Clinical Study Protocol

Drug Substance	AZD9291
Study Code	D5160C00017
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Date	

A Phase II, Open Label, Single-arm Study to Assess the Safety and Efficacy of AZD9291 in Asia Pacific Patients with Locally Advanced/Metastatic Non-Small Cell Lung Cancer whose Disease has Progressed with Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and whose Tumours harbour a T790M mutation within the Epidermal Growth Factor Receptor Gene

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VERSION HISTORY

Version 4.0,

The reasons for this protocol amendment are to update the clinical study protocol to:

- Define the Final data cut-off (DCO) and the associated analysis: the final DCO will happen approximately 95 OS events (about 55% maturity) have been observed out of all enrolled patients. The final analyses will include the analysis for OS, PRO and Safety data at the DCO.
- Define the RECIST modules freeze time and associated analysis: RECIST modules will stop collection after 24 months post Last Subject First Dose (RECIST modules freeze time). Analysis for RECIST related endpoints, like ORR, DoR, tumour shrinkage, DCR and PFS based on the cut-off at RECIST modules freeze time will be performed at final analysis, together with OS, PRO and safety analysis.
- Specify the changes in the data collection: Central Imaging data will not be collected after RECIST modules freeze time (24months post LSFD), local RECIST investigator's assessment frequency will be adjusted to every 12 weeks after RECIST modules freeze time. ctDNA collection frequency will be decreased from every 6 weeks to every 12 weeks after RECIST modules freeze time as well.
- To align with the current product specific safety requirements;
- To provide the instruction and clarification on the continued access: after final DCO, patients receiving AZD9291 at the time of study completion (ie, after final data cut-off date) may continue to receive AZD9291 through continued access.

Changes to the clinical study protocol are summarized as below:

- Protocol Synopsis (Study design), Figure 1 Study Flow Chart, Section 4.2 (Treatment period), Section 4.4 (Patient management post final OS analysis) and Section 7.8 (Post study access to study treatment): These sections were modified to clarify access to treatment will continue to be assured for patients still receiving AZD9291 following final DCO.
- Section 1.5 (Study Design): Figure 1 Study Flow Chart was revised to add a continued access part to show the whole study period.
- Section 3.5 (Restriction): contraception restriction, washout period and concomitant medication restrictions were updated to align with the current product specific safety requirements.
- Section 4 (Study plan and timing of procedures): Table 1:The table title was updated to specify that study plan outlined in Table 1 is valid up until RECIST modules freeze time. Table 2: Section added to provide more details regarding the management of patients after RECIST modules freeze time until the final OS analysis DCO.
- Section 4.3.3 (Progression Follow up): This section was modified to clarify that plasma for ctDNA after RECIST modules freeze time will be collected every 12 weeks up to and

including progression. Tumour investigator's assessments will be performed every 12 weeks per local practice until objective progression or final DCO, both central imaging scans and investigator assessment data will not be collected in eCRF.

- Section 4.4 (patient management in the continued access period), this section was added to provide clarification on the patient management post final analysis.
- Section 5.1.1 (RECIST 1.1) and Section 5.1.2 (RECIST 1.1 Independent Central Review assessment): This section was modified to clarify that prior to RECIST modules freeze time, tumour investigator's assessments will be performed every 6 weeks until disease progression and after RECIST modules freeze time tumour assessments will be performed every 12 weeks per local practice until objective progression or final DCO, scans and data will not be collected.
- Section 5.6.2 (Table 4): Text regarding ctDNA collection on Cycle 7 Day 1 and onwards were added to clarify change in frequency of collection prior to and after RECIST modules freeze time.
- Section 5.8: This section was modified to clarify that post progression outcomes will be collected up to RECIST modules freeze time.
- Section 6.3.1 (Time period for collection of adverse events), Section 6.4 (Reporting of SAE), and Section 6.5 (overdose): these sections were further clarified on the requirement of AE, SAE and overdose collection after final DCO.
- Section 6.6 (pregnancy): This section was modified to further clarify the pregnancy reporting requirement after final DCO, and update to align with the current product specific safety requirements.
- Section 6.7 (Management of Investigational Product related toxicities): This section was modified to reflect the latest Investigator's Brochure (IB) update. A guidance of how to proceed in case of QTcF prolongation to >500 msec was updated. To clarify about patients experiencing corneal ulceration. Interstitial Lung Disease (ILD) and QTc interval prolongation with signs/symptoms of serious arrhythmia are not permitted to restart study treatment.
- Section 7.2 (Dose and treatment regimens) and 7.8 (Post study access to study treatment): These sections were updated to provide more clarity regarding the drug dispensing and drug accountability process post final OS analysis DCO.
- Protocol Synopsis (Statistical methods**),** Section 8.1 (statistical considerations) and section 8.7.4 (Planned analysis): These sections were modified to clarify that updates to the CSR will be undertaken based upon a DCO (also it's the final DCO) at approximately 95 OS events have been observed out of all enrolled patients. In addition, the final analyses will include the analysis for OS, PRO and Safety data at the final DCO, and the analysis for RECIST related data at RECIST modules freeze time.
- Section 9.3 (study timetable and end of study): The expected study end date was updated.

