Revised Clinical Study Protocol

Drug Substance	AZD9291
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A Phase I, Open-Label, Two Parts Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of AZD9291 in Chinese Patients with Advanced Non-Small Cell Lung Cancer who have Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent

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AstraZeneca Research and Development site representative

[redacted]

Date
(Day Month Year)

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

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

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Principal Investigator(s)

For contact details of AstraZeneca personnel see Section 8.1.

PROTOCOL SYNOPSIS

A Phase I, Open-Label, Two Parts Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of AZD9291 in Chinese Patients with Advanced Non-Small Cell Lung Cancer who have Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent

Study site(s) and number of subjects planned

Approximately 24 Chinese patients with Advanced Non-Small Cell Lung Cancer who have Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent will be recruited from China.

Study period		Phase of development
Estimated date of first subject enrolled	Q3 2015	I
Estimated date of last subject completed(Part A)	Q1 2016	
Estimated date of last subject completed(Part B)	Q4 2016	

Objectives

Primary objective

To characterise the pharmacokinetics (PK) of AZD9291 and its metabolites (AZ5104 and AZ7550) after single then multiple doses of AZD9291 in two dose levels (40 mg and 80 mg) administered orally once daily in Chinese patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed following prior therapy with an approved Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor (TKI) agent.

Secondary objective

To investigate the safety and tolerability of AZD9291 when given orally in two dose levels (40 mg and 80 mg) to Chinese patients with locally advanced or metastatic NSCLC who have progressed following prior therapy with an approved EGFR TKI agent.

To obtain a preliminary assessment of the anti-tumour activity of AZD9291 by evaluation of tumour response using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (see Appendix F).

Study design

This is a phase I, open-label, two parts (Part A and Part B) study to determine the pharmacokinetics of AZD9291 administered orally at two dose levels (40 mg and 80 mg) in patients with locally advanced or metastatic NSCLC who have progressed following prior therapy with an EGFR TKI agent (+/- additional chemotherapy regimens).

Approximately 24 patients will enter into this study, with 12 patients at each dose level:

- Cohort 1 will investigate the pharmacokinetics of single then multiple dosing of AZD9291 at 40 mg once daily dose.

- Cohort 2 will investigate the single then multiple dose pharmacokinetics of AZD9291 at 80 mg once daily dose.

The enrollment of Cohort 2 will start after Cohort 1 finishes the enrollment. The first 12 patients enrolled in the study will be in 40mg dose Cohort.

Patients will be administered a single dose of AZD9291 on Day 1, Cycle 0 at the beginning of Part A period. From Day 2 to Day 6, no treatment will be given, but PK samples will be obtained; on Day 8 (Cycle1, Day1), the patients will be administered AZD9291 once daily on a continuous schedule, ie, no break in AZD9291 dosing. Part A will complete after Cycle 4 treatment completion and Part B will start. There will be no dose interruption between Part A and Part B. Following completion of the Part A, patients will continue to Part B if they are still considered to be receiving benefit by the treating physician.

Patients in both cohorts should continue on treatment with AZD9291 at the dose level that they have been enrolled to receive until RECIST 1.1 defined progression or until a treatment discontinuation criterion 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 receive clinical benefit, as judged by the investigator.

The whole study will be nominally divided into two parts: Part A will assess the efficacy, safety and pharmacokinetics of AZD9291, and Part B will assess primarily the safety and efficacy data of AZD9291.

Following completion of the Part A, patients will continue to Part B if they are still considered to be receiving benefit by the treating physician.

There are two data cut offs:

1. PK and preliminary efficacy and safety data base lock will take place approximately 3 months after LSI and after Part A completes, to allow all patients have a minimum of two tumour assessments after the first dose.

2. Safety and efficacy data base cut off will take place at the earlier time point when either all patients have discontinued treatment and completed 28 days post

treatment safety follow-up, or 12 months after the last patient enrolled started investigational product. Data analysis will be performed and a Clinical Study Report written based on this data set. Any patients still receiving investigational product at the time of this 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.

A CSR will be issued after PK and preliminary efficacy and safety database lock; a CSR addendum will be issued for updated safety and efficacy information after final safety data base lock.

Target subject population

Chinese Patients with locally advanced or metastatic Non-Small Cell Lung Cancer who have progressed following prior therapy with an approved EGFR-TKI, other additional lines of treatment may also be administered prior to study.

Investigational product, dosage and mode of administration

AZD9291 is an oral, potent, selective, irreversible inhibitor of both EGFR-TKI sensitising and T790 mutations in NSCLC with a significant selectivity margin over wild-type EGFR. AZD9291 will be administered orally as a tablet once a day. A cycle of treatment is defined as 21 days of once daily AZD9291 treatment.

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

Duration of treatment

Patients in both cohorts (40 mg and 80 mg once daily) may continue on treatment with AZD9291 until a treatment discontinuation criterion 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 receive clinical benefit, as judged by the investigator (see Section 5.2).

Outcomes variable(s)

Primary endpoints/variables

PK exposure parameters derived from plasma concentrations of AZD9291, and metabolites AZ5104 and AZ7550.

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

Maximum plasma concentration (C_{max}), time to Cmax (t_{max}), terminal rate constant (λz), terminal half life ($t_{½\lambda z}$), area under the plasma concentration-time curve from zero to 24 hours ($AUC_{(0-24)}$), from zero to 72 hours ($AUC_{(0-72)}$), from zero to the time of the last measurable concentration ($AUC_{(0-t)}$) and from zero to infinity (AUC), apparent plasma clearance (CL/F) (AZD9291 only), apparent volume of distribution (AZD9291 only), mean residence time (MRT), where possible.

Following the multiple dose part of the study:

Cycle 2 Day 1

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 (AUCss), apparent plasma clearance at steady state (CL_{ss}/F) (AZD9291 only), extent of accumulation on multiple dosing (R_{AC}), time dependency of the pharmacokinetics where possible.

