AstraZeneca

Revised Clinical Study Protocol

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A Phase I/II, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumour Activity of Ascending Doses of AZD9291 in Patients with Advanced Non Small Cell Lung Cancer who have Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent (AURA)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative

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

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
1			
2			
3			

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change
1			
2			

Principal Investigator(s)

For contact details of AstraZeneca personnel see Section 8.1.

INTRODUCTION & STUDY FLOW CHART

A Phase I/II, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumour Activity of Ascending Doses of AZD9291 in Patients with Advanced Non Small Cell Lung Cancer who have Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent (AURA)

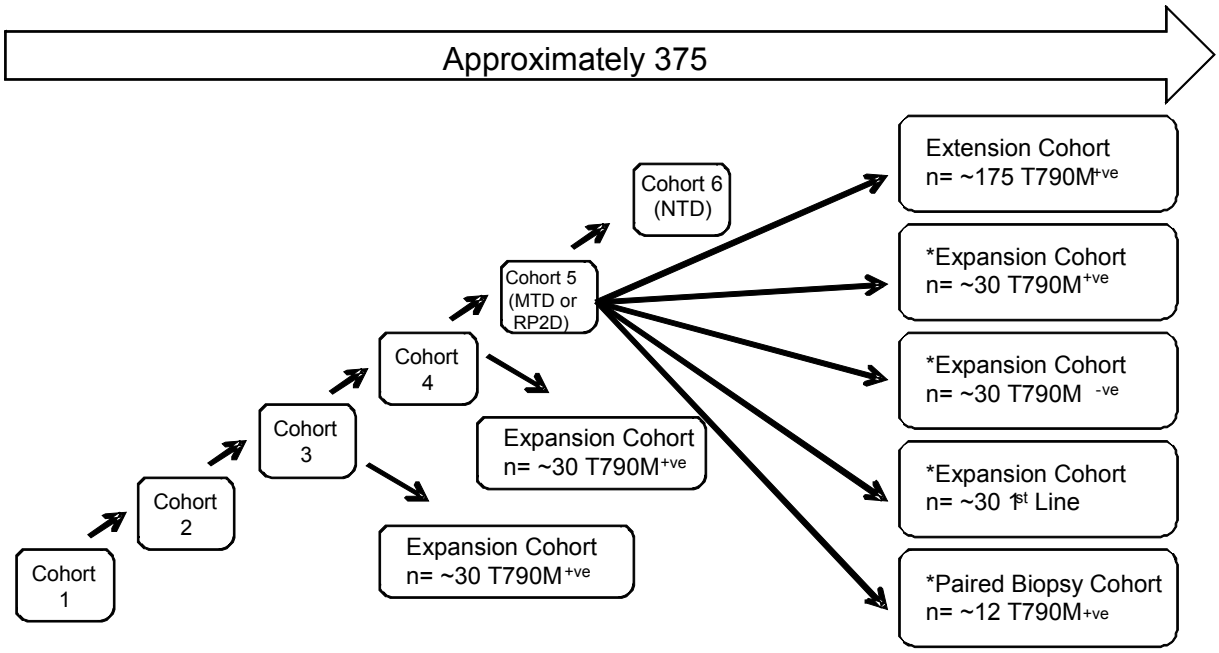
AZD9291 is a potent irreversible inhibitor of both the single Epidermal Growth Factor Receptor mutation positive (Tyrosine Kinase Inhibitor [TKI]-sensitivity conferring mutations, EGFRm+) and T790M positive (TKI-resistance conferring mutation, T790M+) receptor forms of the EGFR. AZD9291 acts on cancer by blocking abnormal EGFR-mediated signalling, leading to profound tumour growth inhibition in EGFR mutation bearing xenografts of non-small cell lung cancer (NSCLC) tumours.

The key findings from the non-clinical were: reductions in food consumption, atrophic changes affecting the epithelia of a number of tissues (including skin, eye, tongue, intestine), marginal increases in QTcR and blood pressure, decreases in heart rate (although the cardiovascular findings were not consistent across species or studies). Histopathological findings include: corneal epithelial ulceration/erosion, tubular degeneration/atrophy in the testes, corpora luteal degeneration in the ovaries, and changes in the skin and/or muzzle (epidermal atrophy, inflammatory cell infiltration, follicular dysplasia, ulceration/erosion of the epidermis).

In this first time in patient study, AZD9291 will initially be administered to patients with advanced NSCLC, whose cancer has progressed following prior therapy with an EGFR TKI agent (and potentially additional regimens of chemotherapy), at a starting dose of $1/10^{th}$ of the Seriously Toxic Dose in 10% of animals in rodent toxicity studies (STD_{10}) in the rat 1-month study, and will be escalated to reach either a maximum tolerated or maximum feasible dose in patients as defined by dose-limiting toxicity. A once daily dose of AZD9291 will be used, as deemed optimal and effective in non-clinical studies, primarily to determine the safety and tolerability of AZD9291 in patients with this clinical indication. Pharmacokinetics of AZD9291 and potential biological activity will also be investigated.

Additional patients will be enrolled to dose expansion cohorts to explore further the efficacy, safety, tolerability, pharmacokinetics and biological activity at selected dose(s) in patients who are selected according to the T790M status of their NSCLC tumour and a further expansion cohort in patients who are EGFR TKI naive.

Study flow chart



SAD/MAD: Patients who have failed prior EGFR TKI

Expansions: T790M status defined prospectively ≥2nd line patients who have failed prior EGFR TKI therapy; 1st line EGFRm+ patients

* Expansions may be at more than one dose depending upon emerging data

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ALT	Alanine aminotransferase
AnLK	Anaplastic lymphoma kinase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
$AUC_{(0-t)}$	Area under plasma concentration-time curve from zero to time t [amount·time/volume]
AUC_{ss}	Area under plasma concentration-time curve during any dosing interval at steady state [amount· time/volume]
cfDNA	Circulating free deoxyribonucleic acid
CL/F	Total body clearance of drug from plasma after an oral dose
CL_{ss}/F	Total body clearance of drug from plasma after an oral dose at steady state
Cmax	Maximum plasma concentration
CPP	Clinical Pharmacology and Pharmacometrics
CR	Complete response
CRF	Case Report Form (electronic/paper)
CSP	Clinical Study Protocol
$C_{ss,max}$	Maximum (peak) steady state drug concentration in plasma during dosing interval [amount/volume]
$C_{ss,min}$	Minimum (trough) steady state drug concentration in plasma during dosing interval [amount/volume]
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CT	Computerised tomography
CTC	Circulating tumour cell
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid

Abbreviation or special term	Explanation
ECG	Electrocardiogram
Echo	Echocardiogram
ECOG	Eastern Co-operative Oncology group
EGFR	Epidermal growth factor receptor
EGFRm+	Epidermal growth factor receptor sensitising mutation positive
EMEA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
FTIP	First Time in Patients
GCP	Good Clinical Practice
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HNSTD	Highest non-seriously toxic dose
HRQoL	Health related quality of life
IATA	International Air Transport Association
IB	Investigators Brochure
ICH	International Conference on Harmonisation
IVRS/IWRS	Interactive Voice Resonse System/Interactive Web Response System
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LIMS	Laboratory Information Management System
LVEF	Left ventricular ejection fraction
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MRT	Mean residence time
MTD	Maximum tolerated dose
MUGA	Multi gated acquisition scan
NE	Not evaluable
NOAEL	No Observed Adverse Effect Level
NSCLC	Non Small Cell Lung Cancer
NTL	Non-target lesion
OAE	Other significant adverse event
PD	Progression of disease

Abbreviation or special term	Explanation
PFS	Progression free survival
PK	Pharmacokinetics
PR	Partial response
PRO	Patient Reported Outcomes
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QTc Fredericia
R_{AC}	Accumulation ratio
RBC	Red blood count
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic Acid
RP2D	Recommended Phase II Dose
SAD	Single ascending dose
SAE	Serious adverse event (see definition in Section 6.4.2)
SD	Stable disease
SRC	Safety Review Committee
STD_{10}	10% of the Severely Toxic Dose in rodents
λ_z	Smallest (slowest) disposition (=hybrid) rate constant [$time^{-1}$]
$t_{½}$	Half-life
$t_{½\lambda z}$	Half-life associated with terminal slope (λ_z) of a semi-logarithmic concentration-time curve [time]
TL	Target lesion
TKI	Tyrosine kinase inhibitor
tmax	Time to maximum plasma concentration
$t_{ss\ max}$	Time to maximum plasma concentration at steady state
ULN	Upper limit of normal
UVA	Ultraviolet A
UVB	Ultraviolet B
V_{ss}/F	Volume of distribution (apparent) at steady state after an oral dose
WBDC	Web Based Data Capture
WHO	World Health Organisation

Abbreviation or special term	Explanation
~	Approximately

1. STUDY OBJECTIVES

1.1 Primary objective

To investigate the safety, tolerability and efficacy (Objective Response Rate)of AZD9291 when given orally to patients with locally advanced or metastatic Non Small Cell Lung Cancer (NSCLC) who have progressed following prior therapy with an Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor (TKI) agent.

1.2 Secondary objective(s)

To define the maximum tolerated dose (MTD), if possible, a dose/exposure predicted to result in biological activity (including but not limited to RECIST, tumour and blood borne biomarkers, hereafter referred to as biological activity) or maximum feasible dose.

To investigate the safety and tolerability of AZD9291 when given orally as first line therapy to patients who are treatment-naive for locally advanced or metastatic EGFRm^{+ve} NSCLC.

To characterise the pharmacokinetics (PK) of AZD9291 and its metabolites (AZ5104 and AZ7550) after a single oral dose and at steady state after multiple oral doses.

Escalation and expansion cohorts: To obtain a preliminary assessment of the anti-tumour activity of AZD9291 by evaluation of duration of response (DoR) and progression free survival using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (see Appendix F).

Extension cohort: To obtain additional assessments of the anti tumour activity of AZD9291 by evaluation of duration of response, disease control rate, tumour shrinkage, progression free survival using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 as assessed by an independent central review of radiological information and overall survival.

To assess the relationship between PK and selected efficacy, pharmacodynamic and/or safety endpoints.

To provide evidence for biological modulation of pharmacodynamic markers in EGFRm^{+}ve T790M^{+ve} tumours at a selected clinical dose.

1.3 Exploratory objective(s)

To collect and store plasma for potential exploratory research of blood borne biomarkers into factors that may influence development of NSCLC and/or response to AZD9291 (where response is defined broadly to include efficacy, tolerability or safety).

To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence PK or response (ie, absorption, distribution, metabolism, excretion, safety, tolerability and efficacy) to AZD9291 treatment and/or susceptibility to cancers.

To collect and store diagnostic tumour sample and any fresh tumour biopsies for potential future exploratory research into factors that may influence development of NSCLC and/or responses to AZD9291 (where response is defined broadly to include efficacy, tolerability or safety).

To collect patient reported outcomes (PRO) data to explore disease-related symptoms and health related quality of life (HRQoL).

To explore the relationship between PK and selected endpoints (which may include PRO and blood borne biomarkers), where deemed appropriate.

To explore patients' self-perceived side-effects, their importance and how they are valued in relation to treatment effect using patient tolerability interviews.

To characterise the pharmacokinetics (PK) of AZD9291 and its metabolites (AZ5104 and AZ7550) in cerebrospinal fluid (CSF).

To collect and store residual CSF for potential exploratory research of factors that may influence development of NSCLC and/or response to AZD9291 (where response is defined broadly to include efficacy, tolerability or safety).

2. BACKGROUND

2.1 Non-small-cell lung cancer

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) (GLOBOCAN 2008) 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 & Le Chevalier 2005). Patients presenting with unselected advanced NSCLC have a median overall survival of 10 to 12 months (Bonomi 2010).

Treatment of advanced NSCLC can be guided by the presence of certain molecular drivers such as *EGFR*, anaplastic lymphoma kinase (*AnLK*) and *KRAS* mutations. EGFR tyrosine kinase inhibitors (TKIs) are now the established first line therapy in patients with NSCLC known to have activating mutations in *EGFR* (EGFRm+) (NCCN 2012). Patients with EGFRm+ NSCLC who receive EGFR TKIs have a median overall survival of more than 2 years (Heuckmann et al 2012). The incidence of EGFRm+ NSCLC is approximately 10-15% and 30-40% 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).

2.2 Investigational agent

AZD9291 is a potent irreversible inhibitor of both the single EGFRm+ (TKI-sensitivity confering mutation) and dual EGFRm+/T790M+ (TKI-resistance confering mutation) receptor forms of EGFR.

Activation of EGFR tyrosine kinase triggers a cascade of intracellular downstream signalling events affecting cell proliferation, survival, angiogenesis and potentially metastases. Selective inhibition of EGFR tyrosine kinase has demonstrated clinical benefit in approximately 70% of patients with advanced NSCLC harbouring the sensitivity mutations (the most common of which are L858R and deletions in exon 19 (Ex19del)). The tumours initially respond to EGFR TKIs, but subsequently develop resistance to therapy, with a median time to progression of 9 months. In at least 50% of these initially EGFR TKI-responsive patients, disease progression is associated with the emergence of a secondary *EGFR* mutation, T790M in exon 20 of *EGFR* which confers resistance to therapy (Pao et al 2005). The T790M gatekeeper resistance mutation is located in the hinge region of the kinase domain of the ATP-binding pocket of the EGFR protein, where the bulky methionine side chain prevents binding of the EGFR TKIs (Heuckmann et al 2012).

2.3 Non-clinical information and correlative studies

Studies *in vitro* showed AZD9291 to be a potent and selective irreversible inhibitor of isolated wild-type and mutant EGFRs (IC50s <10 nM). *In vitro* cellular EGFR phosphorylation assays demonstrated potent inhibition of single-activated (EGFRm+) and double-T790M mutant (EGFRm+/T790M) assays, and much weaker inhibition towards wild-type EGFR was observed. *In vitro* wash-out and time dependent cellular kinetic studies demonstrated an irreversible mechanism of action of AZD9291. Oral treatment of mice bearing EGFRm+ and EGFRm+/T790M xenograft tumours lead to profound tumour growth regression. In contrast, higher doses of AZD9291 were required to achieve significant tumour growth inhibition in wild-type EGFR xenograft models. Xenograft growth regression with AZD9291was accompanied by dose and time-dependent pharmacodynamic inhibition of phospho-EGFR and the key downstream biomarkers phospho-Akt and phospho-Erk across mutant and wild-type EGFR disease models *in vivo*. Furthermore, chronic longer term oral treatment with AZD9291 lead to complete and sustained macroscopic disappearance of an EGFRm+ xenograft tumour suggesting the agent may provide an effective 1st Line treatment (AZ data on file). In support of this hypothesis, the EGFRm+ cell line showed greater time to resistance in response to AZD9291 treatment *in vitro* compared to earlier generation EGFR inhibitors. The active metabolites of AZD9291, AZ5104 and AZ7550, showed similar pharmacological selectivity and activity profiles to parent, although AZ5104 showed a smaller margin of selectivity against wild-type EGFR *in vitro*.

Pharmacokinetic exposure generally increased in proportion to dose. Accumulation was less than 2-fold on multiple daily dosing in rat and dog. *In vitro* data have indicated that CYP3A4 and, to a lesser extent, CYP2C8 are the principal P450 isozymes responsible for human

metabolism. Incubations with hepatocytes from mouse, rat, dog and humans have indicated that conjugation with glutathione, cysteineglycine, glucuronide and sulphate conjugates may be alternative/additional elimination pathways. Based on *in vitro* data, AZD9291 is considered unlikely to cause clinically significnt hepatic drug interactions through inhibition or induction of cytochrome P450 enzyme activity. However, there is a potential for AZD9291 to have an intestinal drug interaction through inhibition of CYP3A4. AZD9291 does not inhibit P-gp but is a weak inhibitor of $OATP_{1B1}$. The potential to inhibit other transporter proteins has not yet been studied. In a rat quantitative whole body autoradiography (QWBA) study, there was persistance of radioactivity in tissues up to at least 100 hours and was still evident in 42% of tissues measured at 60 days after dosing pigmented animals.

The key findings in the toxicology studies were as follows:

- AZD9291 was not mutagenic in the non-GLP Ames test or in the non GLP mouse lymphoma assay (MLA) in the absence of S9. A small increase in mutant frequency was identified at a highly toxic concentration in the presence of S9 in the MLA.

- AZD9291 absorbs light in the ultraviolet visible range, but was not phototoxic when tested in an *in vitro* 3T3 assay

- During the 1 month rat study, repeated administration of AZD9291 was associated with dose-related atrophic, inflammatory and/or degenerative changes affecting the skin, eye, tongue and female reproductive system. There were also histopathological findings in the male reproductive system and mesenteric lymph nodes. Histopathological changes were present in the eye at all doses, but the low dose (4 mg/kg/day) was the no-observed effect level (NOEL) for all of the other findings. Changes in haematology parameters were considered likely to represent a reactive response to the epithelial atrophy and associated inflammatory/degenerative changes seen in tissues such as the skin. All findings showed evidence of reversibility.

- During the 1 month dog study, repeated administration of AZD9291 was associated with dose-related atrophic changes affecting the skin, eye, tongue and intestine. There were also histopathological findings in the male reproductive system. The low dose (2 mg/kg/day) was the NOEL for all histopathological changes with the exception of the findings in the male reproductive system. All findings showed evidence of reversibility.

Secondary and Safety Pharmacology studies have been carried out to investigate the effects of AZD9291 on related and unrelated receptors and enzymes, the cardiovascular, central and peripheral nervous system, respiratory and gastrointestinal systems. The key findings were as follows:

- There was some evidence for an increase in QT interval and decrease in heart rate following administration of AZD9291 to guinea pigs and dogs. However, the changes seen in the dog telemetry study were marginal, transient, not dose-related and were considered not to be adverse (NOAEL at 60 mg/kg). Increases in blood pressure were

observed in the rat and guinea pig. Increases in blood pressure were also seen in the 14 day dog study, but were confined to non-tolerated (≥ 40 mg/kg) or less well tolerated doses (20 mg/kg) and similar changes were not seen in the dog telemetry or 1 month dog studies.

- Reductions in gastric emptying and small intestinal transit were observed in rats following administration of single doses ≥10 mg/kg. A NOEL was not determined.

- There were no notable effects on the central nervous, visual or respiratory systems in rats following administration of single doses up to 100 mg/kg.

Further details are provided in the Investigators' Brochure.