- **Others:**

- Version history was inserted and Appendix sequence was re-adjusted due to new CSP template.
- Corrected some typo errors.

Version 3.0,
All changes of revised CSP V3.0 were summarized in clinical study protocol amendment 2, which was approved on .

Version 2.0,
All changes of revised CSP V2.0 were summarized in clinical study protocol amendment 1, which was approved on 2 .

Version 1.0,
Initial Creation.

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.

CLINICAL STUDY PROTOCOL SYNOPSIS

A Phase II, Open Label, Single-arm Study to Assess the Safety and Efficacy of AZD9291 in Asia Pacific Patients with Locally Advanced/Metastatic Non-Small Cell Lung Cancer whose Disease has Progressed with Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and whose Tumours harbour a T790M mutation within the Epidermal Growth Factor Receptor Gene

International Co-ordinating Investigator

International Co-ordinating Investigator

Study site(s) and number of subjects planned

Approximately 175 patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC; Stage IIIB - IV) will be recruited from approximately 35 centres in Asia Pacific. Of the 175 patients, approximately 150 patients will be recruited from China. The remaining 25 patients will be recruited from other countries in the region as selected by the sponsor.

Study period	Phase of development
Estimated date of first subject enrolled	II
Estimated date of last subject completed	

* _____ is an estimated timing.

Study design

This is a phase II, open label, single arm study assessing the safety and efficacy of AZD9291 (80 mg, orally, once daily) in Asia Pacific patients with a confirmed diagnosis of Epidermal Growth Factor Receptor (EGFR) activating mutation positive (ie, G719X, exon 19 deletion, L858R, L861Q) and T790M mutation positive (hereafter referred to as EGFRm+ and T790M+) un-resectable, locally advanced or metastatic NSCLC (Stage IIIB-IV), who have progressed on or after first line Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI) treatment or a line of EGFR-TKI and a line of platinum containing doublet chemotherapy

In order to enrol approximately 175 patients it is expected that approximately 440 patients will be screened. The 150 patients from China will compose 2 cohorts:

- Approximately 50 patients with EGFRm+ and T790M+ locally advanced or metastatic NSCLC who have progressed following 1st line EGFR-TKI treatment but who have not received further treatment.

- Approximately 100 patients with EGFRm+ and T790M+ locally advanced or metastatic NSCLC who have progressed following prior therapies with an EGFR-TKI and a platinum-based doublet chemotherapy, regardless the sequence of therapy. Patients may have also received additional lines of treatment.

The remaining 25 patients are from other countries. It is expected to enroll patients in a similar ratio between the 2 cohorts as that of the Chinese patient group, ie, approximately 8 patients from 2nd line and 17 patients from 3rd line or beyond.

All patients must have documented radiological progression on EGFR-TKI treatment and on the last treatment administered prior to enrolling to the study.

A mandatory biopsy will be needed for central testing of T790M mutation status following confirmed disease progression on the most recent treatment regimen.

Patients should continue on treatment with AZD9291 until Response Evaluation Criteria in Solid Tumours version 1.1 (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 show clinical benefit, as judged by the investigator.

Patients receiving AZD9291 at the time of study completion (ie, after final data cut-off date) may continue to receive AZD9291 through continued access, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment. Such patients will continue to be monitored and all safety assessments that may be related to IP and drug dispensing/accountability will be performed by site until AZD9291 is permanently discontinued. All SAEs, overdoses and pregnancies would be reported until 30 days after last dose. However, AstraZeneca will not collect these data into eCRF in the continued access.

Study would be opened and provide study medication treatment and collect safety information follow up until last patient treated. Final Last Subject Last visit will be defined as the last visit after last patient's treatment discontinuation and 30 days safety follow up.