Cycle 1 Day 8

$C_{C1D8\ max}$, $t_{C1D8\ max}$, $C_{C1D8\ min}$, AUC_{tau}

Trough concentrations on Cycle 1 Day 8, day 15 and Cycle 2 day 1.

The ratio of metabolite to AZD9291 will also be calculated.

Secondary endpoints/variables

Incidence and severity of AEs and SAEs (graded by CTCAE v4)

Physical examination, WHO performance status, vital signs including pulse and blood pressure, 12 lead ECGs, echocardiogram/MUGA (for LVEF), haematology, clinical chemistry, urinalysis, concomitant medications.

Efficacy endpoint include objective response rate (ORR).

Statistical methods

The primary objective of this study is to characterise the pharmacokinetics (PK) of AZD9291 after a single and multiple oral dosing of AZD9291 tablets at two dose levels: 40 mg and 80 mg. The key secondary objective is to investigate the safety and tolerability of 40 mg and 80mg dose of AZD9291 to recommend dose(s) for evaluation in future clinical studies in Chinese subjects. Hence the number of patients in the cohorts has been based on the desire to obtain adequate tolerability, safety and pharmacokinetic 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 targeted patient population.

Approximately 12 patients with advanced NSCLC will be enrolled in each cohort.

Plasma concentrations of AZD9291, AZ5104 and AZ7550 will be summarised by nominal sample time. Plasma concentrations and derived PK parameters for AUC, $AUC_{(0-24)}$, $AUC_{(0-t)}$, AUC_{ss}, C_{max}, $C_{ss\ max}$ and $C_{ss\ min}$ will be summarised by dose level. The summary statistics will be presented for CL/F, CL_{ss}/F, volume of distribution, $t_{½\lambda z}$, $R_{AC,}$ time dependency. t_{max} and $t_{max\ ss}$ will be summarized by median, minimum, and maximum. Parameters following single and multiple dosing will be summarised separately. The multiple dose data with be summarised separately by sample day.

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 geometric mean concentration (+/-standard deviation) versus time, stratified by dose and the multiple dose data with also be stratified by sample day.

Trough concentrations on Cycle 1 Day 8, day 15 and Cycle 2 day 1 (pre-dose and 24 hour) will be displayed graphically. Scatter plots of PK parameters versus dose, or log-dose will also be considered following both single and multiple dose administration of AZD9291 to visually inspect dose proportionality.

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. At the end of the study, appropriate summaries of all safety data will be produced.

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). The data cut-off for preliminary efficacy analysis will take place approximately 3 months after the last subject has been enrolled, to allow opportunity for all patients to complete a minimum of two RECIST follow-up assessments.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
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]
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
C_{max}	Maximum plasma concentration
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]
CSR	Clinical Study Report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
Echo	Echocardiogram
EGFR	Epidermal growth factor receptor
EGFRm+	Epidermal growth factor receptor sensitising mutation positive
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus

Abbreviation or special term	Explanation
IATA	International Air Transport Association
ICH	International Conference on Harmonisation
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LIMS	Laboratory Information Management System
LVEF	Left ventricular ejection fraction
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
NSCLC	Non-small Cell Lung Cancer
NTL	Non-target lesion
OAE	Other significant adverse event
ORR	Objective response rate
PD	Progression of disease
PFS	Progression free survival
PK	Pharmacokinetics
PR	Partial response
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
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event (see definition in Section 6.4.2)
SD	Stable disease
λ_z	Smallest (slowest) disposition (=hybrid) rate constant [time-1]
$t_{½}$	Half-life
$t_{½\lambda z}$	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve [time]
TL	Target lesion
TKI	Tyrosine kinase inhibitor

Abbreviation or special term	Explanation
t_{max}	Time to maximum plasma concentration
$t_{ss\ max}$	Time to maximum plasma concentration at steady state
ULN	Upper limit of normal
V_{ss}/F	Volume of distribution (apparent) at steady state after an oral dose
WBDC	Web Based Data Capture
WHO	World Health Organisation
~	Approximately

1. STUDY OBJECTIVE

1.1 Primary objective

To characterise the pharmacokinetics (PK) of AZD9291 and its metabolites (AZ5104 and AZ7550) after single then multiple doses of AZD9291 administered orally once daily in Chinese patients with locally advanced or metastatic non-small cell lung Cancer (NSCLC) who have progressed following prior therapy with an approved Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor (TKI) agent.

1.2 Secondary objective(s)

To investigate the safety and tolerability of AZD9291 when given orally to Chinese patients with locally advanced or metastatic NSCLC who have progressed following prior therapy with an approved EGFRTKI agent.

To obtain a preliminary assessment of the anti-tumour activity of AZD9291 by evaluation of tumour response using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (see Appendix F).

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 (ALK) and KRAS mutations. The incidence of EGFRm+ NSCLC is approximately 10-15% and 30-40% of patients in the West and Asia, respectively.

Although first- (eg, erlotinib, gefitinib) and second-generation (eg, afatinib) EGFR-TKIs are established therapies for patients with NSCLC known to have activating mutations in EGFR (EGFRm+), the emergence of a secondary T790M 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 (Pao et al 2005, Kobayashi et al 2005) in approximately 60% of patients (Yu et al 2013).

In the advanced NSCLC post-EGFR TKI treatment failure setting, prolonged survival rates remain very low (median OS in the region of 1 to 2 years, Wang et al 2012, Wu et al 2010, Fukuoka et al 2011). No approved therapy is currently available for patients with T790M+ tumors that have acquired EGFR-TKI resistance or refractoriness. There is no data on response rates with single agent chemotherapy in the specific subset of T790M+ patients after failure of EGFR-TKI.