3. STUDY DESIGN AND RATIONALE

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a phase I/II, open-label, multicentre study of AZD9291 administered orally in patients with advanced NSCLC who have progressed following prior therapy with an EGFR TKI agent (+/- additional chemotherapy regimens). The study design allows an escalation of dose with intensive safety monitoring to ensure the safety of the patients.

Dose escalation

Approximately 36 evaluable patients with advanced NSCLC will be enrolled in the dose escalation part of this study. The total number of patients will depend upon the number of dose escalations necessary. At least 3 and up to 6 evaluable patients will be required for each dose cohort.

Patients will receive a single dose on Day 1 then after 7±2 days washout, multiple dosing, once daily will be initiated. In the first cohort administration of the first dose will be separated from the start dosing of the subsequent patients by at least 7 days for the first patient (see Section 5.1.1). Dosing frequency may be adjusted during the study on the basis of emerging safety and pharmacokinetic data.

Dose expansion

Approximately 162 additional evaluable patients may be included in order to explore further the tolerability, pharmacokinetics, efficacy and biological activity in specific patient sub groups. The total number of patients will depend upon the number of dose expansions necessary. This will include a paired biopsy cohort to further understand the proof of mechanism.

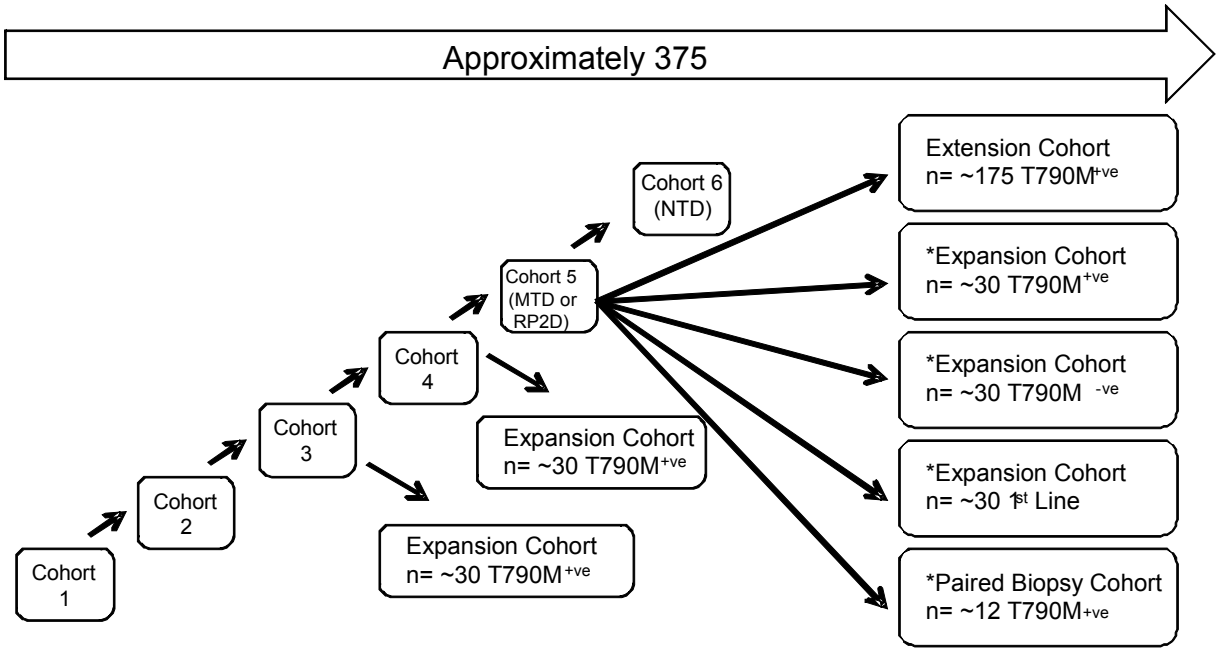
Patients enrolled must have confirmation of tumour T790M mutation status (confirmed positive or negative) from a biopsy sample. One or more dose levels may be investigated dependant on

emerging data. The number of patients to be enrolled in each expansion cohort is planned to be approximately 30, but will be approximately 12 for the paired biopsy cohort.

Extension Cohort

Once the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D) is reached an additional cohort of 175 patients, who have T790M+ status identified by central testing, will be enrolled to further assess the efficacy and tolerability of AZD9291.

Figure 1 Study flow chart



SAD/MAD: Patients who have failed prior EGFR TKI

Expansions: T790M status defined prospectively ≥2nd line patients who have failed prior EGFR TKI therapy; 1st line EGFRm + patients

* Expansions may be at more than one dose depending upon emerging data

3.2 Rationale for conducting this study and for study design

The presence of activating mutations in exons 18-24 of *EGFR* (including L858R and Ex19del, collectively described as EGFRm) in patients with NSCLC tumours confers sensitivity to the EGFR TKI class of drugs in a high percentage of patients. However, the subsequent on treatment emergence of the T790M gatekeeper mutation in patients treated with an EGFR TKI agent has been described as a major route of development of resistance to this class of therapy. AZD9291 is a potent and specific irreversible dual inhibitor of both the sensitising EGFRm mutations and the T790M resistance mutation. Non clinical data suggests that dual inhibition can result in anti proliferative and pro apoptotic activity in tumour models harbouring one or both of the mutations. Therefore AZD9291 has the potential to provide clinical benefit to

patients with NSCLC harbouring both the single sensitivity mutations and the resistance mutation following prior therapy with an EGFR TKI.

This is a first time in patient study primarily designed to evaluate the safety and tolerability of AZD9291, a potent dual inhibitor of EGFRm and T790M at increasing doses in patients with locally advanced or metastatic NSCLC who have progressed following prior therapy with an EGFR TKI agent. Retreatment of these patients with an EGFR TKI agent is within scope of the current treatment guidelines (NCCN 2012). AZD9291 is anticipated to have a lower level of specificity towards wild-type EGFR, and as a result it is anticipated that there should be a lower level of off target toxicity such as rash and diarrhoea than currently seen with first generation EGFR TKI agents. On demonstration of preliminary clinical efficacy and an acceptable safety and tolerability profile in patients whose NSCLC has progressed following therapy with an EGFR TKI agent, additional expansion cohort(s) in first line EGFR TKI treatment-naive patients with EGFRm+ advanced NSCLC tumour will be initiated. The study will also characterise the pharmacokinetics of AZD9291 and explore potential biological activity. The results from this study will form the basis for decisions for future studies.

The starting dose, dose escalation, and cohort size are based upon accepted methodology for phase I oncology studies as defined by European, Japanese and United States regulation (Section 5.2) Careful consideration has been given to the EMEA guideline regarding the mitigation of risk for first-in-human clinical trials, and with regard to the mode of action, the nature of the target and relevance to animal models AZD9291 is considered low risk (EMEA Guideline 2007). The SAD/MAD part of the study will determine the MTD or maximum feasible dose of AZD9291 based upon assessment of the safety, tolerability and pharmacokinetic data collected during the first 21 days of daily dosing. The 21-day assessment period was selected as the major toxicities leading to cessation of dose escalation in such studies (haematological, gastrointestinal, liver enzymes) are anticipated to present within this duration. The cohort size of at least 3 and up to 6 patients ('rolling six design') has been employed to improve the rate of accrual of patients to cohorts nearer the presumed therapeutic dose by reducing the need for late replacement of patients who become non-evaluable during the 21-day assessment period, whilst not compromising collection of safety data (Skolnik et al 2008).

Preliminary efficacy data from this study (see Investigator Brochure) have indicated that objective clinical responses have occurred from the first cohort of patients tested at the starting dose of 20 mg AZD9291 in this study. Patients in the escalation cohorts are not prospectively tested for the tumour T790M status prior to entry, and similarly patients in the expansion cohorts may enter the study following local assessment of the tumour T790M status, which may be from an alternative technology platform with a different level of sensitivity to the companion diagnostic test currently under development in parallel with AZD9291. The extension cohort of 175 evaluable patients with T790M+ NSCLC identified prospectively by the central laboratory test will provide a significantly more robust evaluation of overall efficacy in the target patient population considered most likely to respond to AZD9291 (patients with advanced NSCLC who have progressed following an EGFR TKI agent who harbour the T790M mutation). The statistical justification for the sizing of this extension cohort is described in detail in Section 7.2 of this protocol.

The efficacy assessments of objective response (OR), duration of response (DoR), disease control rate (DCR), progression-free survival (PFS) as assessed by RECIST 1.1 and overall survival (OS) are widely accepted parameters for the assessment of efficacy for advanced NSCLC treated with EGFR TKIs (Sun et al 2010).

Preclinical data (Investigator Brochure Section 4.1.1.2) demonstrates that when the clinical efficacy in a dual mutation (L858R/T790M+) mouse xenograft model eventually develops resistance to low dose AZD9291 (1mg/kg/day) a dose escalation (to 25mg/kg/day) reverses the tumour regrowth and provides additional durable sustained tumour shrinkage. Therefore, an increase in dose of AZD9291 to a currently identified well tolerated dose (80 mg) in patients with initial objective responses but subsequent RECIST confirmed disease progression at a lower dose may have the potential to provide prolongation of the clinical benefit for these patients.

The collection of cerebrospinal fluid (CSF) will enable the investigation of the ability of AZD9291 to cross the blood brain barrier. Brain metastases occur in 20-30% of patients with advanced NSCLC, and are associated with poor prognosis (Porta 2011). The first generation EGFR TKI agents have demonstrated only limited efficacy in treating brain metastases (Bai 2013, Ranson 2013, Shimato 2006) however, preclinical data suggests that AZD9291 may be capable of crossing the blood brain barrier (Investigator Brochure) and potentially may offer better exposures in this anatomically protected location.

The collection of samples to allow investigation of the presence and/or identity of metabolites of AZD9291 and, if appropriate, characterise their pharmacokinetics will generate data to allow AstraZeneca to fulfil regulatory requirements related to the testing of the safety of metabolites.

As part of the clinical drug development program for AZD9291 AstraZeneca plans to include investigations into variations in pharmacodynamic and exploratory biomarker profiles and their relationship to drug effect. These biomarkers may be derived from DNA, ribonucleic acids (RNA), proteins and/or metabolites. There are many potential benefits of this exploratory research, including the possibility to identify patients most likely to benefit from treatment, explain outliers or non-responders or explain adverse reactions related to drug exposure. This research may result in an understanding of the impact of variation between individuals and how it can be utilised to bring better drugs to the clinic. The ability to acquire appropriate consent to collect biological samples is of utmost importance in order to establish an archive and allow future meta-analysis of data derived from a number of studies with AZD9291.

AstraZeneca may perform genetic research in the AZD9291 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD9291. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical studies and possibly, to genetically guided treatment strategies.

Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD9291 but also susceptibility to NSCLC for which AZD9291 may be

evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

3.2.1 Rationale for patient tolerabilty interviews

The aims of the patient tolerability interviews are to provide patient-based information regarding self-perceived side-effects of the treatment, the importance and impact on daily life of these side-effects and how they are evaluated in relation to the treatment effect. Information gained from these interviews will be used to aid in the design of future studies and programs to treat this condition.

4. PATIENT SELECTION AND RESTRICTIONS

Investigators should keep a record ie, patient screening log, of patients who entered pre-study screening.

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

4.1 Inclusion criteria

For inclusion in the study, patients must fulfil all of the following criteria.

1. Provision of signed and dated, written informed consent prior to any study specific procedures, sampling and analyses

   If a patient declines to participate in any voluntary exploratory research and/or genetic component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study

2. Aged at least 18 years. Patients from Japan aged at least 20 years

3. Histological or cytological confirmation diagnosis of NSCLC

4. Radiological documentation of disease progression while on a previous continuous treatment with an EGFR TKI e.g. gefitinib or erlotinib (with the exception of 1st line expansion cohort). In addition other lines of therapy may have been given. All patients must have documented radiological progression on the last treatment administered prior to enrolling in the study.

5. Patients (with the exception of 1st line expansion cohort) must fulfil **one** of the following:

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

or

– Must have experienced clinical benefit from EGFR TKI, according to the Jackman criteria[*] (Jackman et al 2010) followed by systemic objective progression (RECIST or WHO) while on continuous treatment with EGFR TKI

6. **For 1st Line expansion cohort ONLY**, confirmation that the tumour is EGFRm^{+ve} and have had no prior therapy for their advanced disease (for 1st line patients biopsy will be at time of diagnosis of advanced disease).

7. **For dose expansion and extension cohorts,** patients must also have confirmation of tumour T790M mutation status (confirmed positive or negative) from a biopsy sample taken after disease progression on the most recent treatment regimen (irrespective of whether this is EGFR TKI or chemotherapy).

   Prior to entry a result from the central analysis of the patient's T790M mutation status must be obtained.

8. World Health Organisation (WHO) performance status 0-1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks.

9. At least one lesion, not previously irradiated and not chosen for biopsy during the study screening period, that can be accurately measured at baseline as ≥ 10mm in the longest diameter (except lymph nodes which must have short axis ≥ 15mm) with computerised tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements.

10. Females should be using adequate contraceptive measures (see Section 4.3), should not be breast feeding 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

[*] Clinical benefit from treatment with an EGFR TKI as defined by either documented partial or complete response (RECIST or WHO) or significant and durable (≥ 6 months) clinical benefit (stable disease as defined by RECIST or WHO) after initiation of gefitinib or erlotinib. Patients with only symptomatic improvement while on EGFR TKI but no corresponding evidence of radiographic stability of disease should not be routinely considered as having sufficient clinical benefit.

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

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

11. Male patients should be willing to use barrier contraception ie, condoms

12. Patients from Japan should be willing to remain in hospital from the first dosing day until Day 1 Cycle 2

13. **For dose expansion paired biopsy cohort:**

- Presence of at least one non-target lesion suitable for multiple biopsies on treatment

14. **For inclusion in optional genetic research**, patient must

- Provide informed consent for genetic research

4.2 Exclusion criteria

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

1. Treatment with any of the following:

- Treatment with an EGFR TKI (eg, erlotinib or gefitinib) within 8 days or approximately 5x half-life, whichever is the longer, of the first dose of study treatment. (If sufficient wash-out time has not occurred due to schedule or PK properties, an alternative appropriate wash-out time based on known duration and time to reversibility of drug related adverse events could be agreed upon by AstraZeneca and the Investigator)

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

- AZD9291 in the present study (ie, dosing with AZD9291 previously initiated in this study)

- 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 at least 1 week prior to receiving the first dose of AZD9291) medications or herbal supplements known to be potent inhibitors of CYP2C8 and potent inhibitors or inducers of CYP3A4 (Appendix H)

2. Any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) grade 1 at the time of starting study treatment with the exception of alopecia and grade 2, prior platinum-therapy related neuropathy

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

4. 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 trial or which would jeopardise compliance with the protocol, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required

5. Any of the following cardiac criteria:

   - Mean resting corrected QT interval (QTc) > 470 msec obtained from 3 electrocardiograms (ECGs), using the screening clinic ECG machine derived QTc value

   - 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 >250msec

   - 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 in first degree relatives or any concomitant medication known to prolong the QT interval

6. Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease

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

   - Absolute neutrophil count < 1.5 x 10^9/L

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

8. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of AZD9291

9. History of hypersensitivity to active or inactive excipients of AZD9291 or drugs with a similar chemical structure or class to AZD9291

10. Women who are breast feeding

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

12. Judgment 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:

13. Previous allogenic bone marrow transplant

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

4.3 Restrictions

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

1. Females of child-bearing potential should use reliable methods of contraception from the time of screening until *3 months* after discontinuing study treatment. Acceptable methods of contraception include abstinence, tubal ligation, oral or transdermal contraceptives, copper-banded intra-uterine devices and vasectomised partner. All hormonal methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse.

2. Male patients should be asked to-use barrier contraceptives (ie, by use of condoms) during sex with all partners during the trial and for a washout period of 3 months. Patients should avoid procreation for *6 months* after completion of trial treatment. Patients should refrain from donating sperm from the start of dosing until *6 months* after discontinuing study treatment. If male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

3. All patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known potent inducer/inhibitory effects on CYP3A4 and/ or CYP2C8 whenever feasible, but patients may receive any medication that is clinically indicated for treatment of adverse events. 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. All concomitant medications should be captured on the eCRF. Guidance on medicines to avoid, medications that require close monitoring and on washout periods is to be provided.

4. Patients who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE grade ≤2) while receiving treatment with AZD9291 until at least one week after symptoms have resolved. If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade ≥3) ocular events they must discontinue wearing their contact lenses until at least one 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 promptly if they have any concerns.

For restrictions relating to concomitant medications see next Section 4.3.1.

4.3.1 Concomitant 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 Case Report Form (CRF). After permanent discontinuation of AZD9291 and 28 day follow up, only subsequent regimens of anti-cancer therapy will be recorded in CRF. If medically feasible, patients taking regular medication, with the exception of potent inhibitors or inducers of CYP3A4 and inhibitors of CYP2C8 (see Section 4.2 exclusion 1, and Appendix H), should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon intestinal CYP3A4 and/or transporter proteins and/or CYP2C8 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. Guidance on medications that require close monitoring is given in Appendix H.

Other anticancer agents, investigational agents and radiotherapy should not be given while the patient is on study treatment.

Pre-medication will be allowed after, but not before the first dose of study treatment. This includes management of diarrhoea, nausea and vomiting.

Blood transfusions are allowed at any time during the study.

Granulocyte colony stimulating factors should not be used prophylactically during Cycle 1. Use of prophylactic colony stimulating factors may be considered after Cycle 1 following discussion with the AstraZeneca Study Team Physician.

Patients may receive treatment with corticosteroids and/or bisphosphonates for the treatment of bone metastases. Patients may also receive radiotherapy for painful bony metastases.

Supportive care and other medications that are considered necessary for the patient's well-being, may be given at the discretion of the investigator.

5. STUDY TREATMENT AND CONDUCT

5.1 Treatment

AZD9291 is planned to be administered orally as a single daily dose (although alternative frequencies or intermittent schedules may be instigated in response to emerging safety, tolerability or PK data).

AstraZeneca will supply AZD9291 as capsules or tablets for oral dosing. Additional information about the investigational product may be found in the Investigators' Brochure.

Investigational product	Dosage form and strength	Manufacturer
AZD9291	20 mg and 40 mg Capsule	AstraZeneca
AZD9291	40mg and 80mg Tablet	AstraZeneca

Capsules and tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. One or more bottles of AZD9291 will be dispensed at each dispensing visit depending on the dose. Bottles will be dispensed to subjects 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.