If study drug would be approved on market for use in disease under study indication, patients may be discontinued and switched to market product. Drug supply options can be available depending on the country and would be proposed to patient when found as best way to continue treatment by both AZ and investigator.

Objectives

Primary Objective:	**Outcome Measure:**
To assess the efficacy of AZD9291 by assessment of Objective Response Rate (ORR).	ORR according to RECIST 1.1 by an Independent Central Review (ICR). Sensitivity analysis of ORR using investigators assessments of RECIST 1.1.

Secondary Objective:	**Outcome Measure:**
To further assess the efficacy of AZD9291 in terms of: - Progression Free Survival (PFS) - Duration of Response (DoR) - Disease Control Rate (DCR) - Tumour shrinkage - Overall Survival (OS)	PFS, DoR, DCR and tumour shrinkage according to RECIST 1.1 using assessments performed by an ICR. Sensitivity analysis of PFS, DoR, DCR and tumour shrinkage using investigators assessments of RECIST 1.1. Description of OS.
To assess the safety and tolerability profile of AZD9291.	- Adverse events (graded by CTCAE v4) - Clinical chemistry, haematology and urinalysis - Vital signs, Physical Examination, Weight - Digital ECG - WHO Performance Status - Echocardiogram/MUGA (for LVEF)
To assess the impact of AZD9291 on patients' disease-related symptoms and health related quality of life (HRQoL).	EORTC QLQ-C30: Questionnaire consisting of 30 items measuring patients' general cancer symptoms and functioning. EORTC QLQ LC13: A complementary questionnaire measuring lung cancer symptoms and side-effects from conventional chemo- and radiotherapy.

Exploratory Objective:	Outcome Measure:
To explore the impact of AZD9291 treatment and disease state on health state utility.	The EQ-5D-5L health state utility index will be used to derive health state utility based on patient reported data
To describe and evaluate resource use associated with AZD9291 treatment and underlying disease.	Health resource utilization measures including hospitalization, outpatient visits, or emergency department visits
To further characterise AZD9291 effects on survival, including impact of baseline prognostic factors, post progression treatments and the course of disease (further progression and changes in symptoms).	Baseline potentially prognostic variables (eg, tumour stage, performance status, sex, baseline LDH), time from enrolment to second progression (referred to as PFS2), time to subsequent treatments, change in symptoms.
To collect and store tumour samples and plasma for potential exploratory research into factors that may influence susceptibility to/development of NSCLC/cancer and/or response to AZD9291 (where response is defined broadly to include efficacy, tolerability or safety).	Analysis of key genetic and proteomic markers to include, but not limited to, EGFR mutations, HER2 & CMET expression and/or amplification. Collection of plasma samples to include, but not limited to, extraction of circulating tumour DNA (ctDNA) for investigation of biomarkers. Samples may be analysed retrospectively. Any biomarker data generated may be reported separately and may also form part of a pooled analysis with other AZD9291 studies.
To collect and store additional tumour tissue taken following confirmed disease progression on the most recent treatment regimen, for use by a 3rd party diagnostics partner to undertake necessary technical studies for companion diagnostic development and approval.	Technical performance verification studies and clinical reproducibility testing to support the regulatory package for pre-market approval of a companion diagnostic test.
To collect, and store plasma for isolation of ctDNA. Extracted ctDNA will be assessed for the presence of genetic aberrations including, but not limited to, EGFR mutations (T790M, L858R, etc). These samples may be shared with a diagnostic partner for development of a ctDNA test for T790M detection.	Retrospective/real-time analysis of EGFR (and other) mutations in ctDNA from all study patients. More than one method may be used during the course of this study.
To assess adverse events by patient self-reporting of specific CTCAE symptoms.	Collection of approximately 28 PRO-CTCAE symptoms via an electronic device solution.

Exploratory Objective:	Outcome Measure:
To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response to AZD9291, (ie. safety and efficacy) and/or susceptibility to/development of cancers	Correlation of polymorphisms with variation pharmacodynamic, safety or response observed in patients treated with AZD9291 Data generated may be reported separately and may also form part of a pooled analysis with other AZD9291 studies.
To collect and store residual CSF for potential exploratory research of factors that may influence development of NSCLC and/or response to AZD9291 (where response is defined broadly to include efficacy, tolerability or safety).	Collection of CSF for the concentration of AZ9291 and its metabolites (AZ5104 and AZ7550) and/or biomarkers. Samples may be analysed retrospectively.