Patients who have progressed following platinum-containing chemotherapy

In the subset of patients who have failed prior platinum-containing doublet chemotherapy, studies in unselected patient populations (Shepherd et al 2000, Hanna et al 2004, Ramlau et al 2006, Kim et al 2008) highlight the low response rates expected with single-agent chemotherapy. NCCN guidelines state response rates to systemic second-line therapy are generally <10% (NCCN 2012). These agents are also associated with a significant toxicity burden for the patient.

Re-treatment with an EGFR-TKI (eg, switching to erlotinib following failure of gefitinib) provides similarly low response rates of around 10% and PFS in the range 1.7 to 6.2 months (Lee et al 2013, Watanabe et al 2011). Second-generation EGFR-TKIs have shown similar limited efficacy. Single-agent afatinib for example has shown only modest efficacy in patients with acquired resistance to erlotinib or gefitinib (LUX-Lung 1 trial; Miller et al 2012), with a 7% response rate, 2-month improvement over placebo in progression-free survival (median 3.3 versus 1.1 months) and no overall survival benefit shown; a similar 8% response rate and 4.4 months PFS was seen in the LUX-Lung 4 trial (Katakami et al 2013). Furthermore, the efficacy of second-generation EGFR-TKIs is limited by wild-type toxicities.

There is no global standard of care for later lines of therapy after failure of both EGFR-TKI therapy and chemotherapy; current treatment options for this selected patient population are generally limited to chemotherapy or clinical trials (Langer et al 2012).

Patients who have not received platinum-containing chemotherapy

Second-line platinum-based chemotherapy post EGFR-TKI for EGFRm+ NSCLC generally provides response rates in the range of 20 to 30% (Gridelli et al 2012, Goldberg et al 2012, Maemondo et al 2010, Wang et al 2012, Wu et al 2010). Although slightly better than the response rates that can be expected with single-agent chemotherapy in later lines, these data together with the toxicity burden associated with doublet chemotherapy (that includes nausea, vomiting, bone marrow suppression resulting in high risk of infection and bleeding, alopecia, fatigue, and peripheral neuropathy) confirm the unmet medical need that exists in this patient population.

2.2 Background and rationale for conducting this study

Activation of the 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), described collectively as EGFRm). The tumours initially respond to EGFR-TKIs, but subsequently develop resistance to therapy, with a median time to progression of 9 months. In approximately 60% of these initially EGFR-TKI responsive patients (Yu et al 2013), disease progression is associated with the emergence of a secondary EGFR mutation, T790M in exon 20 of EGFR, which confers resistance to EGFR-TKI therapy (Pao et al 2005). The T790M 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).

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

This study is to investigate the pharmacokinetics profile of AZD9291 in Chinese patients. CFDA regulatory submissions of AZD 9291 studies in Chinese subjects are planned in May 2014 onwards.

3. STUDY DESIGN AND RATIONALE

This Clinical Study Protocol (CSP) 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, open-label, two parts (Part A and Part B) study to determine the pharmacokinetics of AZD9291 administered orally at two dose levels (40 mg and 80 mg) in patients with locally advanced or metastatic NSCLC who have progressed following prior therapy with an approved EGFR TKI agent (+/- additional chemotherapy regimens).

Approximately 24 patients will enter into this study, with 12 patients at each dose level

- Cohort 1 will investigate the pharmacokinetics of single then multiple dosing of AZD9291 at 40 mg once daily dose.

- Cohort 2 will investigate the pharmacokinetics of single then multiple dosing of AZD9291 at 80 mg once daily dose.

The enrollment of Cohort 2 will start after Cohort 1 finishes the enrollment. The first 12 patients enrolled in the study will be in 40 mg dose Cohort.

Patients will be administered a single dose of AZD9291 on Day 1, Cycle 0 at the beginning of Part A period. From Day 2 to Day 6, no treatment will be given, but PK samples will be obtained; on Day 8 (Cycle1, Day1), the patients will be administered AZD9291 once daily on a continuous schedule, ie, no break in AZD9291 dosing. Part A will complete after Cycle 4 treatment and Part B will start without treatment interruption.

Patients in both cohorts should continue on treatment with AZD9291 until a treatment discontinuation criterion 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 receive clinical benefit, as judged by the investigator.

The whole study will be divided nominally into two parts: Part A will assess the pharmacokinetics and preliminary efficacy and safety of AZD9291 at 40 mg and 80 mg respectively, and Part B will assess only the safety and efficacy data of AZD9291.

Following completion of the Part A, patients will automatically continue to Part B.

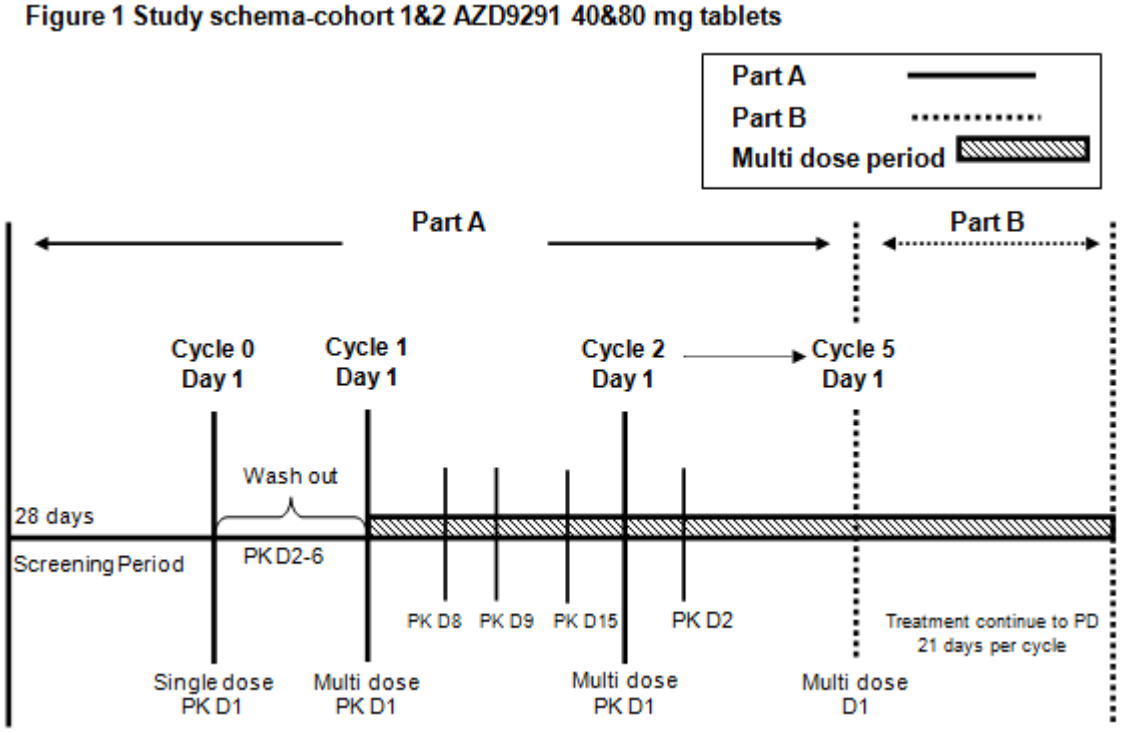
There are two data cut offs:

1. PK and preliminary efficacy and safety data base lock will take place approximately 3 months after LSI and after the part A completes, to allow all patients have two tumor assessments after the first dose.

2. Safety and efficacy data base cut off will take place at the earlier time point when either all patients have discontinued treatment and completed 28 days post treatment safety follow-up, or 12 months after the last patient enrolled started investigational product. Data analysis will be performed and a Clinical Study Report (CSR) written based on this data set. Any patients still receiving investigational product at the time of this 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.

A CSR will be issued after PK and preliminary efficacy and safety data base lock; a CSR addendum will be issued for updated safety and efficacy information after final safety and efficacy data base lock.

Figure 1 Study flow chart



3.2 Rationale for study design

This study is nominally divided into two parts (Part A and Part B), and is a phase I, open label study to determine the pharmacokinetics of AZD9291 and its metabolites (AZ5104 and AZ7550) in Chinese patients with locally advanced or metastatic NSCLC who have progressed following prior therapy with an EGFR TKI agent. Other additional lines of prior treatment may also have been administered. The primary objective for this study is the characterisation of pharmacokinectics of AZD9291 in Chinese patients following two dose levels of 40 mg and 80 mg once daily respectively.

The majority of patients with EGFRm+ NSCLC respond well initially to treatment with EGFR- TKIs with an ORR of approximately 60 to 70%, but eventually vast majority of the EGFRm+ NSCLC patients develop resistance to EGFR-TKI with a median time to progression of around 9-11 months, due to the emergence of a secondary EGFR mutation. T790M mutation in exon 20 of the EGFR gene represents over 50% of those secondary mutations. Currently, there are no effective standard of care therapies for these NSCLC patients with acquired EGFR-TKI resistance who are T790M+. This patient population with a major unmet medical need, and is therefore, appropriate to be enrolled into the current study for the evaluation of PK, safety/tolerability and early efficacy of AZD 9291.

The doses of 40 mg and 80 mg once daily were selected for PK and safety evaluation based on the recommendation of study D5160C00001, which evaluated PK, safety, tolerability, and efficacy data in patients, living outside China, with locally advanced or metastatic NSCLC who have progressed following prior therapy with a prior EGFR-TKI agent. At the Investigator Brochure (IB) data cut-off of 19 November 2013, AZD9291 had been administered across the dose range of 20 to 240 mg 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 20 mg once daily (Ranson, WCLC 2013). The selected 80 mg dose is four fold higher than the minimum efficacious dose tested in study D5160C00001, whilst still being one third of the maximum dose level investigated (240 mg). The 80 mg dose level is considered to have a safety and tolerability profile appropriate for chronic administration to patients with advanced NSCLC and selected to be used in phase II/III trials.

In this study, two dose levels 40 mg and 80 mg once daily will be investigated in Chinese patients for the full pharmacokinetic profile, tolerability and safety. The cohort of 80 mg will start after the enrollment of cohort 40 mg completes.

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 fulfill all of the following criteria:

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

2. Aged at least 18 years

3. Histological or cytological confirmation diagnosis of NSCLC

4. Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy

5. Radiological documentation of disease progression while on a previous continuous treatment with an approved EGFR-TKI eg, gefitinib, erlotinib, icotinib or afatinib. In addition other lines of therapy may have been given.

   – Documented EGFR mutation (at any time since the initial diagnosis of NSCLC) known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q).

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

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

8. 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

   – Women below 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

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

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, gefitinib, icotinib or afatinib) 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 investigational agents or other anticancer drugs from a previous treatment regimen or clinical study within 14 days of the first dose of study treatment

- Previous treatment with AZD9291, or a 3rd generation T790M-directed EGFR TKIs (eg, CO-1686)

- 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 or inducers of CYP3A4 (See Appendix H)

- Treatment with an investigational drug within five half-lives of the compound

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 >250 msec

- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age 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 organs function as demonstrated by any of the following laboratory values:

   - Absolute neutrophil count $<1.5x10^9/L$
   - Platelet count $<100x10^9/L$
   - 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

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 total sexual abstinence, tubal ligation, hormonal contraceptives that are not prone to drug-drug interactions (IUS Levonorgestrel Intra Uterine System (Mirena), Medroxyprogesterone injections (Depo-Provera), copper- banded intra-uterine devices and vasectomised partner. All hormonal methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse.

2. Male patients should be asked to use barrier contraceptives (ie, by use of condoms) during sex with all partners during the 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. Once enrolled all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known potent inducers of CYP3A4 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 provided (see Appendix H).