For the Ph II extension cohort an IVRS/IWRS system will be deployed to manage the supply of AZD9291 tablets to sites and to manage the dispensing of AZD9291 to patients. All patients entering the extension cohort will be dispensed the tablet formulation. All other cohorts of patients will continue to be dispensed the capsule formulation.

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

The label will include the Name of the Sponsor, Study Code, For Clinical trial use only and /or any other market specific requirements

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

Patients (with the exception of patients with insulin dependent diabetes) must fast for ≥1 hours prior to taking a dose to ≥2 hour post dose. Water is permitted during this fasting period.

- Patients will be required to fast (water only) for at least 8 hours prior to the collection of a fasting glucose sample as per the study plan, (see Table 2, Table 3 and Table 4).

5.1.1 Starting dose, dose escalation scheme and stopping criteria

Dosing will begin at 20mg once daily.

A cycle of study treatment will be defined as 21 days of continuous dosing.

In the first cohort, a delay of at least 7 days will be mandatory between the administration of the first (single) dose to the first patient and administration of first (single) dose to subsequent patients. Providing there are no serious or unexplained safety issues, dosing of the remainder of the cohort will continue as suitable patients are identified. However, should ambiguous findings occur, the SRC may choose to stagger the start of dosing for the remainder of the cohort of patients. Providing there are no safety concerns after completion of the first cohort, subsequent cohorts of patients will be dosed as suitable patients are identified. If ambiguous findings occur after the first cohort the SRC may choose to stagger dosing in the second cohort and likewise for subsequent cohorts.

Patients will be enrolled to ensure a minimum of 3 and a maximum of 6 evaluable patients per cohort. Dose escalation and de-escalation will follow the scheme below, according to the following logic:

- If no dose-limiting toxicity (DLT) is observed (for definition see Section 5.1.3) in a cohort of 3-6 evaluable patients then dose escalation may occur. Dose increases will be permitted after review of data from a minimum of 3 evaluable patients has been performed.

- If one patient experiences a DLT in a group of 3 or more evaluable patients then the cohort will be expanded to include 6 evaluable patients. If only one DLT is observed in the complete cohort of 6 evaluable patients then dose escalation may occur.

- If 2 or more patients experience a DLT in a group of up to 6 patients, irrespective of the number of patients enrolled, the dose will be considered not tolerated and recruitment to the cohort and dose escalation will cease. A lower intermediary dose (de-escalation) may be considered in order to better define the MTD.

Prior to achieving MTD, dose escalation will stop if:

- Delivery of the next dose level would require dosing of >8 capsules or tablets per single administration, or

- There is evidence in the dose-exposure relationship of saturation of absorption.

See Table 1 below for the proposed dose escalation scheme. All dose levels beyond cohort 1 may change in light of emerging safety and pharmacokinetic data. The planned dose escalations will not exceed doubling of the dose in principle. However up to a quadrupling of dosing may be permitted in the first two escalations only, if the drug concentrations from the first or second dose level are not measureable or are deemed to be far from predicted drug exposure (eg, greater than 2-fold difference) and there have been no significant safety or tolerability issues.

Table 1 Proposed dose escalation scheme

Cohort	Dose mg (to be administered once daily)
1	20
2	40
3	80
4	160
5	200
X	XXX

There will be a minimum of 2 days between conduct of the last patient assessment required for SRC review from one cohort and the start of dosing in the subsequent cohort.

There will be no intra-patient dose escalations with the exception of patients who were started and have remained on treatment at a dose lower than 80mg for at least 6 months, have shown clinical benefit (as judged by the investigator) and have then developed RECIST confirmed disease progression. The escalated dose must be agreed in advance between the Investigator and AZ Study Physician, and will not exceed 80mg; which has been declared safe and tolerable by the SRC.

The dose for subsequent cohorts or a decision to stop recruitment to the escalation phase of the study will be agreed by the SRC after review of the data from each cohort (see Section 5.1.5).

5.1.2 Expansion and extension cohorts

Patient cohorts at selected doses may be expanded to further investigate the tolerability, PK and biological activity of AZD9291. Patients will have confirmed tumour T790M+ or T790M- status. The number of patients to be enrolled will depend on the number of patients required to ensure approximately 30 evaluable patients in each dose expansion cohort. There are no specific stopping critieria for this part of the study, however, emerging data from the expansion phase will be monitored regularly by the SRC.

An additional cohort of approximately 12 patients with T790M+ NSCLC tumours suitable for repeat biopsy will be enrolled.

5.1.2.1 Phase II extension cohort

Once the MTD or RP2D has been reached an additional cohort of patients with centrally confirmed T790M+ tumour will be enrolled to further assess the efficacy and tolerability of AZD9291. The number of patients to be enrolled will depend on the number of patients required to ensure approximately 175 evaluable patients.

5.1.3 Definition of dose-limiting toxicity

A DLT is defined as any toxicity not attributable to the disease or disease-related processes under investigation, which occurs from the first dose of study treatment (Day 1, Cycle 0) up to the last day of Cycle 1 (21 days after start of multiple dosing) in dose escalation cohorts and which includes, despite optimal therapeutic intervention:

1. Haematological toxicity ≥ CTCAE (version 4) grade 4 present for more than 4 days

2. Non-haematological toxicity ≥ CTCAE grade 3 including:

   - Infection including febrile neutropenia

   - Confirmed QTc prolongation (> 500 msec absolute or > 60msec above baseline)

3. Any other toxicity that:

   - is greater than that at baseline, is clinically significant and/or unacceptable, and is judged to be a DLT by the Safety Review Committee

   - that is a protocol defined stopping criteria (i.e. confirmed corneal ulceration)

   - results in a disruption of dosing schedule of more than 7 days

A DLT excludes:

1. Alopecia of any grade

2. Isolated laboratory changes of any grade without clinical sequelae or clinical significance

However, the incidence and type of DLT-type toxicity from Cycle 2 and beyond will be taken into account by the SRC in determining dose escalation steps.

5.1.3.1 Definition of maximum tolerated dose

A dose will be considered non-tolerated and dose escalation will cease if 2 or more of up to 6 evaluable patients experience a DLT at a dose level. Once the non-tolerated dose is defined the MTD will be confirmed at the previous dose-level below the non-tolerated dose or a dose between the non-tolerated dose and the last tolerated dose may be investigated. Six evaluable patients are required to determine the MTD.

5.1.3.2 Definition of maximum feasible dose

A dose will be considered to be the maximum feasible dose and dose escalation will stop if:

- Delivery of the next dose level would require dosing of >8 capsules per single administration, or
- There is evidence in the dose-exposure relationship of saturation of absorption.

5.1.4 Definition of evaluable patient

For decisions on dose escalation, an evaluable patient is defined as a patient that has received AZD9291 and either:

- has completed minimum safety evaluation requirements during the single dose period and over the first 21 days of continuous dosing

or

- has experienced a DLT during the single dose period or the first 21 days of continuous dosing

5.1.5 Safety Review Committee

After each dose level during the dose escalation phase of the study, a SRC will evaluate the safety, tolerability and pharmacokinetics of AZD9291 to decide the next dose.

The SRC will consist of:

- Study Team Physician, who will chair the committee, or delegate

- Principal Investigator or delegate from each investigational site
- Global Safety Physician or delegate

In addition, one other physician from the following may be invited:

  – Medical Science Director or delegate

  – Senior physician from another project

The Study Pharmacokineticist, Study Statistician, Patient Safety Scientist, Study Leader may also be invited as appropriate. The Safety Review Committee Remit document for this study will define the exact membership and who should be present for decisions to be made.

Further internal or external experts may be consulted by the SRC as necessary. The Global Safety Physician or delegate should always be present at the SRC if there are safety issues for discussion.

Once there are at least 3 evaluable patients at a dose level the SRC will review and assess all available safety data from the cohort together with available PK to make a decision on the dose for the next cohort of patients. Any dose interruptions and reductions will be taken into account.

The decision may be to:

1. Proceed with dose escalation – refer to Section 5.1.1
2. Expand the cohort to a maximum of 6 evaluable patients
3. De-escalate the dose either to a previous lower dose level (up to a maximum of 6 evaluable patients) or to an intermediate lower dose level
4. Stop the dose escalation part of the study
5. Consider alternative dosing frequencies or intermittent dosing schedules

When there are other patients that are ongoing at the time of this review, the SRC may decide to defer their decision until these further patients become evaluable.

Any patient started on treatment in error, as he/she failed to comply with all of the selection criteria but meets the criteria of an evaluable patient, will be reviewed on a case by case basis by the SRC to determine if the patient should be included or excluded in the decision for dose escalation.

The decisions and decision-making of the SRC on the next dose level will be documented and provided to the investigators prior to dosing any new patients.

5.1.6 Toxicity management

If a patient experiences a CTCAE grade 3 and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. Patients with QTcF prolongation fulfilling the DLT criteria (i.e. 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 QTc prolongation toxicity does not resolve to ≤ grade 1 within 21 days the patient will be permanently withdrawn from study treatment.

5.1.6.1 Escalation and expansion patients

If any other toxicity resolves or reverts to ≤ CTCAE grade 2 within 21 days of onset and the patient is showing clinical benefit, treatment with AZD9291 may be restarted at the same dose or a lower dose using the rules below for dose modifications (see Figure 2) and agreement with the AstraZeneca Study Team Physician as needed.

If any other toxicity does not resolve to ≤ CTCAE grade 2 after 21 days, then the patient should be withdrawn from the study and observed until resolution of the toxicity

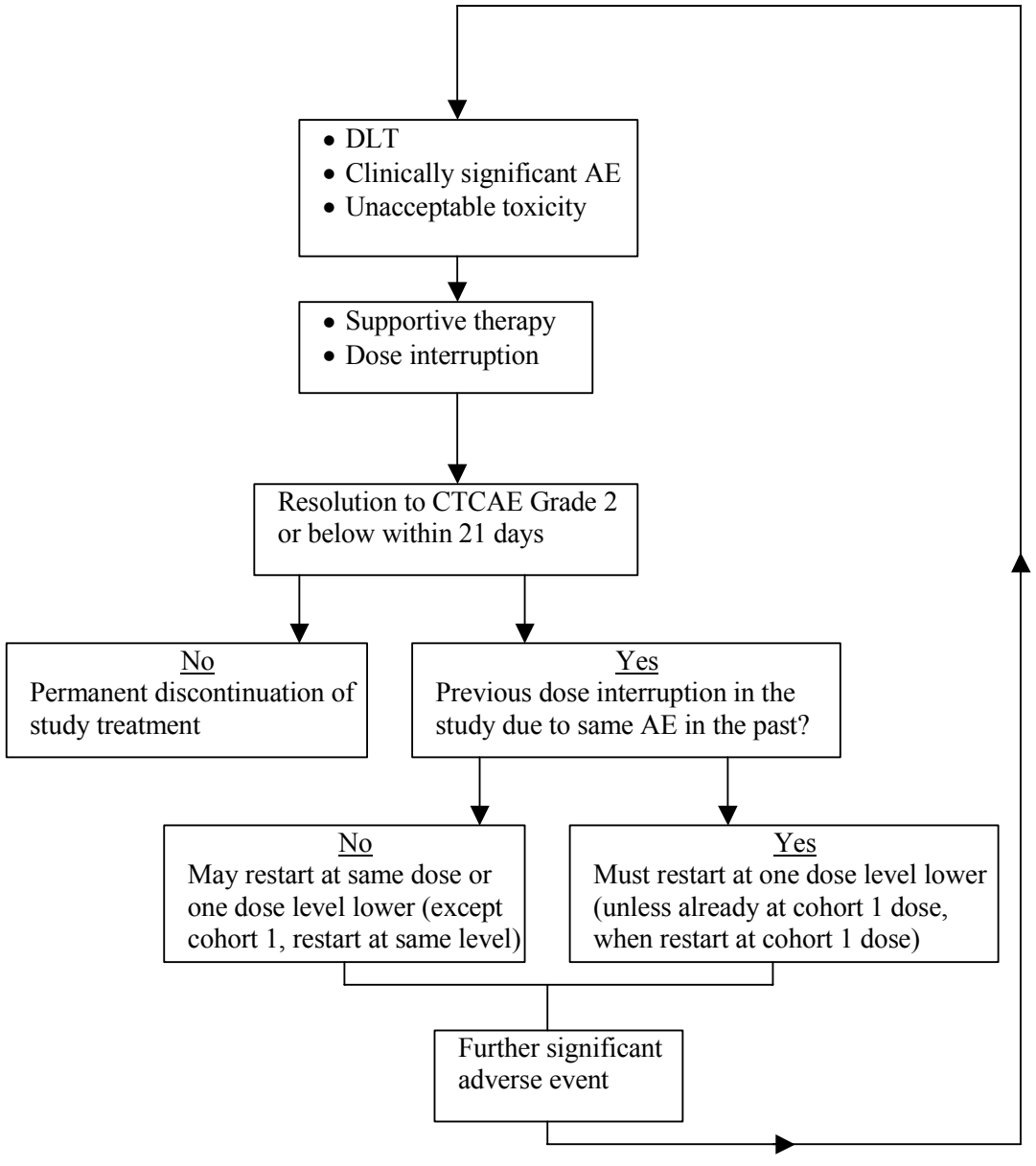
On resolution of toxicity within 21 days:

- If a further episode of the same AE subsequently requires dose interruption, AZD9291 must restart at one dose level lower (unless in Cohort 1, when restart will be at Cohort 1 dose) on improvement of the AE.

- If a different AE subsequently requires dose interruption, AZD9291 may restart at the same or one dose level lower (unless in Cohort 1, when restart will be at Cohort 1 dose) on improvement of the AE at the discretion of the Investigator.

Patients who are at the lowest possible dose ie, who have their dose previously reduced to the Cohort 1 dose and who have demonstrated an acceptable response to the dose interruption may be permitted to restart at the lowest dose level at the discretion of the Investigator.

Figure 2 Dose modifications for toxicity escalation and expansion



5.1.6.2 Phase II extension patients:

If any other toxicity resolves or reverts to ≤CTCAE grade 2 within 21 days of onset, treatment with AZD9291 may be restarted at the same dose (80 mg) or a lower dose (40 mg) following discussion and agreement with the AstraZeneca 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.

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.

5.1.6.3 All patients

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

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in study treatment dosing is recommended, and the AstraZeneca 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 interstitial lung disease should be considered and study treatment permanently discontinued.
In the absence of a diagnosis of interstitial lung disease study treatment may be restarted following consultation with the AstraZeneca Study Team Physician.

Assessment timings if dosing is interupted
If a patient misses any doses of AZD9291 during the 21-day evaluation period of Cycle 1, please contact the AstraZeneca Study Team for advice regarding the evaluability of the patient and appropriate timing of the PK assessments. All other assessments, including laboratory safety assessments, vital signs and RECIST should continue to be performed as per study plan, relative to the baseline assessements.

5.1.7 Duration of therapy

Patients should continue on treatment with AZD9291 until RECIST 1.1 defined progression or until treatment discontinuation criteria is met. There is no maximum duration of treatment as patients may continue to receive AZD9291 beyond RECIST 1.1 defined progression as long as they are continuing to show clinical benefit, as judged by the investigator.

If AZD9291 is discontinued for reasons other than disease progression, the patient must continue RECIST 1.1 assessments every 6 weeks until disease progression, even if further lines of anticancer therapy are administered.

5.1.8 Treatment compliance and accountability

The investigational product should only be used as directed in this protocol. Details of treatment with investigational product for each patient will be recorded in the Case Record Form.

Patients should return all unused medication and empty containers to the investigator.

The study personnel at the investigational site will account for all drugs dispensed and for appropriate destruction. Certificates of delivery and destruction should be signed.

5.2 Rationale for dose regimen, dose escalation scheme and stopping criteria

A dose of 20 mg/day is proposed as the starting dose in the first-into-patient study in patients with advanced NSCLC. This is based on international guidance for starting dose selection for agents in cancer patients (ICH S9) which recommends that the starting dose should be either $1/10^{th}$ of the severely toxic dose in 10% of animals in rodent toxicity studies (STD_{10}) or $1/6^{th}$ of the highest non-seriously toxic dose (HNSTD) observed in non-rodent studies. Female rats tolerated lower doses compared to males, which is partly explained by sex differences in exposure. The rat STD was considered to be between 20 and 40 mg/kg/day (based on females as the most sensitive sex) therefore 20 mg/kg/day has been used in this calculation. In dogs, the HNSTD was the mid dose (6 mg/kg/day) from the 1 month study. Using the conversion factors published on the FDA website (FDA Guidance 2005), the human equivalent dose (HED) derived from 1/10th of the rat STD was calculated to be 19.5 mg/day, whilst the HED derived from 1/6th of the dog HNSTD was calculated to be 32.4 mg/day. As a result of using the most conservative data, a starting dose of 20 mg/day is proposed for this study. The mouse pharmacodynamic and efficacy study data have been used in conjunction with in *vitro* metabolism data in a predictive model to estimate biologically active human doses. Based on a simulation of 75% tumour growth regression and the formation of the active metabolite AZ5104, the biological active daily dose is predicted to be approximately 10 mg for the H1975 (L858R/T790M) or 35 mg for the PC9 (Ex19del) cell lines respectively. Therefore the 20mg starting dose is anticipated to be biologically active.

The dose escalation scheme will not exceed doubling of the dose, in principle. However, up to a quadrupling of the dose may be permitted in the first two escalations only, if the drug concentrations from the first or second dose level are not measurable or are below the predicted target drug exposure for biological effect. This will ensure that the fewest possible cohorts are exposed to AZD9291 below the presumed therapeutic dose. Non-clinical modelling provides only an approximate prediction of human pharmacokinetics, therefore the planned dose escalation scheme has the flexibility to be amended in light of emerging data.

The dose of 80mg once daily was selected for the extension cohort from a review of all available safety, tolerability, PK and efficacy data collected to date from this study At the IB data cut-off of 19 November 2013, AZD9291 had been administered across the dose range of 20 to 240mg once daily in this study: 20 mg (n=21), 40 mg (n=55), 80 mg (n=47), 160 mg (n=40) and 240 mg (n=7). No dose limiting toxicities (DLTs) have been reported at any dose level in the

escalation cohorts during the 21-day DLT evaluation period. Patients have once daily doses of AZD9291 for durations of up to at least 10 months depending on the dose level. Emerging efficacy data has demonstrated durable objective responses from the starting dose level of 20mg once daily (Ranson 2013). The selected 80 mg dose is four fold higher than the minimum efficacious dose tested in study D5160C0001, whilst still being one third of the maximum dose level investigated (240mg). The 80 mg dose level is considered to have a safety and tolerability profile appropriate for chronic administration to patients with advanced NSCLC.

