date in Part B) may continue to receive AZD9291, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment (continued-access phase after Part B).

No further data will be collected during the continued-access phase after Part B other than SAEs and drug dispensing/accountability ie, until AZD9291 is discontinued. These patients will then be followed up for a period of 28 days after the last AZD9291 dose is administered for any new treatment-related SAEs.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

Statistical analyses will be performed by using SAS® v9.2 or higher and, where appropriate, additional validated software.

The primary data-base lock will be based on data obtained in Part A of the study. Data obtained from Part B will form part of a secondary lock of the data and will be reported in a CSR addendum.

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

The primary objective of this study is to investigate the effect of food on the PK of AZD9291. In study D5160C00005, a within-subject coefficient of variation (%CV) 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 %CV for AZD9291 in both AUC and C_{max} is 34%, an approximate 50% increase from that observed in healthy normal subjects. A 6% change in the exposure for AZD9291 when given with food is also assumed. With 30 evaluable patients, the experiment-wide power for the 2 sided 90% confidence interval of the geometric mean ratios (fed/fasted) being completely contained within 70 to 143% 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 on the strategy for dealing with data affected by 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 protocol deviations will be listed and summarised in the CSR.

8.4 Outcome measures for analyses

Outcome measures for analyses are presented in Table 9.

Table 9 Outcome measures

Analysis	Measure[a]
Primary	C_{max} and AUC_{0-72} for AZD9291
Secondary	For AZD9291, t_{max}, AUC_{0-120}, AUC_{0-t}, AUC, $t_{½}$, λ_z, CL/F, and V_z/F. For AZ5104 and AZ7550, C_{max}, AUC, AUC_{0-72}, AUC_{0-120}, AUC_{0-t}, t_{max}, $t_{½}$ and λ_z
Safety	Assessment of AEs, graded by CTCAE (version 4), physical examination, vital signs (blood pressure, pulse rate and body temperature), standard 12-lead ECG, Echo/MUGA (LVEF) and evaluation of laboratory parameters (clinical chemistry, haematology, and urinalysis).

a For definition of abbreviations see: Abbreviation or special term

The PK analyses of the plasma concentration data for AZD9291 and its metabolites will be performed at .

The actual sampling times will be used in the final PK parameter calculations.

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® version 6.3, or higher, (Pharsight Corp., Mountain View, California, United States) and/or SAS® version 9.2, or higher (SAS Institute, Inc., Cary, North Carolina, United States). All descriptive and inferential statistical computations will be performed using SAS® version 9.2, or higher.

Where possible the following PK parameters will be determined for AZD9291 and its metabolites, AZ5104 and AZ7550, as appropriate following dosing on Day 1 in Period 1 and Day 10 in Period 2:

- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (t_{max})
- Terminal rate constant (λ_z)
- Terminal half life ($t_{½}$)
- Area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration (AUC_{0-t})
- Area under the plasma concentration-time curve from zero to 72 hours (AUC_{0-72})
- Area under the plasma concentration-time curve from zero to 120 hours (AUC_{0-120})
- Area under the plasma concentration-time curve from zero to infinity (AUC)

- Apparent plasma clearance (CL/F) for AZD9291 only
- Apparent volume of distribution (V_z/F) for AZD9291 only

Additional PK parameters may be determined if deemed appropriate. If carry-over between periods exceeds 5% of C_{max} for AZD9291 and/or 10% of C_{max} for AZ5104 and AZ7550 at pre-dose in Period 2 in the majority of patients, exploratory PK parameter calculations and analyses may be performed using concentrations adjusted by subtracting the contribution from Period 1.

8.5 Methods for statistical analyses

8.5.1 Demographic and safety analyses

The following text applies to demographic and safety analyses only; PK is discussed separately (Section 8.5.2).

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, mean, standard deviation (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 Evaluable for Safety analysis set will be summarised. Demographic and baseline characteristics will be summarised and listed for the Evaluable for Safety analysis set.

Treatment duration will be summarised for Part B only. Treatment duration is based on the dates of first and last dose.