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). If medically feasible, patients taking regular medication, with the exception of potent inducers of CYP3A4 (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 BRCP and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving AZD9291. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR. Guidance on medications to avoid, medications that require close monitoring and washout periods should be provided (see Appendix H).

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

Concomitant use of regular medications that may prolong the QT interval will be restricted whenever feasible, but patients may receive any medication that is clinically indicated for the treatment of AEs (See Appendix H)

Guidance on medications that require close monitoring is given on Appendix H.

Prohibited Medication/Class of drug:	**Usage:**
Other anticancer agents, investigational agents and radiotherapy	Should not be given while the patient is on study treatment. #see palliative radiotherapy in box below for exception

Rescue/Supportive Medication/Class of drug:	**Usage:**
Pre-medication will be allowed after, but not before the first dose of study treatment.	To be administrated as directed by the investigator. This includes management of diarrhea, nausea and vomiting.
Blood transfusions	Allowed at any time during the study.

Rescue/Supportive Medication/Class of drug:	Usage:
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.
Corticosteroids and/or bisphosphonates	Patients may receive treatment with corticosteroids and/or bisphosphonates for the treatment of bone metastases.
Palliative radiation	Patients may receive radiotherapy for painful bony metastases.
Supportive care and other medications that are considered necessary for the patient's well-being	To be administered as directed by the investigator.

4.3.2 Other concomitant treatment

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

5. STUDY TREATMENT AND CONDUCT

5.1 Identity of investigational product(s)

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 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	40-80 mg Tablets	AstraZeneca

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.

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.

5.2 Dose and treatment regimens

AstraZeneca will supply AZD9291 as tablets for oral administration as a single daily dose of 40 mg and 80 mg respectively. At each dispensing visit, sufficient AZD9291 for 21 days treatment, plus overage, will be dispensed.

Patients will be administered a single dose of AZD9291 on Day 1, Cycle 0 at the beginning of Part A period. From Day 2 to Day 6, no treatment will be given, but PK samples will be obtained; on Day 8 (Cycle1, Day1), the patients will be administered AZD9291 on a continuous schedule. Part A treatment will complete at the end of Cycle 4 and treatment in Part B will continue.

Patients may continue receiving AZD9291 until treatment discontinuation criteria are met. Patients may receive AZD 9291 beyond disease progression as long as they are considered to receive clinical benefit continuously judged by the treating physician.

Patients who were started and have remained on treatment at a dose of 40mg for at least 6 months, have shown clinical benefit (as judged by the investigator) and have then developed RECIST confirmed disease progression, and did not experience any treatment – related grade 3 AE when treated at dose of 40mg, may have dose increased to 80mg after agreement in advance between the Investigator and AZ Study Physician. 80mg has been declared to have an acceptable tolerability profile by the Safety Review Committee.

Tablets should be taken whole with water, 240ml being the recommended volume for PK days. AZD9291 can be taken with or without food at the same time each day. 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 (Table 2).

Doses should be taken approximately 24 hours apart at the same time each day. Doses should not be missed. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their AZD9291, they should not make up for this dose, but should take the next scheduled dose.

Any change from dosing schedule, dose interruptions, dose reductions should be recorded in the eCRF.

Assessment timings if dosing is interrupted

If a patient misses any doses of AZD9291 during the 21-day evaluation period of Cycle 1, please contact the AstraZeneca Study physician or site monitor 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 assessments.

5.2.1 Toxicity management

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

In cohort 1, if the toxicity resolves or reverts to ≤CTCAE grade 2 within 3 weeks of onset, treatment with AZD9291 may be restarted at the same dose. In cohort 2, if the toxicity resolves or reverts to ≤CTCAE grade 2 within 3 weeks of onset, treatment with AZD9291 may be restarted at the same dose (80 mg) or a lower dose (40 mg) using the rules below for dose modifications (Table 1) and with 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.

Table 1 Dose interventions

Starting Dose	Reduced AZD9291 Dose
80 mg daily	40 mg daily
40 mg daily	no dose reduction

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 (as per Table 1), on resolution/improvement of the AE at the discretion of the Investigator.

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 physician 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 Physician if the dosing interruption is no longer than 3 weeks.

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

Patients experiencing corneal ulceration or Interstitial Lung Disease (ILD) will not be permitted to restart study treatment.

5.2.2 Skin reactions

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

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

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

- Changes in the CTCAE grade of skin reactions will be collected in the AE eCRF

Photographs of skin reactions may be collected and these photographs should be available for central review by AstraZeneca and for external expert dermatological review if required. Skin biopsies of skin reactions may be taken as per investigator discretion, as per the standard local medical practice. Skin biopsies should ideally be taken in subjects with clinically significant or grade > 3 skin reaction.

5.2.3 Diarrhoea

Recommendations for appropriate management of diarrhoea, including dose-adjustments for adverse events of diarrhoea that are of CTCAE grade ≥3 or that are clinically significant and/or intolerable and considered by the investigator to be causally related to AZD9291, will be provided to investigators. Changes in CTCAE grade of diarrhoea will be captured in the AE eCRF.

5.2.4 Duration of therapy

Patients should continue on treatment with AZD9291 until 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 any reason, the patient must complete all assessment at discontinuation visit specified in study plan (Table 2).

5.2.5 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.

5.3 Rationale for dose regimen

The dose of 80 mg once daily (with potential dose reduction to 40 mg) was selected for the registration studies outside China. From a review of all available safety, tolerability, PK and efficacy data from study D5160C00001, in patients with advanced NSCLC who have progressed following prior therapy with a prior EGFR-TKI agent. At the Investigator Brochure (IB) data cut-off of 19 November 2013, AZD9291 had been administered across the dose range of 20 to 240 mg 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 20 mg once daily (Ranson, WCLC 2013). The selected 80 mg dose is four fold higher than the minimum efficacious dose tested in study D5160C00001, whilst still being one third of the maximum dose level investigated (240 mg). The 80 mg dose level is considered to have a safety and tolerability profile appropriate for chronic administration to patients with advanced NSCLC.