The relative bioavailability of the tablet formulation of AZD9291 has been investigated in a healthy volunteer study (D5160C00005). Preliminary data from this study indicate that there is no clinically significant different in PK profile between a single 20mg dose of the current capsule formulation and a single 20mg dose of the tablet formulation (AZ data on file). Similarly, preliminary review of emerging PK data from a cohort of patients receiving once daily dosing with 80mg AZD9291 as the tablet formulation in this study indicates no clinically significant difference in the PK profile of the tablet formulation compared with the PK profile of the 80mg capsule formulation dosed to other patients in this study (AZ data on file).

As this is the first administration of a dual EGFRm/T790M inhibitor agent in humans, in the first cohort the administration of the first dose is separated by at least 7 days for the first 2 patients. This will ensure that any acute toxic effects of the administration will have sufficient time to be identified before additional patients are exposed. If ambiguous safety or tolerability findings occur after the first cohort the staggered dosing may be performed again in the second cohort and likewise for subsequent cohorts. The rate of enrolment to Phase I oncology studies is historically significantly slower than healthy volunteer studies, and it is unlikely that there will be rapid recruitment of the remaining 5 patients into a cohort after this initial period. In addition, there is extensive clinical experience with other small molecule EGFR TKI agents which have shown that acute drug related toxicities are usually mild in intensity and manageable. There will be a minimum of 2 days between completion of dosing of Cycle 1, in the last required evaluable patient from one cohort and the start of dosing in the subsequent cohort in order for the SRC meeting to be called, and minutes of the dose escalation decisions to be distributed to all participating sites.

Stopping criteria have been set in accordance with traditional oncology phase I study methodology.

5.3 Benefit/risk and ethical assessment

5.3.1 Potential benefits

This study is a dose escalation study with AZD9291, a potent and specific, irreversible dual inhibitor of both the sensitising EGFRm mutations and the T790M resistance mutation with more potency towards mutant EGFRs compared to wild-type EGFR. Non-clinical data suggests that dual inhibition can result in anti-proliferative and pro-apoptotic activity in tumour models harbouring one or both of these mutations. Therefore AZD9291 may have the potential to provide clinical benefit both in terms of increased efficacy and decreased epidermal growth factor receptor wild type toxicity in patients with advanced EGFRm+ NSCLC who are either

treatment-naïve or who have had disease progression after treatment with an EGFR TKI agent (+/- additional chemotherapy) and are diagnosed with T790M+ NSCLC. In the first line treatment population AZD9291 may have the potential to delay the development of EGFR TKI resistance via the T790M mechanism. Preliminary efficacy data from this study to date (see Investigator Brochure) have indicated that clinical benefit in terms of objective responses and/or prolonged disease stabilisation have occurred from the very first cohort of patients tested at the starting dose of 20 mg AZD9291 in patients with advanced EGFRm+ NSCLC who have had disease progression after treatment with an EGFR TKI agent (+/- additional chemotherapy).

5.3.2 Potential risks

Section 2.3 of this protocol summarizes potential risks based upon non-clinical toxicity studies with AZD9291 in rats and dogs, and in vitro experiments, with further detailed information available in the IB. The monitoring and management of the potential risks is discussed below:

Gastrointestinal tract effects
Patients with refractory nausea, vomiting and chronic gastrointestinal diseases are excluded from participating in this study. Investigators will also be advised to follow the general toxicity management guidelines regarding dose interruption and reduction as detailed in Section 5.1.6

Dermatological effects
No specific dermatological exclusion criteria are included in this study, however, patients with any unresolved adverse event from prior therapy greater than CTCAE Grade 1 will be excluded from participation. Dermatological treatment should be instituted for patients with any CTCAE grade skin reactions, considered by the investigator to be causally related to AZD9291. Investigators will also be advised to follow the general toxicity management guidelines regarding dose interruption and reduction as detailed in Section 5.1.6. Photographs may be performed to record any clinically significant findings. These photographs should be available for central review by AZ and AZ representatives if necessary.

Ocular surface effects
Full ophthalmic assessment, including slit lamp examination, will be performed at screening and should be repeated if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated, as described in Section 5.1.6. 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 AZ and AZ representatives if necessary. Ophthalmology examination results should be collected in the eCRF. Any patient developing corneal ulceration will be permanently discontinued from study treatment and should be followed regularly until resolution of the event.

Patients who wear contact lenses will be advised to discontinue wearing lenses if they have any mild to moderate eye symptoms (CTCAE grade ≤2) while receiving treatment with AZD9291 until at least one week after symptoms have resolved. If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade ≥3) ocular events they should discontinue wearing their contact lenses until at least one week after treatment with AZD9291 is permanently discontinued. Patients should 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 will be advised to consult the clinic promptly if they have any concerns.

Cardiovascular effects

Patients who have unstable cardiac conditions and risk factors for QT prolongations will be excluded from participation in this study. Concomitant use of regular medications that may prolong the QT interval will be restricted whenever feasible (See Appendix H), but patients may receive any medication that is clinically indicated for the treatment of AEs. Electrolyte and vital sign assessments, including pulse rate and blood pressure, will be monitored regularly throughout the study. A series of triplicate digital ECG assessments will be performed over a 24 hour period after the first single dose of AZD9291 and at the time of presumed steady state (Day 8 of continuous dosing), with single ECGs being recorded at the beginning of each subsequent treatment cycle, as described in Section 6.3.4. The investigator or designated physician will review each ECG prior to discharge from the clinic and may refer to a local cardiologist if appropriate for immediate management of the patient. A paper copy should be filed in the patient's medical records. All digital ECG data will be transferred electronically for central analysis of heart rate, PR, R-R and QT intervals by an external cardiologist. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition.

Respiratory effects

Patients with a past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease will be excluded from participation in this study.

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in study treatment dosing is recommended, and the AstraZeneca 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 interstitial lung disease should be considered and study treatment permanently discontinued.

In the absence of a diagnosis of interstitial lung disease study treatment may be restarted following consultation with the AstraZeneca Study Team Physician.

Liver effects
Patients with any evidence of severe or uncontrolled systemic liver disease, including those with known hepatitis B, hepatitis C, human immunodeficiency virus (HIV) or abnormal liver enzymes (defined as AST or ALT >2.5 x upper limit of normal (ULN), total bilirubin >1.5 x ULN if no evidence of liver metastases; AST or ALT >5 x ULN, total bilirubin >3 x ULN in the presence of liver metastases) at screening are excluded from participating in the study. During the study, liver function tests will be monitored regularly during the study and recorded at discontinuation. Patients' laboratory results will be assessed against the FDA's Draft Guidance for Drug Induced Liver Injury (FDA Guidance 2005), with the process described in detail in Appendix G.

Haematopoietic effects
Patients with inadequate bone marrow reserve as demonstrated by any of the following laboratory values (absolute neutrophil count < 1.5 x 109/L; platelet count < 100 x 109/L; haemoglobin <90 g/L) will be excluded from the study. Haematological parameters will be monitored prior to administration of the first dose, weekly during the first cycle of multiple dosing , at the start of each subsequent cycle, and at discontinuation.

Reproductive organ effects
No reproductive toxicology or teratogenicity studies have been conducted with AZD9291 to date, although the male and female reproductive tracts have been assessed as part of the 1 month toxicology studies. Therefore women of child bearing potential and all men will be required to use adequate contraceptive measures during the study and for an appropriate period thereafter (as described in Section 4.3). Women of child bearing potential must have a negative pregnancy test prior to first dose of study treatment. Women who are breast feeding will be excluded from participating in the study. Male patients will be advised to arrange for the freezing of sperm samples prior to the start of the study should they wish to father children, and not to donate sperm until 3 months after discontinuation of study treatment.

CYP450 induction/inhibition
All patients must try to avoid concomitant use of medications, herbal supplements and/or ingestions of foods with known potent inducer or inhibitory effects on CYP3A4 and/or CYP2C8 activity whenever feasible. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 2 weeks after the last dose of AZD9291. Patients taking concomitant medications whose disposition is dependent upon intestinal CYP3A4 and/or transporter proteins and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result increased exposure of the concomitant medication whilst receiving AZD9291. Guidance on medications to avoid, medications that require close monitoring and on washout periods is given in Appendix H. If medically feasible, patients taking regular medication, with the exception of potent inhibitors or inducers of CYP3A4 and inhibitors of CYP2C8, should be maintained on them throughout the study period. Patients may receive any medication that is clinically indicated for treatment of adverse events.

5.3.3 Overall benefit-risk and ethical assessment

In the advanced NSCLC post-EGFR TKI treatment failure setting that has been chosen for initial study with AZD9291, prolonged survival rates are very low (~16 months for second line therapy,

~10 months for third line therapy) and there is a huge unmet clinical need for novel therapeutic agents for patients who have developed the resistance mutation. There are no established well proven therapeutic options for this specific T790M+ NSCLC patient population. Although there can be no certainty of clinical benefit to patients, the biological hypothesis, non-clinical and preliminary clinical efficacy data with AZD9291 support the notion that dual EGFR mutation inhibition may be a valid target for the treatment of NSCLC tumours driven via this pathway and may, in addition, delay the development of resistance via T790M in the first line therapy naive population.

The selected starting dose for this study is within the range that is predicted to provide biological activity based upon non-clinical explant models, in accordance with the ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Section III.A principle of selecting a dose 'that is expected to have pharmacologic effects'. The preliminary efficacy data from this study (see Investigator Brochure) showed that objective responses occurred at the starting dose**.** The toxicological profile of AZD9291 has been evaluated in rats and dogs in studies of up to one month in duration. In accordance with ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals which states in Section III.C that 'In Phase 1 clinical trials, treatment can continue according to the patient's response' (ICH S9), dosing of AZD9291 will extend beyond one month if there is some evidence of therapeutic benefit (ie, lack of disease progression with an acceptable tolerability profile). The non-clinical safety profile has not identified any risks that would preclude investigation in this setting. The study design aims to minimise potential risks, and monitoring is in place for those risks deemed to be most likely or serious.

The investigation of AZD9291 in this patient population appears acceptable, based upon the non-clinical safety profile, preliminary signals for clinical efficacy, and the lack of effective alternative treatments available to patients, the limited life expectancy due to malignant disease, and the strength of the scientific hypothesis under evaluation. Thus the benefit/risk assessment for this first-into-man Phase I study support the oral administration of AZD9291 to patients with advanced NSCLC in the post-EGFR TKI treatment failure and treatment-naive settings, according to the proposed study design.

5.4 Discontinuation of investigational product and withdrawal from study

Patients **may** be discontinued from investigational product in the following situations:

- Patient decision. The patient is at any time free to withdraw his/her participation in the study, without prejudice
- Adverse events
- Pregnancy
- Severe non-compliance to this protocol as judged by the investigator and/or AstraZeneca

- Confirmed disease progression

- Patients incorrectly initated on investigational product (Section 5.4.2)

Patients that are withdrawn from the study but are evaluable will not be replaced. Any patient that is withdrawn and is not evaluable will be replaced to ensure a minimum number of evaluable patients.

Patients may withdraw from any aspects of the voluntary exploratory research (see Section 6.9.5) at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study. Procedures for withdrawal from the exploratory research are outlined in Section 6.9.5

5.4.1 Procedures for discontinuation of a patient from investigational product

Once study medication is permanently discontinued it cannot be restarted.

A patient who discontinues study treatment is not always automatically withdrawn from the study. If a patient is withdrawn from study, see Section 5.4.3

Any patients who discontinue study treatment for reasons other than objective disease progression should have tumour assessments scans performed as scheduled in the protocol (see Table 2, Table 3 and Table 4 until objective disease progression is documented or death occurs, unless consent is withdrawn. Study procedure related SAEs and concomitant medication must be captured until the patient no longer has RECIST 1.1 assessments (disease progression or permanent withdrawal from the study).

5.4.2 Procedures for handling patients incorrectly initiated on investigational product

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

Where patients that do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the investigator should inform the AstraZeneca Global Study Team Physician immediately. The decision on when to discontinue the ineligible patient from the study is based on the medical/ safety risk for the patient. The AstraZeneca Global Study Team Physician is to ensure all such contacts are appropriately documented.

5.4.3 Procedures for withdrawal from study

Patients are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen by an investigator and undergo the assessments and procedures scheduled for the post study assessment (see Section 6.3.8) and inform AstraZeneca of the withdrawal. Adverse events should be followed up (see Sections 6.4.3 and 6.4.4); questionnaires (eg, for patient reported outcomes) and study drug should be returned by the patient.

5.5 Study timetable and end of study

Planned duration of the study:

Study period:

Dose escalation, paired biopsy and expansion cohorts

The primary analysis of the expansions will take place 7.5 months after the last patient recruited starts investigational product or approximately 28 days after the final patient discontinues investigational product. The initial CSR will report the analysis of all primary and secondary endpoints and summarise the exploratory endpoints where data is available. During the primary analysis of the extension cohort an updated analysis of DoR from one or more of the expansion cohorts may be performed.

Extension cohort

The primary analysis of ORR will take place after all patients have completed at least two RECIST follow-up assessments (i.e. 3months). At this time, DoR and safety/tolerability will also be summarised. The primary analysis CSR will report the analysis of ORR supported by duration of response, and safety and tolerability data.

The full CSR will report the analysis of all primary and secondary endpoints (including updated ORR and DoR, DCR, PFS, OS, HRQoL and PK). This analysis will take place approximately 8 months after the last subject has been enrolled into the extension cohort, to allow responding patients to have a DoR greater than 6 months.

All cohorts

All patients will continue to be followed up for an updated analysis that will occur between 12-24 months after the last patient has been enrolled. All endpoints will be updated and summarised in an addendum to the CSR.

Any patients still receiving investigational product at the time of the final data cut-off will be able to continue to receive AZD9291 while deriving clinical benefit. Such patients will continue to be monitored for all Serious Adverse Events up to 28 days after the last dose of investigational product. Drug Accountability information must still be collected until all patients have completed treatment.

6. STUDY PLAN AND COLLECTION OF STUDY VARIABLES

6.1 Study Plan

Table 2 Study Plan Dose Escalation

	screening	Single dose/Cycle 0 (7 day cycle)					Multiple Dose/Cycle 1 (21 day cycle)			Cycles 2 -6 (21 day cycle)	Cycle 7 and every 6 weeks onwards	Discontinuation	28-day follow-up	Progression	Details in section
Day	-28 to -1	D1	D2	D3	D4	D6	D1	D8	D15	D1	D1				
Informed consent	X														4
Demography & baseline characteristics	X														6.3.1
Medical/surgical history	X														6.3.1
Inclusion/exclusion criteria	X														4
Physical examination	X	X					X			X	X	X			6.3.2
WHO performance status	X	X					X			X	X	X			6.3.2
Pregnancy test (pre-menopausal females only)	X														6.3.5
Ophthalmologic assessment	X														6.3.6
EGFR mutation status (archival tumour tissue)	X														6.8.1.1
Archival tumour tissue	X														6.8.1.1
Tumour biopsy (optional)	X								X			X			6.8.1.1
Vital signs	X	X	X				X	X	X	X	X	X			6.3.3
Height	X														6.3.3
Weight	X	X					X			X	X	X			6.3.3

Table 2 Study Plan Dose Escalation

	screening	Single dose/Cycle 0 (7 day cycle)					Multiple Dose/Cycle 1 (21 day cycle)			Cycles 2 -6 (21 day cycle)	Cycle 7 and every 6 weeks onwards	Discontinuation	28-day follow-up	Progression	Details in section
Day	-28 to -1	D1	D2	D3	D4	D6	D1	D8	D15	D1	D1				
Clinical chemistry/ Haematology/Urinalysis	X	X					X	X	X	X	X	X			6.3.5
ECG	X	X	X				X	X	X	X	X	X			6.3.4
PK blood samples (including metabolites)		X	X	X	X	X	X	X	X	X (cycle 2 only)					6.6.1
Blood sample for cfDNA	X	X								6 wkly at RECIST visit				X	6.8.1.2
Genetics consent and blood sample (optional)	X														6.8.2
CSF (optional)										X (once only)					6.8.3
RECIST assessments	X						Every 6 weeks (relative to first dose of multiple dosing) until progression								6.10.1
Dispense study medication		X					X			X	X				5
Dose with AZD9291		X					Daily dosing								5
Concomitant medication															4.3.1
Adverse events															6.4

Table 3 Study Plan Phase I Expansion and paired Biopsy Cohorts

	Screening	Multiple Dose/Cycle 1 (21 day cycle)			Cycles 2-6 (21 day cycle)	Cycle 7 and every 6 weeks onwards	Discontinuation	28-day Follow up	Progression	Detail in section
Day	-28 to -1	D1	D8	D15	D1	D1				
Informed consent	X									4
Demography & baseline characteristics	X									6.3.1
Medical/surgical history	X									6.3.1
Inclusion/exclusion criteria	X									4
Physical examination	X	X			X	X	X			6.3.2
WHO performance status	X	X			X	X	X			6.3.2
Ophthalmologic assessment	X									6.3.6
HRQoL form	X	X			Every 6 weeks (relative to first dose) until progression		X		X	6.5
Pregnancy test (pre-menopausal females only)	X									6.3.5
T790M mutation status tumour sample (mandatory)	X									6.8.1.1
Archival tumour tissue	X									6.8.1.1
Tumour biopsy (Paired biopsy cohort - mandatory)	X			X						6.8.1.1
Tumour biopsy (optional)	X			X			X			6.8.1.1

Table 3 Study Plan Phase I Expansion and paired Biopsy Cohorts

	Screening	Multiple Dose/Cycle 1 (21 day cycle)			Cycles 2-6 (21 day cycle)	Cycle 7 and every 6 weeks onwards	Discontinuation	28-day Follow up	Progression	Detail in section
Day	-28 to -1	D1	D8	D15	D1	D1				
Vital signs	X	X	X	X	X	X	X			6.3.3
Height	X									6.3.3
Weight	X	X			X	X	X			6.3.3
Clinical chemistry /Haematology/Urinalysis	X	X	X	X	X	X	X			6.3.5
ECG	X	X	X	X	X	X	X			6.3.4
PK blood sample (including metabolites)		X	X	X	X (cycle 2 only)					6.6.1
Blood sample for cfDNA	X	X			← 6 wkly at RECIST visit →				X	6.8.1.2
Genetic consent and blood sample (optional)	X									6.8.2
CSF (optional)					X (once only)					6.8.3
RECIST assessments	X	← Every 6 weeks (relative to first dose) until progression →								6.10.1
Cognitive patient interview (optional)		4-6wks + 4-6 months								6.5.3
Dispense study medication		X			X	X				5
Dose with AZD9291		← Daily dosing →								5
Concomitant medication	← →									4.3.1
Adverse events	← →									6.4