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 part is missing from the date, but is required in the calculation of time to randomisation, day part 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 analyses will be presented using the safety analysis set and will be done by means of descriptive statistics. Safety profiles will be assessed in terms of AEs, vital signs (including BP, pulse rate and body temperature), 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. However, when

reporting Part B, Part A and Part B data will be presented for any AEs that started in Part A and are ongoing into Part B. Laboratory data, vital signs, physical examination and ECGs will be summarised by treatment (fed/fasted) in Part A, and by study day (where appropriate) for Part 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 IP.

The number of patients experiencing AEs following administration of AZD9291 tablets 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 tablets 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).

A treatment emergent AE will be defined as an AE with the start date and time on or after the first dose date of the respective treatment period (Part A) or first dose date and time (Part B) for that part up to (and including) 30 days after the last dose date. Similarly, the number of patients experiencing SAEs, other significant AEs (OAE), 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.

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 (clinical chemistry, haematology, and urinalysis) will be summarised and listed. Shift tables will be provided for selected 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 if receiving the medication more than once.

The remaining safety variables will be presented using summary statistics for quantitative data and frequency counts for qualitative parameters.

All data will be summarised and listed appropriately.

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 may be produced to aid interpretation.

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

8.5.2 Pharmacokinetic analysis (Part A only)

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 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, SD, %CV, median, minimum, and maximum values. Additionally, geometric means and geometric coefficient of variation (%GCV) will be reported for PK variables (concentrations and all PK parameters, except for t_{max}).

The PK data will be presented by treatment (fed/fasted) (Part A).

For AZD9291 and its metabolites, natural log-transformed AUC_{0-72} and C_{max}, will be compared between treatments using a mixed effects analysis of variance model with sequence, period, and treatment as a fixed effects, and patient nested within sequence as a random effect. Estimates of the mean difference between treatments (fed - fasted) 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 (fed/fasted) and the associated 90% CIs. Additionally, back transformed geometric means together with 95% CIs for AUC_{0-72} and C_{max} will be estimated and presented for each food condition. Additional AUCs will be analysed if appropriate. No effect on the PK of AZD9291 after given with food will be concluded if the 2-sided 90% CIs for the ratios of AZD9291 AUC_{0-72} and C_{max} are both within the range of 70% to 143%. Similar analyses may be performed for AUC (AZD9291) and AUC_{0-120} (all analytes), as appropriate.

For AZD9291 and its metabolites, analyses of t_{max} will be performed using the Wilcoxon Signed Rank Test. The Hodges-Lehmann median estimator of the difference in treatments (fed–fasted) and 90% CIs will be presented.

In the event of relevant carry-over exposure across periods (see Section 8.4), a secondary statistical analysis may be performed including all patients, irrespective of the degree of carry-over. If appropriate, an exploratory analysis on carry-over adjusted concentrations and PK parameters may also be performed.

8.5.3 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.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

This study will be managed by on behalf of AstraZeneca, and will act as the AstraZeneca representative.

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 representative 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/hospital 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 representative will be available between visits if the Investigator(s) or other staff at the study site needs information and advice about the study conduct.

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The PI at each/the study site should comply with all the terms, conditions, and obligations of the 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'. End of treatment will not occur until the last visit of the last patient occurs of the patient who was deriving clinical benefit or when AZD9291 is discontinued.

The study is expected to start in Q3 2014, with Part A to be completed in Q1, 2015 and Part B to be completed in Q1, 2016.

The study may be terminated at individual study sites 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 of MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by the Medical Coding Team at

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), an interim database lock will be performed. All Part A data for patients who have completed by the time of the interim 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.

Serious Adverse Event Reconciliation

Serious Adverse Event 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 in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples.

The results of 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 (synonymous to Institutional Review Board [IRB] and Independent Ethics Committee [IEC], hereafter referred to as EC) 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 EC, and to the study site staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca or its representative before enrolment of any patient into the study. The EC should approve all advertising used to recruit patients for the study. AstraZeneca or its representative 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 EC 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 or its representative will handle the distribution of any of these documents to the National Regulatory Authorities. AstraZeneca or delegate will provide Regulatory Authorities, ECs and PIs with safety updates/reports according to local requirements.

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

10.4 Informed consent

The PI(s) or sub-investigator(s) at each study site 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 informed consent 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 ICF that is approved by an EC.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the 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 EC 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(s). For distribution to EC see Section 10.3.

If a protocol amendment requires a change to a study site's ICF, AstraZeneca and the study site's EC 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 EC.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the study site, 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 study site.

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