Target subject population

Male and female locally advanced or metastatic NSCLC (Stage IIIB-IV) patients aged 18 years or over with EGFRm+ T790M+, who have progressed following first line therapy with an approved EGFR-TKI agent or a line of EGFR-TKI and a line of platinum containing doublet chemotherapy regardless the sequence of treatment. Patients must have measurable disease (using Computer Tomography [CT]/Magnetic Resonance Imaging [MRI]) as defined by RECIST 1.1 guidelines, confirmation of histological or cytological NSCLC and WHO Performance Status of 0-1. The patients from Asia Pacific will be enrolled.

Duration of treatment

Patients may continue to receive AZD9291 after disease progression as long as they are continuing to receive clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria (see Section 3.6).

Investigational product, dosage and mode of administration

AZD9291 is an oral, potent, selective, irreversible inhibitor of both EGFR mutation and T790 mutations in NSCLC with a significant selectivity margin over wild-type EGFR. AZD9291 will be administered orally as a 80 mg tablet once a day. A cycle of treatment is defined as 21 days of once daily AZD9291 treatment.

Statistical methods

One primary objective of the study is to assess the efficacy of AZD9291 defined by assessment of best ORR which is defined as the number (%) of patients with measurable disease who had confirmed CR or PR assessed by ICR per RECIST 1.1.

The study was designed to estimate the response rates in patients with EGFRm+ and T790M+ locally advanced or metastatic NSCLC who have progressed on or after first line EGFR-TKI treatment or a line of EGFR-TKI and a line of platinum containing doublet chemotherapy regardless the sequence of treatment. ORR will be estimated with 95% exact CIs. With 175

patients the precision of the estimation of ORR in the overall study population will be within +/-8% (eg, ORR 40%, 95% CI 33.0%, 47.4%, ORR 50%, 95% CI 42.1%, 57.4%). The ORR will also be presented by patient cohort: patients who received previous TKI only; patients who received a TKI and a platinum-based doublet chemotherapy (patients may have also received additional lines of treatment).

Secondary efficacy variables include: DoR, DCR, tumor shrinkage, PFS (according to RECIST 1.1 as assessed by ICR); HRQoL and symptoms; overall survival (OS).

For the primary analysis, ORR will be based on ICR defined visit responses. The imaging scans will be reviewed by two independent radiologists blinded to individual patient data using RECIST 1.1 criteria and will be adjudicated if required. For each patient, the ICR will define the overall visit response data and the relevant scan dates for each time point (ie, for visits where response or progression is/is not identified). Endpoints (ORR, DoR, DCR, PFS) will be derived from the overall visit response data and the scan dates. Sensitivity analyses of ORR, DoR, DCR and PFS from the investigators assessment will also be performed. The concordance between ORR as assessed by ICR and by investigator will be presented.

The data cut-off for the primary analysis of ORR will take place approximately 18 weeks after the last subject has been enrolled, to allow opportunity for all patients to complete two RECIST follow-up assessments. At this time, DoR and safety/tolerability will also be summarised. The primary analysis will report the analysis of ORR supported by DoR, and safety and tolerability data.

The data cut-off for the full analysis will take place approximately 12 months after the last subject has been enrolled, to allow responding patients to have a DoR greater than 6 months. The full analysis will report the analysis of all primary and secondary endpoints (including updated ORR and DoR, DCR, tumour shrinkage, PFS, OS, Safety and HRQoL) and summarise the exploratory endpoint of patient reported adverse events (PRO-CTCAE).

All patients will continue to be followed up in order to capture the reliable overall survival data based on a later data cut-off when approximately 95 OS events (about 55% maturity) have been observed out of all enrolled patients. A final analysis for OS, PRO and Safety will be performed based on this DCO. Analysis for RECIST related endpoints (ORR, DoR, tumour shrinkage, DCR and PFS) cut-off at RECIST modules freeze time will be also performed at final analysis.

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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
ALT	Alanine aminotransferase
AnLK	Anaplastic lymphoma kinase
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC(0-24)	Area under the plasma concentration-time curve from zero to 24 hours
AUCss	From zero to the end of the dosing interval
BoR	Best overall response
BCRP	Breast Cancer Resistance Protein
CI	Confidence interval
CLss/F	Apparent plasma clearance at steady state
Cmax	Maximum plasma concentration
CMET	MET or MNNG HOS Transforming gene
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
Css max	Maximum plasma concentration at steady state
Css min	Minimum plasma concentration at steady state
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumour DNA
CYP3A4	Cytochrome P450 3A4
DAE	Discontinuation of Investigational Product due to Adverse Event
DCO	Data Cut-Off