Table 4 Study Plan Phase II Extension Cohort

	Screening	Multiple Dose/Cycle 1 (21 day cycle)			Cycles 2-6 (21 day cycle)	Cycle 7 and every 6 weeks onwards	Discontinuation	28-day Follow up	Progression	Post progression survival F/U	Detail in section
Day	-28 to -1	D1	D8	D15	D1	D1				6 weekly relative to progression	
Informed consent	X										4
Demography & baseline characteristics	X										6.3.1
Medical/surgical history	X										6.3.1
Inclusion/exclusion criteria	X										4
Physical examination	X	X			X	X	X				6.3.2
WHO performance status	X	X			X	X	X				6.3.2
Ophthalmologic assessment	X										6.3.6
HRQoL form	X	X			Every 6 weeks (relative to first dose) until progression		X		X		6.5
Pregnancy test (pre-menopausal females only)	X										6.3.5
T790M mutation status tumour sample (mandatory)	X										6.8.1.1
Archival tumour tissue	X										6.8.1.1

Table 4 Study Plan Phase II Extension Cohort

	Screening	Multiple Dose/Cycle 1 (21 day cycle)			Cycles 2-6 (21 day cycle)	Cycle 7 and every 6 weeks onwards	Discontinuation	28-day Follow up	Progression	Post progression survival F/U	Detail in section
Day	-28 to -1	D1	D8	D15	D1	D1				6 weekly relative to progression	
Tumour biopsy (optional)	X			X			X				6.8.1.1
Vital signs	X	X	X	X	X	X	X				6.3.3
Height	X										6.3.3
Weight	X	X			X	X	X				6.3.3
Clinical chemistry /Haematology/Urinalysis	X	X	X	X	X	X	X				6.3.5
ECG	X	X	X	X	X	X	X				6.3.4
Echocadiogram/MUGA	X	← 12 weekly relative to first dose →									6.3.7
PK blood sample (including metabolites)		X	X	X	X (cycle 2 only)						6.6.1
Blood sample for cfDNA	X	X			← 6 wkly at RECIST visit →				**X**		6.8.1.2
Genetic consent and blood sample (optional)	X										6.8.2
CSF (optional)					X (once only)						6.8.3
RECIST assessments	X	Every 6 weeks (relative to first dose) until progression)									6.10.1

Table 4 Study Plan Phase II Extension Cohort

	Screening	Multiple Dose/Cycle 1 (21 day cycle)			Cycles 2-6 (21 day cycle)	Cycle 7 and every 6 weeks onwards	Discontinuation	28-day Follow up	Progression	Post progression survival F/U	Detail in section
Day	-28 to -1	D1	D8	D15	D1	D1				6 weekly relative to progression	
Cognitive patient interview (optional)					4-6wks + 4-6 months						6.5.3
Dispense study medication		X			X	X					5
Dose with AZD9291		Daily dosing									5
Concomitant medication	←									→	4.3.1
Adverse events	←										6.4
Survival										X	6.3.8.3

6.2 Recording of data

Web Based Data Capture (WBDC) will be used for data collection on the observations, tests and assessments specified in the protocol and query handling. The investigator will ensure that data are recorded on the Case Report Forms as specified in the protocol and in accordance with the instructions provided. These instructions provide guidance for the recording of study data in the CRF including how to change data incorrectly recorded.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and for the provision of answers to data queries according to the Clinical Study Agreement or applicable information.

The investigator will sign the completed Case Report Forms. A copy of the completed Case Report Forms will be archived at the study site.

For details of data and study management see Appendix E of this Clinical Study Protocol.

6.3 Safety procedures

6.3.1 Enrolment and screening

At enrolment, each potential patient will provide informed consent prior to starting any study specific procedures (see Appendix D of this Clinical Study Protocol for Ethics and Regulatory Requirements).

Each potential patient is assigned a unique enrolment number by a nominated person at AstraZeneca. Recruitment into the study will be conducted in a controlled manner. No patient will be enrolled without prior authorisation from AstraZeneca to ensure adherence with the rolling 6 recruitment design and subsequent allocation to expansion cohorts. If a patient withdraws from the study, then the enrolment code cannot be reused.

Demographic data and other characteristics will be recorded and will include date of birth or age, gender, race and/or ethnicity according to local regulations, smoking history.

A standard medical, medication and surgical history will be obtained with review of the selection criteria with the patient.

Each patient will undergo screening (see Study Plan Table 2, Table 3 and Table 4) during the 28 days prior to admission to confirm eligibility (see Sections 4.1. and 4.2). Tumour assessments and other clinical data obtained as standard of care prior to consent may be used for the study provided the assessments fall within the protocol specified period prior to the first dose of study treatment. Tumour receptor/mutation status will be recorded including EGFRm, T790M and cMET etc.

Prior to discharge from each in-patient and clinic visit, the Investigator or their deputy will be responsible for reviewing all available data including vital signs and ECG tracings.

6.3.2 Physical examination

A complete physical examination will be performed at the visits as indicated in the Study Plan (see Study Plan Table 2, Table 3 and Table 4)

Performance status will be assessed at screening, prior to the first dose of study treatment, at the beginning of each Cycle, and at discontinuation according to WHO criteria as follows:

0 = Fully active, able to carry out all pre-disease activities without restrictions

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature eg, light housework, office work

2 = Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair

6.3.3 Vital signs

Pulse rate and blood pressure

Supine blood pressure and pulse rate will be measured after 10 minutes rest. Assessments will be performed at the visits as shown in the Study Plan (See Table 2, Table 3 and Table 4). Pulse rate and blood pressure will be recorded at the following times:

- Screening
- First dosing day (Day 1 Cycle 0) for dose escalation cohorts
  - pre-dose, 1, 2, 4, 6, 10 and 24 hours (Day 2) post-dose
- First dosing day (Day 1 Cycle 1) for expansion, extension and paired biopsy cohorts
  - pre-dose, 1, 2, 4, 6 and 10 hours post-dose
- Day 1 Cycle 1 for dose escalation cohorts
  - Pre-dose only
- Day 8 and Day 15, Cycle 1 (Multiple Dosing for all cohorts)
  - Pre-dose only
- Day 1, Cycle 2 (Multiple dosing all cohorts)

- pre-dose, 1, 2, 4, 6, 10 and 24 hours (Day 2) post-dose

- On Day 1 of each subsequent Cycle; one assessment at any time during day
- On occurrence of any cardiac AE
- Discontinuation visit

Weight will be performed at screening and then Day 1 of each cycle and at the discontinuation visit.

Height will be assessed at screening only.

Any changes in vitial signs should be recorded as an AE if applicable.

6.3.4 ECG

Resting 12-lead ECG

Twelve-lead ECG will be performed at the visit indicated in the Study Plan (see Table 2, Table 3 and Table 4).

Twelve-lead ECGs will be recorded at the following times:

- Screening
- First dosing day (Day 1 Cycle 0) for dose escalation cohorts
  - pre-dose, 1, 2, 4, 6, 10 and 24 hours (Day 2) post-dose
- First dosing day (Day 1 Cycle 1) for expansion, extension and paired biopsy cohorts
  - pre-dose, 1, 2, 4, 6 and 10 hours post-dose
- Day 1 Cycle 1 for dose escalation cohorts
  - Pre-dose only
- Day 8 and Day 15, Cycle 1 (Multiple Dosing for all cohorts)
  - Pre-dose only
- Day 1, Cycle 2 (Multiple dosing all cohorts)
  - pre-dose, 1, 2, 4, 6, 10 and 24 hours (Day 2) post-dose
- On Day 1 of each subsequent Cycle; one assessment at any time during day

- On occurrence of any cardiac AE
- Discontinuation visit

The timing and number of ECGs may be altered depending on the emerging PK and safety profile.

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position. For each time point three ECG recordings should be taken at about 5 minute intervals. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study if possible.

After paper ECGs have been recorded, the investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition. For all ECGs details of rhythm, ECG intervals and an overall evaluation will be recorded.

All ECG data (with the exception of the screening ECGs) will also be collected digitally and will be transferred electronically for central analysis as described in the study specific ECG manual. Heart rate, PR, R-R, QRS and QT intervals will be determined and reviewed by an external cardiologist.

6.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the visits as indicated in the Study Plan (see Table 2, Table 3 and Table 4). Laboratory tests do not need to be repeated at baseline if the baseline visit is within 7 days of the screening sample.

Blood and urine samples for safety assessment will be collected at the following times:

- Screening
- First dosing day (Day 1 Cycle 0 for dose escalation, Day 1 Cycle 1 for expansions and extension); pre-dose (baseline)
- First day of multiple dosing, Day 1 Cycle 1 dose escalation only; pre-dose
- Multiple dosing, Days 8 and 15 of Cycle 1; pre-dose
- On Day 1 of each subsequent Cycle; pre-dose
- Discontinuation visit

The date of each collection will be recorded in the appropriate CRF.

Following review of data from a group of patients the timing of blood samples may be adjusted for subsequent groups of patient. Additional sampling times may be added if indicated by the emerging data.

Laboratory values that meet the criteria for CTCAEv4 grade 3 or have changed significantly from baseline and are considered to be of clinical concern will be repeated/confirmed within 7 days and followed up as appropriate.

The following laboratory variables will be measured:

Clinical chemistry

Serum (S)/Plasma (P)-Albumin

S/P-ALT

S/P-AST

S/P-Alkaline phosphatase

S/P-Bilirubin, total

S/P-Calcium, total

S/P-Creatinine

S/P-Glucose (fasting on PK days only)

S/P-HbA1C

S/P-Magnesium

S/P-Potassium

S/P-Sodium

S/P-Urea nitrogen

Haematology

Blood (B)-Haemoglobin

B-Leukocyte

B-Haematocrit

B-Red blood cell (RBC) count

B-Absolute leukocyte differential count:

- Neutrophils
- Lymphocytes
- Monocytes
- Basophils
- Eosinophils

B-Platelet count

B-Reticulocytes

Urinalysis

U-Glucose

U-Protein

U-Blood

Additionally a urine/serum sample will be collected from all females of child bearing potential at screening, before first dose for a pregnancy test.

NB. In case a subject shows an AST or ALT ≥ 3xULN or total bilirubin ≥ 2xULN please refer to Appendix G ‘Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy’s Law’ for further instructions.

For blood volume see Section 6.9.1

6.3.6 Ophthalmologic examination

Full ophthalmic assessment, including slit lamp examination, should be performed at screening and if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. 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 AZ and AZ representatives if necessary. Ophthalmology examination results should be collected in the eCRF.

6.3.7 Echocardiogram/MUGA Scan

For extension cohort patients, an Echocardiogram or MUGA scan to assess LVEF will be conducted at baseline (prior to first dose of AZD9291), 12 weeks after the first dose of AZD9291 and 12-weekly thereafter (± 1 week). The modality of the cardiac function assessments must be consistent within a patient i.e. if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans if required. The patients should also be examined using the same machine and operator whenever possible.

6.3.8 Follow-up

6.3.8.1 Safety Follow-Up

A post study assessment will be performed at the time investigational product is permanently discontinued (Study Plan Table 2, Table 3 and Table 4).

In addition for safety follow-up as a minimum, telephone contact should be made with the patient 28 +/-7 days following the discontinuation of AZD9291 to follow up on any SAE/AE's and concomitant medications (including any subsequent cancer therapy). Any SAEs will be followed to resolution where possible.

6.3.8.2 Progression follow-up

Patients who discontinue AZD9291 for reasons other than progression will continue RECIST 1.1 assessments every 6 weeks (relative to first dose of multiple dosing). Details of concomitant medications (including any subsequent cancer therapy) should continue to be collected as detailed in the study plan (see Table 2, Table 3 and Table 4) up to the 28-day follow up visit. Only new SAEs due to study procedures should be collected. For those patients in the expansion cohorts an additional PRO QoL questionnaire should be completed on progression (Table 3). Beyond the 28-day follow up visit only subsequent cancer therapy should be collected.

6.3.8.3 Survival follow-up

In the Phase II extension, following disease progression, the patient, patient's family, or the patient's current physician must be contacted every 6 weeks for survival information, for collection of details of subsequent treatment regimens received following withdrawal from

study drug and to follow up unresolved AEs (unless the patient withdraws consent) regardless of date of last contact, as detailed in the study plan (see Table 4).

6.4 Adverse events

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

6.4.1 Definition of adverse events

An adverse event 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, electrocardiogram). 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.

For patients in Japan*:* For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected.

Any deterioration of the disease under study and associated symptoms or findings should not be regarded as an adverse event as far as the deterioration can be anticipated (see Section 6.4.3).

The term adverse event is used generally to include any AE whether serious or non-serious.

6.4.2 Definitions of serious adverse events

A serious adverse event (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 or results in 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 of this Clinical Study Protocol.

For definition of other significant adverse events (OAE) see Section 7.3.1

6.4.3 Recording of adverse events

Time period for collection of adverse events

AEs will be collected throughout the study, from informed consent until the end of the follow-up period. The follow-up period is defined as 28 +/-7 days after study treatment is discontinued. SAEs occurring in the follow-up period should be reported to AstraZeneca in the usual manner (see Section 6.4.4).

Following discontinuation of AZD9291, SAEs considered related to study procedures should continue to be collected while patients are followed up for disease progression.

After the final database lock, there may be some patients remaining on study treatment. For these patients who are continuing to receive AZD9291 AZ will collect information (during the treatment period and for 28 +/- 7 days after last dose) on SAEs, deaths (including those due to disease progression), discontinuation due to AEs/SAEs and drug accountability only.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s) at the end of the study, if judged necessary.

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

Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date when the AE started and stopped
- Maximum CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product

- Outcome

For SAEs other variables will be collected including treatment given for the event.

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 6.4.2. 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. 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.

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).

Causality collection

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

For SAEs causal relationship will also be assessed for other medication and study procedure. 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 of this Clinical Study Protocol.

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 CRF. 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.

Adverse events based on examinations and tests

The results from protocol mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarised in the Clinical Study Report. Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfil any of the criteria for a SAE, a DLT or are the reason for discontinuation of treatment with the investigational product unless clearly due to progression of disease under study (see Disease progression).

If deterioration in a laboratory value, vital sign, ECG or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or other finding will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs and symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE.

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.

Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. **Events that are unequivocally due to disease progression should not be reported as AEs during the study.**

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.

Handling of deaths

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

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the CRF 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 to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes

- Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem

results (with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes

6.4.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then investigators 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 the necessary information is provided to the appropriate AstraZeneca patient safety data entry site within **one calendar day** of initial receipt for fatal and life threatening events and within **five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events 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 immediately, or **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

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

The reference document for definition of expectedness is Section 5.4 of the Investigators' Brochure for AZD9291.

6.5 Patient Reported Outcomes

Patient reported outcomes (PROs) is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical trials. The following PROs will be administered: EORTC QLQ C-30 and QLQ-LC13.

6.5.1 EORTC QLQ-C30 and QlQ-LC13

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group 1993. It consists of 30 items and measures cancer patients' functioning (HRQoL) and symptoms (Aaronson NK et al 1993). The QLQ-LC13 is a complementary module measuring lung cancer-associated symptoms and side-effects from conventional chemotherapy and radiotherapy (Bergman B et al 1994).

6.5.2 Administration of PROs

Questionnaires will be administered using paper questionnaires. The patient should complete the questionnaires at the scheduled clinic visit at screening, and every 6 weeks relative to the first dose of multiple dosing, discontinuation and progression as specified in the study plan (Table 2, Table 3 and Table 4).The patient should also complete a questionnaire progression. If any scheduled PRO assessment is not completed the reason for non-completion should be recorded.

PROs will be filled out prior to any other site activities and encounters with physician. The patients will be instructed to complete the PRO independently. This site will have a designated quiet space for patients to use when completing the assessments. Each centre should allocate responsibility for PRO assessment to a specified individual (e.g. a research nurse). The research nurse or appointed individual should stress the information is confidential.

It is important that the value and relevance of HRQoL data are explained carefully to participating patients so that they are motivated to comply with data collection. The research nurse or appointed individual should also stress that the information is confidential. Therefore, if the patient has any medical problems she should discuss them with the doctor or research nurse separately from their HRQoL assessment.

The instructions for completion of questionnaires are:

- It must be completed before any investigations or discussions about the status of the patient's disease with the clinic staff.
- The patient must complete it themselves without any intervention from family, friends, centre staff etc.
- The only exception to this is if the patient is blind or illiterate. In this case the questionnaire may be read to the patient verbatim, however the reader must not aid in the interpretation of questions or in the selection of answers.
- Only one answer to every question should be checked.
- Centre personnel should not review the responses to the questionnaire with the patient or with any other centre staff.

Following completion, the nurse or appointed individual may quickly scan the questionnaire visually for completeness and should confirm verbally with the patient that the questionnaire has been completed fully.

6.5.3 Cognitive patient interviews (optional)

Site staff in at least two countries will be asked to consent patients for optional interviews.

Patient contact information will be provided by site staff to an external CRO, Health Research Associates, Inc (HRA). The HRA interview study coordinator will contact patients by phone to schedule a date for the interview. Not all patients who consent may be able to participate. The goal is to conduct two interviews each (4-6 weeks and 4-6 months after treatment start, respectively) in approximately 50 patients and each interview will last 60 minutes.

Patients will be interviewed by trained qualitative interviewers who are experienced in qualitative research. All data will be confidential and the patient identifiers used will conform to applicable regulations, so as to preserve patient confidentiality (e.g., to assure matching between the audio recording and the subsequent transcript). Data from the audio recordings of the interviews will be transcribed to paper and analyzed using a number of qualitative techniques particular to this methodology (Ericsson 1980, Campanelli 1991). Due to the qualitative nature of the data and the analysis, the results will be presented in a separate report (i.e., not in the clinical study report) and the data (i.e., transcriptions) will not be entered into the study database.

Copies of the interview transcripts will be stored at HRA in locked files until they are packaged for storage in an off-site archive facility, where they will remain for a period of seven years and then be destroyed. Electronic files are all stored on password protected computers with routine back up onto a secure, firewalled server system. Individual files are password protected when shipped outside the secured server system. The voice files from the audio recordings are placed on a secure file transfer protocol (FTP) site where they can be accessed by password by the transcription vendor.