Based on data for study D5160C00001 there is no difference in PK between Western and Asian patients and study D5160C00001 contained a high proportion of patients from Asian countries. Therefore 40 and 80 mg have been chosen as the dose for investigation in this pharmacokinetic study as PK exposure is expected to be similar to that seen in study D5160C00001, is expected to be well tolerated and produce durable objective responses (in T790M positive tumours).

5.4 Benefit/risk and ethical assessment

5.4.1 Potential benefits

This study is a PK study with AZD9291, a potent and specific, irreversible dual inhibitor of both the sensitising EGFR 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.

5.4.2 Overall benefit-risk and ethical assessment

In the locally advanced or metastatic NSCLC patients who became refractory to a prior EGFR TKI treatment, their overall survival duration is very low (~16 months for the 2nd line patients, ~10 months for third line patients). There is a huge unmet clinical need for novel therapeutic agents for those 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 and non-clinical 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 explants 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 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, 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 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.

Patients will receive a single dose of AZD9291 as the tablet formulation on Day 1 then after 7±2 days washout, multiple dosing, once daily will be initiated. PK samples will be collected following single dose (Cycle 0) and multiple dose (Cycle 1 Day 8 and Cycle 2 Day 1) to enable characterisation of the AZD9291 phamacokenitics.

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 fulfill regulatory requirements related to the testing of the safety of metabolites.

5.5 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 initiated on investigational product (Section 5.5.2)
- Patient lost to follow-up

Patients that are withdrawn from the study but are evaluable will not be replaced.

Patients may withdraw from any aspects of the voluntary exploratory research (see Section 5.5.3) at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study.

5.5.1 Procedures for discontinuation of a patient from investigational product

The Principal Investigator/Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. They will also immediately inform AstraZeneca of the withdrawal. Adverse events will be followed up; all unused study drug should be returned by the subject or representative (e.g. caretaker, family member).

If AZD9291 is discontinued for any reason, the patient must complete all assessment at discontinuation visit specified in study plan (Table 2). Study procedure related SAEs and concomitant medication must be captured till 28 day safety follow-up visit.

5.5.2 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.

5.5.3 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 6.4.3) and inform AstraZeneca of the withdrawal. Adverse events should be followed up (see Sections 6.4.3 and 6.4.4) and study drug should be returned by the patient.

5.6 Study timetable and

Planned duration of the study:

Study period: Q2 2015- Q4 2016

The end of the study is defined as ‘the last visit of the last subject undergoing the study’, this may be due to all the patients having discontinued treatment due to PD and/or meeting discontinuation criteria and completed 28 days post treatment safety follow-up/withdraw from the study.

6. STUDY PLAN AND COLLECTION OF STUDY VARIABLES

6.1 Study Plan

Table 2 Study Plan 40 & 80 mg tablet cohort

	Screening	Single dose /Cycle 0 (7 day cycle)					Multiple Dosing/ Cycle 1 (21 Day cycle)				Cycle 2 – Cycle 4 (21 Day Cycle)	Cycle 2 only	Cycle 5 onwards (21 Day cycle)	Discontinuation	28-day Follow-Up	Details in Section
Visit	**1**	**2**	**3**	**4**	**5**		**6**	**7**	**8**	**9**	**10+**					
Day	**-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D6**	**D1**	**D8**	**D9**	**D15**	**D1**	**D2**				
Window (Days)		0	0	0	0	0	0	0	0	0	±7	0	±7	0	±7	
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	← As clinically indicated →														6.3.6
Vital Signs	X	X	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
ClinicalChemistry/Haematology/Urinalysis	X	X					X	X		X	X		X	X		6.3.5
ECG	X	X					X				X		X	X		6.3.4
Echo/MUGA	X	12 weekly(±1 week) relative to first dose														6.3.7
PK blood samples (including metabolites)		X	X	X	X	X	X	X	X	X	X (Cycle 2 only)	X				6.5.1
RECIST assessments	X[b]	Every 6 weeks(±1 week) [c]														6.7.1
Dispense Study Medication		X					X				X		X			5
Dose with AZD9291		X					Daily dosing									5
Concomitant Medication																4.3.1
Adverse Events[d,e]																6.4

(a) If assessments were performed within 7 days prior to the first dose of study treatment and the patient meets the eligibility criteria, these assessments do not need to be repeated during visit 2.
(b) This assessment does not need to be repeated if it is performed within 28 days prior to the start of study treatment, unless the investigator has a reason to believe that there has been a change in the patient's tumour burden. If imaging is repeated before the start of study treatment, the most recent assessment would then be recorded as the screening tumour assessment.
(c) RECIST assessments should be performed every 6 weeks (± 7 days) from visit 6(C1D1).
(d) Following AZD9291 discontinuation, SAEs considered related to study procedures should continue to be collected
(e) Continued to collect unresolved AEs post 28-day Follow-up visit (if applicable).

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 eCRFs as specified in the protocol and in accordance with the instructions provided. These instructions provide guidance for the recording of study data in the eCRF 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 eCRFs. 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 Enrollment and screening

The principal investigator (PI) will:

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

2. Assign potential patient a unique enrollment number, beginning with "E#".

3. Determine patient eligibility. See Sections 4.1 and 4.2.

As patients are screened for the study, they must be allocated an enrollment code (E-code). The E-code is a 7-digit number made up of the centre number and the patient number within that particular centre (eg, the first patient screened at centre number 0001 would be assigned the E-code E0001001, the second patient screened would be E0001002 and so on). This number is the patient's unique identifier and is used to identify the patient on the eCRFs.

If a patient withdraws from participation in the study, then his/her enrollment 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) 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.