Abbreviation or special term	Explanation
DCR	Disease Control Rate
DES	Data Entry Site
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DoR	Duration of Response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EGFR	Epidermal Growth Factor Receptor
EGFRm+	Epidermal Growth Factor Receptor mutation positive
EGFR-TKI	Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items
EORTC QLQ LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items
Ex19Del	Deletions in exon 19
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin Fixed and Paraffin Embedded
FSH	Follicle-Stimulating Hormone
G719X	an in-frame amino acid (glycine (G)) deletion at position 719 in EGFR
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDPE	High-Density-Polyethylene
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
HRQoL	Health related quality of life
IB	Investigator’s Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICR	Independent Central Review

Abbreviation or special term	Explanation
ILD	Interstitial lung disease
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
L858R	an amino acid substitution at position 858 in EGFR, from a leucine (L) to an arginine (R)
L861Q	an amino acid substitution at position 861 in EGFR, from a leucine (L) to a glutamine (Q)
LDH	Lactate dehydrogenase
LH	Luteinizing Hormone
LIMS	Laboratory Information Management System
LSFD	Last Subject First Dose
LSLV	Last Subject Last Visit
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MRT	Mean residence time
MUGA	Multiple Gated Acquisition Scan
NCI	National Cancer Institute
NE	Non-evaluable
NSCLC	Non small cell lung cancer
NTL	Non target lesion
OAE	Other Significant Adverse Event
ORR	Overall Response Rate
OS	Overall Survival
PD	Progression of disease
PFS	Progression Free Survival
PFS2	Time from enrolment to second progression
PGx	Pharmacogenetic

Abbreviation or special term	Explanation
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per protocol
PR	Partial Response
Pre-medication	Medication used to prevent study drug side effects, for example, to treat diarrhoea once it is detected, and used as long as needed. It can also be used prophylactically in case subjects are prone to develop a particular adverse event.
PRO	Patient reported outcome
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
QT	Interval on the electrocardiogram representing the duration of depolarization and repolarization of the heart
QTc	The QT interval corrected for heart rate
RAC	Extent of accumulation on multiple dosing
RBC	Red Blood Cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumours version 1.1
RR	Response Rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SPC	EU Summary of Product Characteristics
T790M	an amino acid substitution at position 790 in EGFR, from a Threonine (T) to a Methionine (M)
T790M+	T790M mutation positive
TCS	Tata Consultancy Services
TKI	Tyrosine Kinase Inhibitor
TL	Target Lesion
tmax	Time to Cmax
tss max	Time to Css max
ULN	Upper limit of normal
US	United States

Abbreviation or special term	Explanation
WBDC	Web Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

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

Treatment of advanced NSCLC can be guided by the presence of certain molecular drivers such as EGFR, anaplastic lymphoma kinase (AnLK) and KRAS mutations. 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) Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (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.

1.2 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 resistance mutation following prior therapy with an EGFR-TKI. The clinical development programme with AZD9291 will initially assess the safety and efficacy of AZD9291 in patients with advanced NSCLC whose cancers have progressed following an EGFR-TKI regimen (with or without additional

chemotherapy regimens), as they currently represent a major unmet medical need population. Importantly, preliminary data from an ongoing phase I study (D5160C00001) in this patient population has demonstrated good evidence of efficacy, while treatment with AZD9291 has been well tolerated across a range of doses (refer to the latest edition of the Investigator Brochure for further details) (Ranson, WCLC 2013).

1.3 Rationale for study design

No approved therapies currently exist to specifically target T790M+ acquired EGFR-TKI resistance, which represents the most common resistance mechanism in the majority of NSCLC patients with acquired EGFR-TKI resistance. The purpose of this study is to further characterise and confirm in an Asian Pacific patient population the efficacy and safety of AZD9291 in EGFRm+/T790M+ NSCLC patients who have acquired resistance to an EGFR-TKI (with or without additional chemotherapy regimens) observed in the ongoing phase 1 study (D5160C00001).

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 develop resistance with a median time to progression of around 9-11 months. In at least half of initially TKI-responsive patients, disease progression is associated with the emergence of a secondary EGFR mutation, called T790M mutation in exon 20 of the EGFR gene. There are no current effective recommended 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 is therefore appropriate to evaluate the efficacy and safety of AZD9291 in this study.

The study design has been discussed with the US FDA and Swedish MPA during Scientific Advice consultations and all key aspects of the Phase II 2nd line study design including Response Rate (RR) as primary endpoint, dose rationale and patient population (both chemo treated and chemo-naive) were supported.