Should a patient withdraw from the study he/she will be asked if they are willing to participate in the follow-up interview.

6.6 Pharmacokinetics

6.6.1 Collection of pharmacokinetic samples

Venous blood samples for determination of concentrations of AZD9291 and its metabolites (AZ5104 and AZ7550) in plasma will be taken at the times presented in Table 5. Discussions will be required with the AZ PK representative as to any effect on the PK sample schedule if dose interruption occurs within 3 days of PK sampling. The date and time of collection of each sample and the date and time of dose will be recorded.

Table 5 PK blood sample schedule

Time relative to Dose	Dose Escalation only					All patients			
	Single Dosing Cycle 0					Multiple Dosing Cycle 1			Multiple Dosing Cycle 2
	D1	D2	D3	D4	D6	D1	D8	**D15**	**D1**
Pre-dose	X					X	X	X	X
1h	X								X
1.5h	X								X
2h	X								X
4h	X								X
6h	X								X
8h	X								X
10h	X								X
12h	X								X
24h		X							X (D2, pre-dose)
48h			X						
72h				X					
120h					X				
At time of biopsy								X[a]	

a Cycle 1 Day 15 predose PK sample collected for all patients. Collection of the Cycle 1 Day 15 "at time of biopsy" PK sample is only required if biopsy taken and, where optional, is feasible to do so

A 5min window will be allowed for samples taken at 1h; a 10min window for samples taken at 1.5-10h; a 1h window for samples taken at 12h and 24h, a 2h window at 48h,-72h and a 24h window at 120h.

The timing of the pharmacokinetic samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the plasma concentration-time profiles. The total number of samples and the total volume of blood taken from each patient will not exceed that detailed in Section 6.9.1. Residual samples may be analysed for exploratory biomarkers.

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

6.6.2 Determination of drug concentration in pharmacokinetic samples

Samples for determination of AZD9291 (and metabolite) concentrations in plasma will be analysed by on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical 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 pharmacokinetic samples may be subjected to further analyses by AstraZeneca in order to further investigate the presence and/or identity of additional drug metabolites. Any results from such analyses will be reported separately from the Clinical Study Report.

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

6.7 Pharmacodynamics

6.7.1 Collection of pharmacodynamic assessments

Details on sample processing, handling, shipment and storage are provided in the Laboratory Manual. For sample schedule, see Study Plan (Table 2, Table 3 and Table 4)

6.8 Exploratory research

6.8.1 Exploratory biomarker research

If a patient agrees to participate in the exploratory biomarker research component of the study biological samples (eg, plasma, serum, archived and study-obtained tumour, etc) will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug and clinical outcomes.

The results of this exploratory biomarker research will be reported separately and will not form part of the Clinical Study Report.

The results of this exploratory biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future studies.

6.8.1.1 Collection of tumour biopsy samples

All patients will be asked to provide consent to supply a sample of their archival tumour blocks if a sample taken at the time of diagnosis is available. Any archival biopsy samples taken following previous lines of therapy will also be requested, if available. In each case the previous patient treatment must be clearly indicated for each sample provided.

For timings of biopsies see Table 6 below.

Table 6 Tumour biopsy samples

Time Relative to dose	Escalation	Expansions	Ph II Extension	Paired Biopsy
Archival	**M***	**M***	**M***	**M***
Screening	**O**	**M + O**	**M + O**	**M + O**
Day 15	**O**	**O**	**O**	**M**
Discontinuation	**O**	**O**	**O**	**O**

M = Mandatory O = Optional M* = mandatory if available

All patients will be asked to consent to optional biopsies as detailed in Table 6. These biopsy samples will be used to support the development of the diagnostic assay and further exploratory research.

The optional screening sample should be obtained at the same time and as part of the same sample procedure as the mandatory biopsy for T790M status.

For patients in the paired biopsy cohort the mandatory screening biopsy will be used as the 1st of their Paired Biopsies as well as for identifying T790M status.

Tumour samples will preferably be in the form of a formalin fixed paraffin embedded block (tissue derived from the diagnostic tumour or a metastatic site). If this is not possible, 10-20 slides of freshly prepared unstained 5 micron sections from the archival tumour block may be provided.

The biomarkers to be investigated using tumour samples collected from the paired biopsy cohort will not necessarily be limited to but will include all or some of the following:

- pEGFR
- pERK
- pAKT
- pPRAS40
- pS6
- PGSK3β
- P4EBP1
- Cleaved caspase 3

- Ki67

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

6.8.1.2 Collection of plasma for exploratory analysis of cfDNA

All patients will be requested to provide plasma samples. These samples will be used for the extraction and analysis of circulating free tumour DNA (cfDNA). The sample may be used to further investigate the relationship between PK and blood-borne biomarkers.

Plasma samples will be taken at the following times:

Screening

Pre-dose Day 1

Every 6 weeks up to and including progression (corresponding with the RECIST assessments)

Discontinuation of treatment

The samples will be analysed for a range of oncology biomarkers which may correlate with drug response.

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

6.8.2 Pharmacogenetics

If a patient agrees to participate in the host pharmacogenetics research component of the study a blood sample will be collected. The results of this pharmacogenetic research will be reported separately and will not form part of the Clinical Study Report.

6.8.2.1 Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from the patients immediately 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 adverse event. 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 patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

6.8.3 Collection of cerebrospinal fluid (optional)

If the patient agrees a sample of CSF will be obtained at one time point taken at any time from Cycle 2 day 1 onwards. Samples will be collected, labelled and stored and shipped as detailed in the laboratory manual.

Any residual CSF after PK analysis may be used for exploratory research into factors that may influence development of NSCLC and/or response to AZD9291.

6.9 Biological sampling procedures

6.9.1 Volume of blood

The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data on AZD9291 become available. The estimated total volume of blood that will be drawn from each patient in this study for mandatory samples up to the end of Cycle 2 is; dose escalation 150ml, dose expansion 100ml and dose extension 70ml

Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change.

6.9.2 Handling, storage and destruction of biological samples

The samples will be used up, or disposed of after analyses or retained for further use as described below.

Any pharmacokinetic sample remaining after analysis for AZD9291 and its metabolites may be used for exploratory biomarker analyses. These analyses are for AstraZeneca use only and will not be included in the Clinical Study Report.

Biological samples for future research will be retained at AstraZeneca or it's designee for a maximum of 15 years following the finalisation of the Clinical Study Report. The results from future analysis will not be reported in the Clinical Study Report but separately in a bioanalytical method validation report.

6.9.2.1 Pharmacokinetic samples

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report.

Key samples for metabolite identification and/or analysis will be retained at , on behalf of Drug Metabolism and Pharmacokinetics (DMPK), AstraZeneca for a maximum of one year following the finalisation of the Clinical Study Report. The results from the investigation will not be reported in the Clinical Study Report but separately in a DMPK report.

6.9.2.2 Samples for exploratory research

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual.

Each sample for exploratory research will be identified with the study number and patient enrolment number. In this way exploratory biomarker and genetic data may be correlated with clinical data, samples destroyed in the case of withdrawal of consent and regulatory audit enabled.

Where genetic analysis will be undertaken the processes adopted for the coding and storage of samples will be more stringent in order to maintain patient confidentiality. As an added precaution, irrespective of the type of 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 will be used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff) working with the DNA.

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment code and the DNA number will be maintained and stored in a secure environment, with restricted access within the 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.

6.9.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C of this Clinical Study Protocol 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

All archival tumour samples should be shipped at ambient temperature as per the Laboratory Manual to the AstraZeneca designated central Contract Research Organisation.

6.9.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

6.9.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of voluntarily donated biological samples, then the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research. The patient may continue in the study.

The Principal Investigator:

- Ensures AstraZeneca is notified immediately of the patient's withdrawal of informed consent to the use of donated biological samples
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the document returned to the study site.

6.10 Anti-tumour activity

6.10.1 Tumour assessments

RECIST 1.1 guidelines for measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumour response criteria are presented in Appendix F of this Clinical Study Protocol.

Baseline CT or MRI assessments of chest and abdomen (including liver and adrenal glands) must be performed no more than 28 days before the start of study treatment, and ideally

should be performed as close as possible to the start of study treatment. Additional imaging may be performed based on individual patient signs and symptoms. CT/MRI scan of the brain should be performed in patients with known or suspected brain mestastases.

The methods of assessment used at baseline should be used at each subsequent follow-up assessment. Follow-up assessments should be performed every 6 weeks (± 7 days) after the start of multiple dosing until objective disease progression as defined by RECIST 1.1 even if a patient discontinues treatment prior to progression.

Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits whilst the patient remains on study treatment.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 guidelines for response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion progression will be calculated in comparison to when the tumour burden was at a minimum (i.e. smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment and reassess the patient's status at the next scheduled assessment or sooner if clinically indicated. If repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal disease progression status.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in Section 6.1 and Appendix F, Section 4.1.

All RECIST 1.1 assessment images will be reviewed at site. Duplicates may be collected and stored by an AZ appointed representative, and sent for independent central RECIST 1.1 review, if deemed appropriate.

For the expansion cohort, the independent central RECIST 1.1 review will be conducted on all scans for all patients. Details of the independent central review will be documented in the Independent Review Charter.

7. EVALUATION AND CALCULATION OF VARIABLES AND STATISTICAL METHODS

7.1 Definition of study endpoints

To meet the objectives for this study, data for the following endpoints will be collected:

- Safety and Tolerability (Primary for escalation and expansion)
- AZD9291 pharmacokinetics (and metabolites AZ5104 and AZ7550) (Secondary)
- Pharmacodynamics (Secondary)
- Tumour response including ORR (Primary for extension, secondary for escalation and expansion), DOR, DCR and PFS (Secondary)
- Overall survival (Secondary for extension only)
- Pharmacodynamic markers in EGFRm+ T790M+ tumours at selected clinical doses (Secondary)
- Patient Reported Outcomes (Exploratory)
- Metabolite identification (Exploratory)
- Other biomarker data (Exploratory)
- Pharmacogenetics (Exploratory)
- Diagnostic tumour samples (Exploratory)
- For the extension cohort only, an independent central review (ICR) of the RECIST assessments will be used for the primary analysis of ORR and other RECIST-based outcomes.

Safety endpoints are defined in Section 6.4. Derivations, calculations and analysis plans for each of these endpoints are presented below.

7.2 Determination of sample size

The primary objective of this study is to investigate the safety and tolerability and thereby identify the MTD, if possible, or maximum feasible dose of AZD9291 and to recommend dose(s) for evaluation in future clinical studies. Hence the number of patients in the cohorts has been based on the desire to obtain adequate tolerability, safety and pharmacokinetic and

pharmacodynamic data while exposing as few patients as possible to the investigational product and procedures. Tumour response as measured using RECIST 1.1 will be assessed to provide preliminary anti-tumour activity in a patient population thought most likely to respond to AZD9291.

7.2.1 Dose Escalation Cohorts

For the dose escalation phase of the study, cohorts of 3-6 evaluable patients will be required. The total number of patients will depend upon the number of dose escalations necessary.

7.2.2 Expansion Cohorts

Patients are evaluable for the assessment of response in the expansion cohorts if they were dosed and have a baseline RECIST assessment. In addition, for the purposes of decision making on the expansion cohorts, a patient's T790M status must have also been identified via central testing and match the cohort expansion population under assessment (i.e. T790M+).

7.2.2.1 ≥2nd line and 1st line cohorts

Cohort expansion will be in patients whose NSCLC has progressed following therapy with an EGFR TKI agent and whose tumour status is T790M+. Data from these cohorts will provide a preliminary assessment of anti-tumour activity based on ORR (providing an acceptable false-negative risk of concluding that there is no activity if the true response rate is at least 30%).

A conclusion of no evidence of activity will be reached if no objective RECIST responses (confirmed PR or CR) are observed. If the true response rate is ≥30%, the chance of observing no responses in 30 evaluable patients is <1%.

In the case that anti tumour activity, in the form of responses, is observed, 30 evaluable patients will provide reasonable confidence of estimating what the true response rate would be in this population as well as in the ≥2nd line T790M- population and a 1st line population of EGFR TKI treatment-naive patients with EGFRm+ advanced NSCLC. Confidence intervals will be constructed (using the Clopper-Pearson interval) around the response rates observed in each population to enable decisions to be made about the likely success of future studies in each of the populations. For example:

- 17% ORR (5/30 responses); 80% CI [8%, 29%]
- 30% ORR (9/30 responses); 80% CI [19%, 43%]
- 50% ORR (15/30 responses); 80% CI [37%, 63%]
- 70% ORR (21/30 responses); 80% CI [57%, 81%]

In the event that there is little evidence of anti tumour activity being observed within the cohort expansions, individual cohorts may be closed prior to 30 evaluable patients being recruited. This will avoid exposing patients to a potentially ineffective therapy, providing the evidence of no anti tumour activity is strong enough at that time. For example, if 8 evaluable

patients are recruited to a cohort, and no responses are observed, it may be appropriate to conclude no evidence of activity because if the true response was ≥30%, the chance of observing no responses in 8 evaluable patients is <6%.

If an individual cohort expansion is terminated prior to the full 30 evaluable patients being recruited, other cohorts within the expansion will still be able to complete recruitment as planned if it is deemed appropriate to do so. Any such decision will be at the discretion of AstraZeneca.

7.2.3 Paired Biopsy Cohort

Patients are evaluable for the paired biopsy cohort if they have provided at a minimum the pre-study tumour biopsy and one tumour biopsy on study treatment. The number of patients has been based on the desire to obtain adequate data whilst exposing as few patients as possible to the study procedures.

There are currently no data available, which adequately characterise or describe the variability of the biomarkers of interest in this subject population, thus the sample size cannot be calculated with consideration to statistical power. Data from 12 evaluable subjects is considered to be adequate to allow a preliminary investigation of the objectives of this study (Julious 2005).

7.2.4 Phase II Extension Cohort

The primary endpoint of the extension phase is ORR. The extension will recruit approximately 175 patients with T790M mutation positive advanced NSCLC, whose disease has progressed following either one prior therapy with an EGFR-TKI (chemotherapy-naïve, n=50) or following treatment with both EGFR-TKI and other anti-cancer therapy (n=125). With 175 patients the precision of the estimation of ORR in the overall study population will be within +/-8% (e.g. ORR 40%, 95% CI 33.0%, 47.4%). The precision of the estimation of ORR will be within +/-13% in the 50 patient cohort who have only received previous TKI treatment and within +/-9% in the 125 patient cohort who have received previous TKI treatment and other anti-cancer therapy. The study will also provide an adequate number of patients in which to assess the safety and tolerability of AZD9291; if zero events are observed in the 175 patients, there is 95% confidence that the true event rate is less than 2.2%.

7.3 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs, ECG changes. These will be collected for all patients. Appropriate summaries of these data will be presented as described in Section 7.9.

ECG Changes

QTc will be calculated by AstraZeneca using both Bazett's and Fridericia's formulae.

Creatinine Clearance

Estimated creatinine clearance will be calculated using the Cockcroft and Gault formula.

7.3.1 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation of investigational product. Based on the expert's judgement, adverse events of particular clinical importance may, after consultation with the Global Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the Clinical Study Report. A similar review of laboratory values, vital signs, ECGs and other safety assessments will be performed for identification of other significant adverse events.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

7.4 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analysis of the plasma concentration data for AZD9291 and its metabolites will be performed by

The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard non-compartmental methods.

Where possible the following PK parameters will be determined for AZD9291.

Following the single dose part (or first dose) of the study:

Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal rate constant (λ_z), terminal half life ($t_{½\lambda z}$), area under the plasma concentration-time curve from zero to 24 hours ($AUC_{(0\text{-}24)}$), from zero to the time of the last measurable concentration ($AUC_{(0\text{-}t)}$) and from zero to infinity (AUC), apparent plasma clearance (CL/F), apparent volume of distribution, mean residence time (MRT).

Following the multiple dose part of the study:

Maximum plasma concentration at steady state ($C_{ss\ max}$), time to $C_{ss\ max}$ ($t_{ss\ max}$), minimum plasma concentration at steady state ($C_{ss\ min}$), area under the plasma concentration-time curve from zero to the end of the dosing interval (AUC_{ss}), apparent plasma clearance at steady state (CL_{ss}/F), extent of accumulation on multiple dosing (R_{AC}), time dependency of the pharmacokinetics.

The maximum plasma concentration (C_{max}), the C_{max} at steady state ($C_{ss\ max}$), the time of maximum concentration (t_{max}) and the t_{max} at steady state ($t_{ss\ max}$) will be determined by inspection of the concentration-time profiles. Where possible the terminal elimination rate constant (λ_z) will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data and the terminal half-life ($t_{½\lambda z}$) will be calculated as $\ln 2/\lambda_z$. The area under the concentration-time curve up to the last quantifiable sample ($AUC_{(0\text{-}t)}$) and the area under the concentration-time curve up to 24 hours ($AUC_{(0\text{-}24)}$) will be calculated using the linear trapezoidal rule. Where appropriate, the $AUC_{(0\text{-}}$

$_{t)}$ will be extrapolated to infinity using λ_z to obtain AUC. The area under the concentration-time curve across the dosing interval, AUC_{ss} will be calculated using the linear trapezoidal rule. The apparent clearance (CL/F following the single dose and CL_{ss}/F following multiple dosing) will be determined from the ratio of dose/AUC or dose/AUC_{ss}. The volume of distribution (V_{ss}/F or V_z/F) will be determined from the mean residence time (MRT) x CL/F and/or the accumulation ratio (R_{AC}) will be calculated as the ratio of the $AUC_{(0-24)}$ on Day 15 and Day 1. The time dependency of the pharmacokinetics on multiple dosing will be assessed by the calculation of the ratio of $AUC_{(0-24)}$ Day 15/AUC Day 1.

Where possible the appropriate pharmacokinetic parameters will also be determined for the metabolites of AZD9291.

7.5 Calculation or derivation of pharmacodynamic variables

7.5.1 Population analysis of pharmacokinetic/pharmacodynamic variables

The plasma concentration data for AZD9291 (and the metabolites AZ5104 and AZ7550) will be analysed using a population pharmacokinetic approach, which may include exploring the influence of covariates on PK, if the data allows. A population pharmacodynamic approach will be used to investigate the relationship between PK and selected primary, secondary and/or exploratory endpoints, where deemed appropriate. Results may be reported separately from the Clinical Study Report for the main study.