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 (Table 2).

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 e.g., 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

6.3.3.1 Pulse and blood pressure

Supine blood pressure and pulse rate will be measured after 10 minutes rest. Assessments will be performed pre-dose, at the visits as shown in the Study Plan (see Table 2) and on occurrence of any cardiac AE. Additionally at the discretion of the investigator if clinically indicated.

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

6.3.3.2 Weight and height

Weight will be performed at screening and then Day 1 of each cycle as well as the Discontinuation Visit.

Height will be assessed at screening only.

6.3.4 ECG

Resting 12-lead ECG

Twelve-lead ECG will be performed at the visit indicated in the Study Plan (Table 2).

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

- Screening
- On Day 1 of Cycle 0
  - Pre-dose only
- Day 1 of Cycle 1 and each subsequent cycle
  - Pre-dose only
- 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.

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). 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); pre-dose (baseline)
- First day of multiple dosing, Day 1 Cycle 1; 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 eCRF.

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	**Haematology**
Serum (S)/Plasma (P)-Albumin	Blood (B)-Haemoglobin
S/P-ALT	B-Leukocyte
S/P-AST	B-Haematocrit
S/P-Alkaline phosphatase	B-Red blood cell (RBC) count
S/P-Bilirubin, total	B-Absolute leukocyte differential count
S/P-Calcium, total	Neutrophils
S/P-Creatinine	Lymphocytes
S/P-Glucose (fasting on PK days only)	Monocytes
S/P-Magnesium	Basophils
S/P-Potassium	Eosinophils
S/P-Sodium	B-Platelet count
S/P-Urea nitrogen	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 ≥3x ULN and total bilirubin ≥2x ULN 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 6.6.1.

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. Ophthalmology examination results should be collected in the eCRF.

Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs should be performed to record any clinically significant findings. These photographs should be available for central review by AstraZeneca and AstraZeneca representatives if necessary.

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

6.3.7 Echocardiogram/MUGA Scan

An Echocardiogram or MUGA scan to assess LVEF will be performed at screening (prior to first dose of AZD9291) and every 12 weeks relative to first dose. 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. The patients should also be examined using the same machine and operator whenever possible.

6.3.8 Follow-up

6.3.8.1 Discontinuation Visit

A discontinuation Visit will be performed at the time of AZD9291 is permanently stopped. Refer to the study plan (Table 2) for full details.

6.3.8.2 Safety Follow-Up

In addition for safety follow-up as a minimum, telephone contact should be made with the patient 28 days following the discontinuation of AZD9291 to follow-up on any SAE/AE's and concomitant medications (including any subsequent cancer therapy). Any SAE will be followed to resolution where possible (Refer to Study Plan Table 2).

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.

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 hospitalization
- 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 G 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 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, as outlined in Table 3.

Table 3 Summary of recording and follow-up of adverse events and deaths

	Consent to Treatment Period	Until 28-day Follow-up Visit (safety follow-up period)	Post 28-day Follow-up visit
Collect all new AEs in eCRF	Yes	Yes	No
Collect all ongoing AEs in eCRF	Yes	Yes	No
Collect all study procedure- related SAEs in eCRF	Yes	Yes	Yes
Death due to AE, or unknown cause	Yes	Yes	No

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 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 (28-day follow-up visit) in the study are followed up by the investigator for as long as medically indicated. 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
- Changes in CTCAE grade (for skin reactions and diarrhoea only); maximum CTCAE grade for all other AEs
- Whether the AE is serious or not
- Investigator causality rating against the 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 an 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 eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

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 CSR. Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfil any of the criteria for an 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 eCRF module, but should not be reported as a SAE during the study.

- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported 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 eCRF.

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 aSAE 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 Pharmacokinetics

6.5.1 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 4. 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 4 PK blood sample schedule

Time relative to Dose	Single Dosing Cycle 0					Multiple Dosing Cycle 1				Multiple Dosing Cycle 2	
	D1	D2	D3	D4	D6	D1	D8	D9 (pre-dose)	D15 (pre-dose)	D1	D2 (pre-dose)
Pre-dose	X					X	X		X	X	
0.5h	X						X				
1h	X						X			X	
1.5h	X						X			X	
2h	X						X			X	
3h	X						X				
4h	X						X			X	
6h	X						X			X	
8h	X						X			X	
10h	X						X			X	
12h	X						X			X	
24h		X						X			X
48h			X								
72h				X							
120h					X						

A 5 min window will be allowed for samples taken at 1h; a 10 min 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 6.6.1. Residual samples may be analysed for exploratory biomarkers.

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

6.5.2 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 storage are provided in the Laboratory Manual.

6.6 Biological sampling procedures

6.6.1 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 subject in this study is as follows.

Assessment		Sample volume[a](mL)	No. of samples[b]	Total volume (mL)
Safety	Clinical chemistry	5	9	45
	Haematology	2	9	18
Pharmacokinetics		2	39	78
Serum β-HCG[c]		4	1	4
Total				145

(a) The sample volume for safety assessments, serum β-HCG are approximate volumes that refers to site-specific change.
(b) Number of samples is estimated based on patients onaverage completing 4 cycles.
(c) Only for pre-menopausal women.

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.

6.6.2 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 EGFR gene mutation detection as exploratory biomarker analyses. These analyses are for AstraZeneca use only and will not be included in the CSR.

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.

6.6.2.1 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.

6.6.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labeled 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 materials should not be 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.

6.6.4 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.

6.6.5 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.

6.7 Anti-tumour activity

6.7.1 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 metastases. The methods of assessment used at baseline should be used at each subsequent follow-up assessment.

Follow-up assessment should be performed every 6 weeks (±7 days) up to and including progression (corresponding with the RECIST assessments – and continuing after treatment discontinuation in the absence of disease 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 (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 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, Section4.1.

All RECIST 1.1 assessment images will be reviewed at site.