The pharmacokinetic, pharmacodynamic, demographic, safety and tumour response data collected in this study may also be combined with similar data from other studies and explored using population pharmacokinetic and/or pharmacokinetic-pharmacodynamic methods. The results of any such analyses will be reported separately from the Clinical Study Report.

7.6 Calculation or derivation of exploratory research variables

Results from the exploratory biomarker and pharmacogenetic research, and PROs may be reported separately from the Clinical Study Report for the main study.

7.7 Calculation or derivation of tumour response variables

For the investigator's assessment, at each visit patients will be programmatically assigned a RECIST visit response of CR, PR, SD or PD depending on the status of their disease compared to baseline and previous assessments.

Progression of TLs will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If a patient has had a tumour assessment, which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) unless there is evidence of progression in which case the response will be assigned as PD.

For TL measurements, if ≤ 1/3 of the TL sizes are missing then a scaling up rule will be applied as follows:

- If ≤ 1/3 of lesions recorded at baseline are missing then the results will be scaled up (based on the nadir sizes) to give an estimated sum of diameters and this will be used in calculations (this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions that are missing and determining at what rate the lesions are changing)

- If > 1/3 of lesions recorded at baseline are missing then the TL response will be NE. However, if the sum of non-missing TL diameters would result in PD (ie, if using a value of 0 for missing lesions the sum of diameters has still increased by 20% or more compared to the smallest sum of diameters on study, with an absolute increase of ≥5mm), PD takes precedence over NE

- A visit response of CR will not be allowed if any of the TL data is missing

For endpoints assessed by Independent Central Review, review of all radiological imaging data will be carried out using RECIST version 1.1. All radiological scans for all patients (including those at unscheduled visits, or outside visit windows), will be provided to the ICR. Prior radiotherapy and biopsied lesion reports for patients (at baseline) will also be provided to the ICR to allow the selection of appropriate target lesions. The imaging scans will be reviewed by two independent radiologists, using RECIST 1.1 criteria and will be adjudicated if required. For each patient, the ICR will define the overall visit response data (CR, PR, SD, PD or NE) and the relevent scan dates for each time point (i.e. for visits where response or progression is/is not identified).

7.7.1 Objective response

Objective response rate is defined as the percentage of patients who have at least one confirmed response of CR or PR prior to any evidence of progression (as defined by RECIST 1.1).

A visit response of CR is defined when all TL and NTL lesions present at baseline have disappeared (with the exception of lymph nodes which must be <10mm to be considered non-pathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions. A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits.

In the case of stable disease, measurements should have met the stable disease criteria for a minumum interval of 5 weeks (6 weeks minus the 7-day visit window) following the start of treatment.

When the investigator is in doubt as to whether progression of disease has occurred and therefore reassesses the patient at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

For the extension cohort, ORR rate is defined as the number (%) of subjects with measurable disease with at least one visit response of CR or PR that is confirmed at least 4 weeks later (according to ICR for the primary analysis). Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, any complete response or partial response which occurred after a further anti-cancer therapy was received will not be included in numerator of the ORR calculation.

7.7.2 Progression Free Survival

PFS is defined as the time from date of first dosing until the date of objective disease progression as defined by RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the subject withdraws from AZD9291 therapy or receives another anti-cancer therapy prior to progression.

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. If the patient has no evaluable visits or does not have baseline data they will be censored at 0 days unless they die within two visits of baseline.

If a patient discontinues treatment prior to progression and/or receives a subsequent therapy prior to progression then these patients will continue to be followed until evidence of objective disease progression as defined by RECIST 1.1 and their PFS time will be derived as defined above.

Note: Symptomatic deterioration will not be regarded as a progression event.

7.7.3 Duration of Response

Duration of response will be defined as the time from the date of first documented response**,** (that is subsequently confirmed (as defined in Section 7.7.2)) until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

If a subject does not progress following a response, then their duration of response will use the PFS censoring time.

7.7.3.1 Disease control rate

Disease control rate is defined as the proportion of patients with a best overall response of CR, PR or SD.

7.7.4 Change in tumour size

Tumour size is defined as the sum of the lengths of the longest diameters of the RECIST 1.1 target lesions. Percentage change in tumour size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of TLs compared to baseline.

For further details see Appendix F of this Clinical Study Protocol.

7.7.5 Overall Survival

Overall survival will be assessed based on the date of first dose and survival status at the time of analysis.

Overall survival is defined as the interval between the date of first dose and the date of patient death due to any cause. Patients who have not died at the time of the statistical analysis will be censored at the time they were last known to be alive.

7.7.6 Tumour Response by independent central review

For the independent central review, the same RECIST 1.1 definitions will be applied, and programmatic details will be detailed in the Independent Review Charter.

7.8 Description of analysis sets

The analysis of data will be based on different subsets according to the purpose of the analysis. Throughout the safety results sections, erroneously treated patients (eg, those assigned to receive dose A who actually received dose B, those who failed to meet the selection criteria) will be accounted for in the actual dose group received.

Analysis sets are presented in Table 7

Table 7 Analysis sets

Analysis Set	Definition
Safety	All patients who received at least 1 dose of AZD9291.
Pharmacokinetics	Dosed patients who have at least 1 measurable plasma concentration collected post-dose.
Evaluable for response	Dosed patients with a baseline RECIST assessment.
Exploratory biomarkers	All patients that participate in the exploratory biomarker research

Analysis Set	Definition
Paired biopsy	Dosed patients with a pre-study tumour biopsy and one tumour biopsy on study treatment

7.9 Methods of statistical analysis

The statistical analyses will be performed by or other designated third party providers, under the direction of the .

With the exception of some safety and PK summaries that may be combined, data from the dose escalation and the dose expansion cohorts will be presented separately. Data from the extension cohort will always be presented separately. Summaries from the extension cohort will be presented as a cohort and by previous treatment cohort (TKI only or TKI plus additional treatments).

The intent of all efficacy analyses from the expansion phase is that it be focussed on the population whose tumour T790M mutation status is identified via central testing. Patients central test results must match the cohort expansion group to which they were assigned (i.e. T790M+ in the 1st expansion). However, concordance between local and central testing of T790M status will be reviewed, and if deemed appropriate summaries incorporating local testing status may be produced. All summaries will present data by dose group.

Demographic data

Characteristics of the patients, including medical history and disease characteristics at baseline will be listed for each patient and summarised by dose group.

Reasons for discontinuation of investigational product will be listed including the study day of treatment discontinuation and will be summarised by dose group.

Exposure

Exposure to investigational product ie, total amount of study drug received will be listed for all patients.

Total exposure and total time on study (date of last dose minus date of first dose) will be summarised by the following: mean, standard deviation, minimum, maximum, median and number of observations. In addition, the number and percentage of patients with at least one dose interruption/dose delay and at least one dose reduction will be presented separately for the initial period defined as 21 days of multiple dosing (cycle 1) and for any time following this initial period of the study.

Safety

Safety data will not be formally analysed. All patients who receive at least one dose of AZD9291 will be included in the assessment of the safety profile (safety analysis set). At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

Data from all cycles of initial treatment will be combined in the presentation of safety data. AEs will be listed individually by patient and dose group. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group. The number of patients experiencing each AE will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade. The number and percentage of patients with adverse events in different categories (eg, causally related, CTCAE grade $\geq$3 etc) will be summarised by dose group, and events in each category will be further summarised by MedDRA system organ class and preferred term, by dose group. SAEs will be summarised separately if a sufficient number occur.

Any AE occurring before the first dose of investigational product (ie, before study Day 1) will be included in the data listings but will not be included in the summary tables of adverse events.

Any AE occurring within the defined 28 day follow-up period after discontinuation of investigational product will be included in the AE summaries. Any adverse events in this period that occur after a patient has received further therapy for cancer (following discontinuation of investigational product) will be flagged in the data listings. AEs occurring after the 28 day follow-up period after discontinuation of investigational product will be listed separately, but not included in the summaries.

Haematology, clinical chemistry, vital signs, ECG data, ophthalmic examination data, demographic data and concomitant medications will be listed individually by patient and suitably summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations will be used.

Details of any deaths will be listed for all patients.

Any qualitative assessments will be summarised for all patients using the number of patients with results of negative, trace or positive.

Graphical presentations of safety data will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared to baseline.

Pharmacokinetics

Plasma concentrations of AZD9291, AZ5104 and AZ7550 will be summarised by nominal sample time. Plasma concentrations and derived PK parameters will be summarised by dose level. Parameters following single and multiple dosing will be summarised separately. Plasma concentrations at each time point will be summarised according to dose by the following summary statistics:

- The geometric mean (gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (CV, calculated as 100 √ [exp(s^2)-1], where s is the standard deviation of the data on a log scale)
- Gmean ± standard deviation (calculated as exp[μ±s])
- Arithmetic mean calculated using untransformed data
- Standard Deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for AUC, $AUC_{(0-24)}$, $AUC_{(0-t)}$, AUC_{ss}, C_{max}, $C_{ss\ max}$ and $C_{ss\ min}$:

- Gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- CV, calculated as 100 √ [exp(s^2)-1], where s is the standard deviation of the data on a log scale)
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for CL/F, CL_{ss}/F, volume of distribution, $t_{½\lambda z}$, $R_{AC,}$ time dependency:

- Arithmetic mean
- Standard deviation
- Minimum
- Maximum
- Number of observation

The following summary statistics will be presented for t_{max} and $t_{max\ ss}$:

- Median
- Minimum
- Maximum
- Number of observations

The pharmacokinetic data for AZD9291, AZ5104 and AZ7550 after a single-dose and separately, at steady state will also be displayed graphically. Displays will include plasma concentration patient profiles (on the linear and log-scale) versus time and gmean concentration (+/-standard deviation) versus time, stratified by dose.

Scatter plots of PK parameters versus dose, or log-dose will also be considered following both single and multiple dose administration of AZD9291 to assess dose proportionality.

In a preliminary assessment of dose proportionality, log-transformed AUC and C_{max} parameter estimates will be examined using the Power Model:

$$\text{parameter} = e^{a} (\text{dose})^{b}$$

$$\text{ie,} \quad \log(\text{parameter}) = a + (b * \log(\text{dose}))$$

where a is the intercept, depending on patients, and b is the slope, measuring the extent of dose proportionality. Dose proportionality implies that $\beta=1$ and will be assessed by estimating β along with its confidence interval.

If there is evidence of departures from dose proportionality, log-transformed dose-normalised AUC and C_{max}, of AZD9291 will be analysed separately using a mixed effects model. Dose will be fitted as a fixed effect and patient as a random effect. Point estimates and associated 90% confidence intervals for the differences between each dose level and the reference dose (the lowest dose) will be constructed using the residual variance. The estimates will then be back-transformed to provide point estimates and corresponding 90% confidence intervals for the ratios of each dose level to the reference dose on the original scale. No adjustments for

pre-planned multiple comparisons will be made. This analysis will only be performed provided there are sufficient data.

Pharmacodynamics

The pharmacodynamic effects of AZD9291 will be evaluated in tumour tissue from paired biopsies (A tumour biopsy pre-dose and a paired tumour biopsy post-dose). The biomarkers investigated may include, but are not limited to pEGFR, pERK, pAKT, pS6, pGSK3b, p4EBP1, cleaved caspase 3 and Ki67. The technological platform for the pharmacodynamic analysis will be immunohistochemistry, but may not be limited to this.

Exploratory biomarker research and pharmacogenetics

The number of patients that will agree to participate in the exploratory biomarker and genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated.

Patient Reports Outcomes

Analyses on the EORTC QLQ C-30 and QLQ-LC13 will be based on the instruments' scoring manual.

Tumour response

The analysis population for objective tumour response rate will be the "evaluable for response" population.

For the escalation cohorts, summaries of tumour response data will be by dose.

For the expansion cohorts, the summaries will be by dose and centrally confirmed T790M status (positive, negative, unknown). First line cohort(s) will be summarised separately to pre-treated cohorts. A sensitivity analysis may be performed using local T790M status for patients whose central T790M status is not available.

For the extension cohort, all summaries will be presented as a cohort and by previous treatment cohort (TKI only or TKI plus additional treatments).. For the primary objective all RECIST outcomes will be based on the independent central review, and ORR will be summarised for the patients who have measurable disease at baseline as defined by ICR.

Tumour response data will be listed and summarised by dose group,and if appropriate using the following response categories: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) and Non-Evaluable (NE).

Objective tumour response rates will be presented together with 80% and 95% confidence intervals (calculated using the Clopper-Pearson interval), where appropriate.

Duration of response

For the expansion and extension cohorts duration of response in responding patients will be summarised and the number (%) of responding patients with a duration of response >3; >6; >9; >12 months will be presented. A Kaplan Meier plot and median duration of response with 95% CI (calculated from the Kaplan Meier plot) will be presented. DCR will be summarised with 95% confidence intervals.

Progression free survival and overall survival

The analysis population for progression free survival and overall survival will be the safety population.

PFS will be summarised for the expansion phase and the extension phase. OS will be summarised for the extension phase only.

PFS and OS will be displayed using Kaplan Meier plots. The number of events, median (calculated from the Kaplan Meier plot), and proportion of patients without an event at 6, 12 and 18 months will be summarised.

As appropriate, summaries of the number and percentage of patients who have died, are still in survival follow-up, are lost to follow-up and have withdrawn consent will be presented.

Sensitivity analysis:

The same methods of analysis will be applied to analyse ORR, DoR, DCR, tumour shrinkage and PFS based on the RECIST data assessed by the Investigator

Change in tumour size

The analysis population for change in tumour size will be the “evaluable for response” population who have measurable disease at baseline per RECIST 1.1 criteria

Summaries and waterfall plots (bar charts) indicating percentage change from baseline in the sum of the diameters of target lesions at week 6 may be produced, if appropriate, depending on how much data is obtained in patients with measurable disease at baseline. If there is only limited data then percentage change in tumour size will be listed only.

8. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

8.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes a SAE and is to be reported as such, see Section 6.4.4**

In the case of a medical emergency the investigator may contact the Study Team Physician. If the Study Team Physician is not available, contact the Study Leader at AstraZeneca Research and Development.

Name	Role in the study	Address & telephone number
	Study Team Physician responsible for the protocol at central R&D site	
	Study Leader responsible for the protocol at central R&D site	
	24-hour emergency cover at central R&D site.	

8.2 Overdose

There are no data on overdosing since this is the first study in humans with AZD9291. There is no definition of what constitutes an overdose. There is no known antidote. Investigators will be advised that any patient who receives a higher dose than that 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/SAEs is recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the CRF and on the overdose CRF module.
- An overdose with no associated symptoms is only reported on the overdose CRF module.

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

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

For overdoses associated with a SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 28 days.

8.3 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to AstraZeneca using the appropriate forms.

8.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product 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 a pregnancy should be followed up and documented even if the patient was withdrawn from the study.

If a pregnancy occurs during exposure to investigational product or in the 28 days after discontinuing investigational product, then investigators 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 within 1 or 5 days for SAEs, (see Section 6.4.4) and within 28 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.3.2 Paternal exposure

Pregnancy of a patient's partner is not considered to be an adverse event. However, any conception occurring from the date of dosing until 16 weeks after dosing should be reported to AstraZeneca and followed up for its outcome.

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Clinical Study Protocol Appendix B

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Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

Clinical Study Protocol Appendix C

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories (http://www.iata.org/whatwedo/cargo/dgr/Documents/DGR52_InfectiousSubstances(DGR362).pdf). For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- **http://www.iata.org/whatwedo/cargo/dgr/Documents/DGR52_PI650_EN.pdf**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

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Clinical Study Protocol Appendix D

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Appendix D
Ethical and Regulatory Requirements

1. ETHICAL AND REGULATORY REQUIREMENTS

1.1 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 the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

The applicable regulatory requirements in Japan are 'Good Clinical Practice for Trials on Drugs (MHLW Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications.

1.2 Ethics and regulatory review

An Ethics Committee should approve the final Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. This will include approval of the exploratory biomarker and pharmacogenetic research and associated consents forms. The investigator/ The Head of the study site will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study. If applicable this approval should clearly state that the exploratory biomarker and pharmacogenetic research is approved. In Japan, the Head of the study site should submit a notification of direction/determination as well as a copy of the Institutional Review Board (IRB) written approval to AstraZeneca. A valid contract between the study site and AstraZeneca Japan should be signed before the investigator can enrol any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

In Japan, the protocol should be re-approved by the IRB annually. The Principal Investigator should submit progress reports to the IRB via the Head of the study site at the time of the protocol re-approval.

Before enrolment of any patient into the study, the final Clinical Study Protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the Ethics Committees/Institutional Review Board (IRB) 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 Principal Investigator so that he/she can meet these reporting requirements.

1.3 Informed consent

Any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation should be described in the informed consent form that is approved by an Ethics Committee.

The Principal Investigator at each centre will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study and the optional exploratory biomarker and genetic research components
- Ensure that each patient is notified that they are free to withdraw from the study or the research components 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 each original, signed Informed Consent Form is stored in the Investigator's Study File/medical records
- Ensure a copy of each signed Informed Consent Form is given to the patient

The exploratory biomarker and genetic research components of this study are voluntary and the patient may participate in the main study without participating in the exploratory biomarker and/or genetic research parts of the study. To participate in the exploratory biomarker and/or genetic component of the study the patient should sign and date the consent form for the main study and as applicable separate consent forms for the exploratory biomarker and/or the genetic components of the study.

In Japan, if any new information on the study medication becomes available which may influence the decision of the patient to continue the study, the investigator(s) should inform

the patient of such information immediately, record this in a written form, and confirm with the patient if he or she wishes to continue participation in the study. In addition, if the investigator(s) deem it necessary to revise the Informed Consent Form, they should revise it immediately. The investigator(s) should re-explain the information to the patients using the updated Informed Consent Form even though the patients have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.

1.4 Changes to the protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

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

The amendment should be approved by each Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for Revised Protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator. For distribution to Ethics Committee see Section 1.2.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee should approve the revised Informed Consent Form before the revised form is used.

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

1.5 Audits and inspections

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

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Clinical Study Protocol Appendix E

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Appendix E
Data and Study Management

1. DATA AND STUDY MANAGEMENT

1.1 Patient data protection

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

Due to the exploratory nature of the biomarker and genetic research, there will be no routine communication of these results to patients. AstraZeneca will not provide individual 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.

Extra 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.

1.2 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator

1.3 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will visit the study site to review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also to train them in any study specific procedures including collection of samples and the WBDC system utilised. The additional requirements for the collection of the patients' samples for the exploratory biomarker and genetic research will also be clarified.

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

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

1.4 Source data

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

1.5 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study sites, 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 including the specific requirements of the biomarker and genetic research, that data are being accurately and timely recorded in the CRFs, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of the Informed Consent Form(s)of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- If applicable, 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 centre needs information and advice about the study conduct.

1.6 Data management by AstraZeneca

Data management will be performed by the AstraZeneca Data Management Centre.

Data entered in the WBDC system or data captured electronically will be immediately saved to the applicable database and changes tracked to provide an audit trail.

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 the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

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 Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment-revealing data may thereafter be added and the final database will be locked.

Genotype data generated in this study will be stored in the AstraZeneca genotyping Laboratory Information Management System (LIMS) database, or other appropriate secure system, separate from the database used for the main study.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database. The results from this genetic research will be reported separately from the Clinical Study Report for the main study.

1.7 Study agreements

The Principal Investigator at each centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, the terms of the Clinical study Agreement shall prevail.

Specific reference to requirements relating to this optional biomarker and genetic research will be included in the study agreement(s).

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

1.7.1 Archiving of study documents

The investigator follows the principles outlined in the Clinical Study Agreement.

1.8 End of study

The end of the study is defined as the last visit of the last patient undergoing the study plus 28-days safety follow-up.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca

may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD9291.

Discontinuation or suspension of the whole study programme (Japan)

If AstraZeneca decides to prematurely terminate or suspend the study, the Principal Investigator, Sub-Investigator, the Head of the institution and regulatory authorities should receive written notification of the reasons for the premature termination or suspension.

The Principal Investigator/Sub-Investigator will immediately notify the decision to the patients, give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

Completion of the study (Japan)

Upon terminating the study, the Principal Investigator/Sub-Investigator will report in writing the completion of the study as well as the summary of the results to the Head of the study site in accordance with the institution's rules. The Head of the study site who is informed of the termination by the investigator will provide a written notification of the results to the Institutional Review Board and AstraZeneca.

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Clinical Study Protocol Appendix F

Drug Substance	AZD9291
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Appendix F
Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumours)

1. INTRODUCTION

This appendix details the implementation of RECIST (Response Evaluation Criteria in Solid Tumours) 1.1 guidelines (Eisenhauer et al 2009)for the study with regards to investigator assessment of tumour burden including protocol-specific requirements for this study.

2. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Patients with at least one lesion measurable that can be accurately assessed at baseline by computerised tomography (CT), magnetic resonance imaging (MRI) or plain X-ray should be included in this study.

Measurable lesions

At least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10mm in the longest diameter (except lymph nodes which must have short access ≥ 15mm) with computered tomograpghy (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements.

Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis at baseline. Nodes with < 10 mm short axis are considered non-pathological and should not be recorded as non-target lesions (NTLs)

- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by CT or MRI

- Previously irradiated lesions as localised post-radiation changes, which affect lesion sizes, may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and should be selected as NTLs at baseline and followed up as part of the NTL assessment

- Skin lesions assessed by clinical examination

- Brain metastasis

Special cases

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these non-cystic lesions should be selected as the target lesions (TLs).

Target lesions

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline.

Non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline.

3. METHODS OF MEASUREMENT

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up.

The methods to be used for RECIST assessment are summarised in Table 1 and those excluded for tumour assessments in this study are discussed below, with the rationale provided.

Table 1 Summary of Methods of Assessment

Target Lesions	Non target lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, chest X-ray	X-ray, chest X-ray
		Ultrasound
		Bone scan
		FDG-PET

3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TLs selected for response assessment and to assess NTLs and identification of new lesions.

In this study it is recommended that CT examinations of the chest and abdomen will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For assessment of brain lesions MRI is the preferred method.

3.2 Clinical examination

Clinical examination will not be used for assessment of TLs. Clinically detected lesions can be selected as TLs if they are then assessed by CT or MRI scans. Clinical examination can be used to assess NTLs in patients that also have other lesions assessable by CT, MRI or plain Xray and to identify the presence of new lesions.

3.3 X-rays

3.3.1 Plain X-ray

Plain X-rays may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

3.3.2 Chest X-ray

Chest X-rays will not be used for assessment of TLs as they will be assessed by CT or MRI examination. Chest X-rays can, however, be used to assess NTLs and to identify the presence of new lesions.

3.4 Ultrasound

Ultrasound examination will not be used for assessment of TLs and NTLs as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour measurements.

3.6 Tumour markers

Tumour markers will not be used for tumour response assessments per RECIST 1.1.

3.7 Cytology and histology

Histology will not be used as part of the tumour response assessment per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or the appearance of a clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTLs or disease progression due to new lesions.

3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTLs and followed by the same method as per baseline assessment.

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

3.9 FDG-PET scan

FDG-PET (fluorodeoxyglucose positron emission tomography) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake (defined as when an uptake greater than twice that of the surrounding tissue is observed) not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

CT examinations of the chest and abdomen (including liver adrenal glands) will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous contract media administration is the preferred method. MRI should be used where CT is no feasible or it is medically contra-indicated.

Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. Follow-up assessments should be performed every 6 weeks (± 7 days) after the start of treatment until discontinuation of study treatment or withdrawal of consent. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments as their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at different frequency than other patients.

4.2 Target lesions

4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved, should be identified as TLs at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions) but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimetres. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts

- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s)
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion
- When a TL has had any intervention eg, radiotherapy, embolisation, surgery etc, during the study, the size of the TL should still be provided where possible

4.2.2 Evaluation of target lesions

Table 2 provides the definitions of the criteria used to determine objective tumour visit response for TLs.

Table 2 Overall Visit Response for Target Lesions

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response

4.3 Non-Target lesions

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be

recorded by the investigator. Table 3 provides the definitions of the criteria used to determine and record overall response for NTLs at the investigational site at each visit.

Table 3 Overall Visit Response for Non-Target Lesions

Complete Response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more NTLs.
Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST clinically significant for the physician to consider changing or stopping therapy.
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and in the investigator's opinion they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

4.4 New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of study treatment without objective evidence of disease progression at that time should continue to undergo RECIST 1.1 assessments according to the clinical study protocol until objective disease progression is observed.

4.6 Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table 4.

Table 4 Overall Visit Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non-CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non CR/Non PD	No	SD (Non CR/non PD)
NE	Non-PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease
IR = incomplete response, NE = not evaluable, NA = not applicable (relevant when no NTLs at baseline)

5. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies. The use of standardised protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

5.1 CT Scan

CT scans of chest and abdomen (including liver and adrenal glands) should be contiguous throughout all the anatomical regions of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

Anatomic coverage

Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

Intravenous contrast administration

Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of intravenous contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvic MRI with contrast. If MRI cannot be performed then CT without intravenous contrast is an option for the thorax, abdomen and pelvic examinations. For assessment of brain lesions MRI is the preferred method.

Slice thickness and reconstruction material

It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for the measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TLs should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

5.2 MRI Scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

5.3 FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

5.3.1 PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

6. REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer. 45 (2009) 228-247.

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Clinical Study Protocol Appendix G	
Drug Substance	AZD9291
Study Code	D5160C00001
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Appendix G
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

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1. INTRODUCTION

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

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

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

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥ 3x ULN **and** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

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

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

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

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

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

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

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

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

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

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

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

The instructions in this Section should be followed for all cases where PHL criteria are met.

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

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

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

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

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

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

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

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

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

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

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

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

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

This section is applicable to patients who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being, even if there has been no significant change the patient's condition[#] compared with pre-study treatment visits, the Investigator will:

- Notify the AstraZeneca representative who will inform the central Study Team.
- Follow the subsequent process described is Section 4.2 of this Appendix.

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

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

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

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

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

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

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

If Yes:

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

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

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

8. REFERENCES

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

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

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Clinical Study Protocol Appendix H	
Drug Substance	AZD9291
Study Code	D5160C00001
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Appendix H
Guidance regarding Potential Interactions With Concomitant Medications

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GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

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

AZD9291 is an investigational drug for which no data on in vivo interactions are currently available. Based on in vitro data and predicted clinical exposure data, AZD9291 is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have shown that the principal CYP enzymes responsible for the Phase I metabolism of AZD9291 are CYP2C8 and CYP 3A4.

1. DRUGS INHIBITING CYP3A4 OR CYP2C8 METABOLISM THAT ASTRAZENECA STRONGLY RECOMMEND ARE NOT COMBINED WITH AZD9291

The contribution of Phase I metabolism to the total clearance of AZD9291 is currently unknown but, to ensure patient safety, the following potent inhibitors of CYP2C8 and CYP3A4 must not be used during this study for any patient receiving AZD9291.

Table 1 Drugs inhibiting CYP3A4 or CYP2C8

Contraindicated drugs	Withdrawal period prior to AZD9291 start
Clarithromycin, telithromycin, troleandomycin	1 week
Gemfibrozil	
Indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, telaprevir	
Itraconazole, ketoconazole, posaconazole, voriconazole	
Mibefradil	
Nefadozone	

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 or CYP2C8 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

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

Table 2 Drugs inducing CYP3A4

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

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

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

Table 3 Exposure, pharmacological action and toxicity may be increased by AZD9291

Warning of possible interaction	Advice
Alfentanil	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD9291.
Amodiaquine	
Repaglinide	
Sirolimus	
Tacrolimus	
Torsemide	
All statins	

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between these agents and AZD9291; *in vitro* data suggests AZD9291 has the potential to cause drug interactions at the intestinal level through CYP3A4, it has also been shown to be an inhibitor of CYP2C8, and a weak inhibitor of $OATP_{1B1}$. The potential for AZD9291 to inhibit other transporter systems is currently unknown. This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to depend on CYP3A4**,** CYP2C8 and/or transporter proteins for metabolism. Appropriate medical judgement is required. Please contact AstraZeneca with any queries you have on this issue

4. DRUGS THAT MAY PROLONG QT INTERVAL

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

4.1 Drugs known to prolong QT interval

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

Table 4 Drugs prolonging QT interval

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

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

4.2 Drugs that may possibly prolong QT interval

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

Table 5 Drugs that may prolong QT interval

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

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Clinical Study Protocol Appendix I	
Drug Substance	AZD9291
Study Code	D5160C00001
Edition Number	1
Date	

Appendix I
Patient Reported Outcomes (LC13)

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

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Clinical Study Protocol Appendix J	
Drug Substance	AZD9291
Study Code	D5160C00001
Edition Number	1
Date	

Appendix J
Patient Reported Outcomes (QLQ-C30)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌊_⌊_⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1 2	3		4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1 2	3		4
27. Has your physical condition or medical treatment interfered with your social activities?	1 2	3		4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

Clinical Study Protocol Amendment

Amendment Number	4
Drug Substance	AZD9291
Study Code	D5160C00001
Date	
Protocol Dated	

A Phase I/II, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumour Activity of Ascending Doses of AZD9291 in Patients with Advanced Non Small Cell Lung Cancer who have Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent (AURA)

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Centres affected by the Amendment:

All participating sites

The protocol for the study is to be amended as follows:

Original text ~~Removed text~~ *Amended text* **Added text**

Section of protocol affected:

Title page

Previous text:

Principal Investigator(s)

Revised text:

Section of protocol affected:

4.3 Restrictions

Previous text:

1. Females of child-bearing potential should use reliable methods of contraception from the time of screening until 3 months after discontinuing study treatment. Acceptable methods of contraception include abstinence, tubal ligation, ~~oral or transdermal contraceptives~~, 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.

Revised text:

1. Females of child-bearing potential should use reliable methods of contraception from the time of screening until 3 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.

Section of protocol affected:

4.3.1 Concomitant treatments

Previous text:

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 Case Report Form (CRF). After permanent discontinuation of AZD9291 and 28 day follow up, only subsequent regimens of anti-cancer therapy will be recorded in CRF. If medically feasible, patients taking regular medication, with the exception of potent inhibitors or inducers of CYP3A4 and inhibitors of CYP2C8 (see Section 4.2 exclusion 1, and Appendix H), should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon ~~intestinal~~ CYP3A4 ~~and/or transporter proteins and/or~~ CYP2C8 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. Guidance on medications that require close monitoring is given in Appendix H.

Revised text:

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 Case Report Form (CRF). After permanent discontinuation of AZD9291 and 28 day follow up, only subsequent regimens of anti-cancer therapy will be recorded in CRF. If medically feasible, patients taking regular medication, with the exception of potent inhibitors or inducers of CYP3A4 and inhibitors of CYP2C8 (see Section 4.2 exclusion 1, and Appendix H), should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon CYP3A4, CYP2C8 **or BCRP** and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving AZD9291. **Patients taking concomitant medications whose disposition is dependent upon CYP3A4, CYP1A2, CYP2C or p-glycoprotein 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.** Guidance on medications that require close monitoring is given in Appendix H.

Up to 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 (LDL) cholesterol levels is advised. If the patient experiences any potentially relevant adverse events 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 (CK) levels should be checked, and any appropriate further management should be taken.

Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR.

Section of protocol affected:

6.5.2 Administration of PROs

Previous text:

Questionnaires will be administered using paper questionnaires. The patient should complete the questionnaires at the scheduled clinic visit at screening, and every 6 weeks relative to the first dose of multiple dosing, discontinuation and progression as specified in the study plan (Table 2, Table 3 and Table 4). The patient should also complete a questionnaire progression. If any scheduled PRO assessment is not completed the reason for non-completion should be recorded.

Revised text:

Questionnaires will be administered using paper questionnaires. The patient should complete the questionnaires at the scheduled clinic visit at screening, **baseline (cycle 1 day 1)** and every 6 weeks relative to the first dose of multiple dosing, discontinuation and progression as specified in the study plan (~~Table 2,~~ Table 3 and Table 4) The patient should also complete a questionnaire progression. If any scheduled PRO assessment is not completed the reason for non-completion should be recorded.

6.8.1.1 Collection of tumour biopsy samples

Previous Text:

Table 6 Tumour biopsy samples

Time Relative to dose	Escalation	Expansions	Ph II Extension	Paired Biopsy
Archival	M*	M*	M*	M*
Screening	O	M + O	M + O	M + O
Day 15	O	O	O	M
Discontinuation	O	O	O	O

M = Mandatory O = Optional M* = mandatory if available

Revised Text:

Table 6 Tumour biopsy samples

Time Relative to dose	Escalation	Expansions	Ph II Extension	Paired Biopsy
Archival	M*	M*	M*	M*
Screening	O	M + O	M + O	M + O
Day 15[a]	O	O	O	M
Discontinuation **or progression[b]**	O	O	O	O

M = Mandatory O = Optional M* = mandatory if available

[a] A time window of ±7 days will be allowed. The timing may be further adjusted in response to emerging data but no additional samples will be required.

[b] to be taken at discontinuation or progression, whichever occurs first

Section of protocol affected:

Appendix H Guidance regarding potential interactions with concomitant medications

1. DRUGS INHIBITING CYP3A4 OR CYP2C8 METABOLISM THAT ASTRAZENECA STRONGLY RECOMMEND ARE NOT COMBINED WITH AZD9291

Previous text:

Table 1 Drugs inhibiting CYP3A4 or CYP2C8

Contraindicated drugs	Withdrawal period prior to AZD9291 start
Clarithromycin, telithromycin, troleandomycin	1 week
Gemfibrozil	
Indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, telaprevir	
Itraconazole, ketoconazole, posaconazole, voriconazole	
Mibefradil	
Nefadozone	

Revised text:

Table 1 Drugs inhibiting CYP3A4 or CYP2C8

Contraindicated drugs	Withdrawal period prior to AZD9291 start
Clarithromycin, telithromycin, troleandomycin	1 week
Conivaptan	
Gemfibrozil	
Indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, telaprevir**, boceprevir, elvitegravir**	
Itraconazole, ketoconazole, posaconazole, voriconazole	
Mibefradil	
Nefadozone	

Previous text:

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

Table 3 Exposure, pharmacological action and toxicity may be by AZD9291

Warning of possible interaction	**Advice**
Alfentanil Amodiaquine Repaglinide	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD9291.
Sirolimus	
Tacrolimus	
Torsemide	
All statins	

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between these agents and AZD9291; *in vitro* data suggests AZD9291 has the potential to cause drug interactions at the intestinal level through CYP3A4, it has also been shown to be an inhibitor of CYP2C8, ~~and a weak inhibitor of OATP$_{1B1}$~~. The potential for AZD9291 to inhibit other transporter systems is currently unknown. This list is not intended to be

exhaustive, and a similar restriction will apply to other agents that are known to depend on CYP3A4**,** CYP2C8 ~~and/or transporter proteins for metabolism~~. Appropriate medical judgement is required. Please contact AstraZeneca with any queries you have on this issue

Revised text:

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

Table 3 Exposure, pharmacological action and toxicity may be increased or decreased by AZD9291

Warning of possible interaction	Advice
Alfentanil Amodiaquine Repaglinide Sirolimus Tacrolimus Torsemide **Fentanyl** **Dihydroergotamine** **Ergotamine** **Simvastatin** **Lovastatin** **Atorvastatin**	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD9291.

Table 3 Exposure, pharmacological action and toxicity may be increased or decreased by AZD9291

Warning of possible interaction	Advice
Rosuvastatin **Fluvastatin** **Sulfasalazine** **Warfarin** **Phenytoin (also see Table 2)** **s-Mephenytoin** **Cyclosporine** **Theophylline** **Tizanidine** **Aliskiren** **Ambrisentan** **Colchicine** **Dabigatran etexilate** **Digoxin** **Fexofenadine** **Maraviroc** **Ranolazine** **Talinolol** **Tolvaptan**	There are currently no data confirming that there is a pharmacokinetic (PK) interaction between these agents and AZD9291; *in vitro* data suggests AZD9291 has the potential to cause drug interactions at the intestinal level through CYP3A4 **and BCRP**, it has also been shown to be an inhibitor of CYP2C8 **and inducer of CYP3A4, CYP1A2 and CYP2C and p-glycoprotein**. The potential for AZD9291 to inhibit other transporter systems is currently unknown. This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to depend on CYP3A4, CYP2C8, **CYP1A2 and CYP2C for metabolism or BRCP and p-glycoprotein for deposition**. Appropriate medical judgement is required. Please contact AstraZeneca with any queries you have on this issue

Reason for Amendment:

To update the drug-drug interaction guidance and contraceptive advice in light of new emerging *in vitro* data from recently reported DMPK studies.

Addition of a time window for taking of on-study biopsy for Paired Biopsy cohort.

Change of study Principal Investigator.

Persons who initiated the Amendment:

AZ project team