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:

Primary endpoints

- PK exposure parameters derived from plasma concentrations of AZD9291, and metabolites AZ5104 and AZ7550

- 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 (λz), terminal half life ($t_{½\lambda z}$), area under the plasma concentration-time curve from zero to 24 hours ($AUC_{(0-}$

$_{24)}$), from zero to 72 hours ($AUC_{(0-72)}$), from zero to the time of the last measurable concentration (AUC(0-t)) and from zero to infinity (AUC), apparent plasma clearance (CL/F) (AZD9291 only), apparent volume of distribution (AZD9291 only), mean residence time (MRT), where possible.

- Following the multiple dose part of the study:

Cycle 2 Day 1

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 (AUCss), apparent plasma clearance at steady state (CL_{ss}/F) (AZD9291 only), extent of accumulation on multiple dosing (R_{AC}), time dependency of the pharmacokinetics where possible.

Cycle 1 Day 8

C_{C1D8} max, t_{C1D8} max, C_{C1D8} min, AUCtau.

Trough concentrations on Cycle 1 Day 8, day 15 and Cycle 2 day 1.

- The ratio of metabolite to AZD9291 will also be calculated.

Secondary endpoints

- Safety and Tolerability-AEs (both in terms of MedDRA preferred terms and CTCAE grade)
- Physical examination, WHO performance status, vital signs including pulse and blood pressure, 12 lead ECGs, echocardiogram/MUGA (for LVEF), haematology, clinical chemistry, urinalysis, concomitant medications.
- Tumour response including objecive response.
- 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 characterise the pharmacokinetics (PK) of AZD9291 after a single then multiple oral doses of AZD929. The key secondary objective is to investigate the safety and tolerability of AZD9291 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 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 targeted patient population.

Approximately 12 patients with advanced NSCLC will be enrolled in each cohort

7.3 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, physicial examination, laboratory data, vital signs, ECG and echocardiogram/MUGA (for LVEF) changes. These will be collected for all patients. Appropriate summaries of these data will be presented as described in Section 7.7.

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 Quantitative Clinical Pharmacology, Alderley Park, AstraZeneca or delegate on behalf of Quantitative Clinical Pharmacology. 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, AZ5104 and AZ7550.

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 ($AUC_{(0-24)}$), from zero to 72 hours ($AUC_{(0-72)}$), from zero to the time of the last measurable concentration ($AUC_{(0-t)}$) and from zero to infinity (AUC), apparent plasma clearance (CL/F)

(AZD9291 only), apparent volume of distribution, mean residence time (MRT),where possible.

Following the multiple dose part of the study:

Cycle 2 Day 1:

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) (AZD9291 only), extent of accumulation on multiple dosing (R_{AC}), time dependency of the pharmacokinetics.

Cycle 1 Day 8:

$CC1D8_{max}$, $tC1D8_{max}$, $CC1D8_{min}$, AUC_{tau}.

Trough concentrations on Cycle 1 Day 8, day 15 and Cycle 2 day 1.

The ratio of metabolite to AZD9291 will also be calculated.

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 up log down trapezoidal rule. Where appropriate, the AUC(0-t) will be extrapolated to infinity using λz to obtain AUC. The area under the concentration-time curve across the dosing interval, AUCss will be calculated using the linear up log down trapezoidal rule. The apparent clearance (CL/F following the single dose and CLss/F following multiple dosing) will be determined from the ratio of dose/AUC or dose/AUCss. The volume of distribution (Vss/F or Vz/F) will be determined from the mean residence time (MRT) x CL/F and/or the accumulation ratio (RAC) will be calculated as the ratio of the AUC(0-*24*) on Cycle 2 Day 1 and Cycle 0 Day 1. The time dependency of the pharmacokinetics on multiple dosing will be assessed by the calculation of the ratio of AUC(0 -*24*) Cycle 2 day 1/AUC Cycle 0 Day 1.

7.4.1 Population analysis of pharmacokinetic variables

The relationship between PK and selected efficacy and/or safety endpoints may be assessed, as deemed appropriate. Results will be reported separately from the CSR.

The pharmacokinetic, 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 methods. The results of any such analyses will be reported separately from the CSR.

7.5 Calculation or derivation of tumour response variables

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.

7.5.1 Objective response

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 <10 mm 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.

7.5.2 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.

7.6 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 5

Table 5 Analysis sets

Analysis Set	Definition
Full analysis set	All patients who received at least 1 dose ofAZD9291. **Safety data summaries and analyses will be produced based on the full analysis set**.
PK analysis	Pharmacokinetics Patients in the Safety Analysis Set who have at least one measurable PK concentration, supported by the relevant date and time of this sample and for each time a **PK** sample was taken the dosing data for that day; and for samples taken after multiple dosing the dosing data for the 2 days prior to the sample day as well as the sample day, and have no important protocol deviations (e.g co-meds) or AEs that may impact PK. For any individual sample to be included in the PK analysis set the full sample data and dosing data needs to be present for that sample.
Evaluable for response	Dosed patients with a baseline RECIST assessment.

7.7 Methods of statistical analysis

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

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(s2)-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}, $C_{ss\ max}$, $C_{ss\ min}$, CL/F, CL_{ss}/F, volume of distribution, $t_{½\lambda z}$, R_{AC}, time dependency, lambda_z, R-square, % AUC extrapolated, MRC_{max} and MRAUC:

- Gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- CV, calculated as 100 √ [exp(s2)-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 t_{max} and $t_{max\ ss}$:

- Median
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for MRT:

- Arithmetic mean
- Standard deviation
- 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 visually inspect dose proportionality.

Tumour response

The analysis population for objective tumour response will be the “evaluable for response” population.

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

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 an 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.

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 eCRF and on the overdose eCRF module.
- An overdose with no associated symptoms is only reported on the overdose eCRF 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 an 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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