Given the unmet medical need that exists in the aforementioned patient population alongside with the lack of well-proven treatment options and associated with the good evidence of efficacy (50% RR in T790M+ population) and well tolerated profile reported in ongoing phase I study in T790M+ patient population (Ranson, WCLC 2013), it is considered appropriate to assess efficacy and safety of AZD9291 in an open label, single arm (non-randomised) phase II study.

The primary objective of this study is ORR. This is an appropriate primary efficacy endpoint in this NSCLC population and will provide evidence of tumour shrinkage that may be associated with an improvement in PFS, symptom control, and quality of life. Secondary efficacy endpoints are those that are appropriate to this patient population and include PFS, DoR, Disease Control Rate [(DCR): CR+PR+SD] and overall survival.

Several exploratory endpoints will be evaluated (see Section 8.7.6). These include assessment of the effect of AZD9291 on health state utility (using EQ-5D-5L health state utility index) and resource utilization (eg, hospital visits). Additional exploratory endpoints will include

patient self-reporting of adverse events, further characterisation AZD9291 effects on survival (ie, impact of baseline potentially prognostic factors on survival, assessment of the course of the disease [post-progression treatment and time from study baseline to progression on post AZD9291 treatment (PFS2)] and tumour samples and biomarkers (ctDNA for the assessment of biomarkers) and tumour biopsy for companion diagnostic development.

The collection of cerebrospinal fluid (CSF) will enable the investigation of the ability of AZD9291 and its metabolites (AZ5104 and AZ7550) to cross the blood brain barrier. Brain metastases occur in 20%-30% of patients with advanced NSCLC, and are associated with poor prognosis (Porta 2011). The first generation EGFR TKI agents have demonstrated only limited efficacy in treating brain metastases (Bai et al 2013, Shimato et al 2006), however, preclinical data suggests that AZD9291 may be capable of crossing the blood brain barrier (see Investigator Brochure) and potentially may offer better exposures in this anatomically protected location.

Overall, the totality of primary, secondary and exploratory endpoints is AURA2 study will allow a robust characterisation of overall benefit/risk of AZD9291 in a T790M+ advanced NSCLC patient population.

The dose of 80 mg once daily was selected 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.

1.4 Benefit/risk and ethical assessment

In the advanced NSCLC post EGFR-TKI treatment failure setting that has been chosen for initial study with AZD9291, median survival is modest (~16 months for second line therapy, ~10 months for third line therapy) with no effective treatment options currently available. This population therefore represents a major unmet medical need. Although there can be no certainty of clinical benefit to patients, the biological hypothesis, non-clinical and, in particular, the preliminary clinical efficacy and safety data with AZD9291 in the ongoing phase 1 study (D5160C00001) support the notion that dual EGFR mutation inhibition may be a valid target for the treatment of NSCLC tumours driven via this pathway. Specifically the safety profile of AZD9291 is (in the ongoing phase 1 study) modest with the majority of adverse events being non-clinically significant EGFR-related adverse events (ie, diarrhoea and

skin rash). All trials of AZD9291 exclude patients with clinically significant toxicities related to prior treatments in addition to specifically excluding patients with a history of interstitial lung disease or clinically active interstitial lung disease as this is an uncommon but well documented EGFR related toxicity. All patients are assessed for possible known EGFR-related toxicities (see Section 6) and detailed information on the management of EGFR-related gastrointestinal, dermatological and ophthalmic is provided for all AZD9291 studies.

It is therefore reasonable and appropriate to evaluate AZD9291 in this unmet medical need NSCLC patient population.

1.5 Study design

This is a phase II, open label, single arm study assessing the safety and efficacy of AZD9291 (80 mg, orally, once daily) in patients with a confirmed diagnosis of EGFRm+ and T790M+ locally advanced or metastatic NSCLC (Stage IIIB-IV), who have progressed following prior therapy with an approved EGFR-TKI agent.

In order to enrol approximately 175 patients it is expected that approximately 440 patients will be screened. The 150 patients from China will compose 2 cohorts:

- Approximately 50 patients with EGFRm+ and T790M+ NSCLC who have progressed following 1st line EGFR-TKI treatment but who have not received further treatment

- Approximately 100 patients with EGFRm+ and T790M+ NSCLC who have progressed following prior therapy with an EGFR-TKI and a platinum-based doublet chemotherapy. Patients may have also received additional lines of treatment.

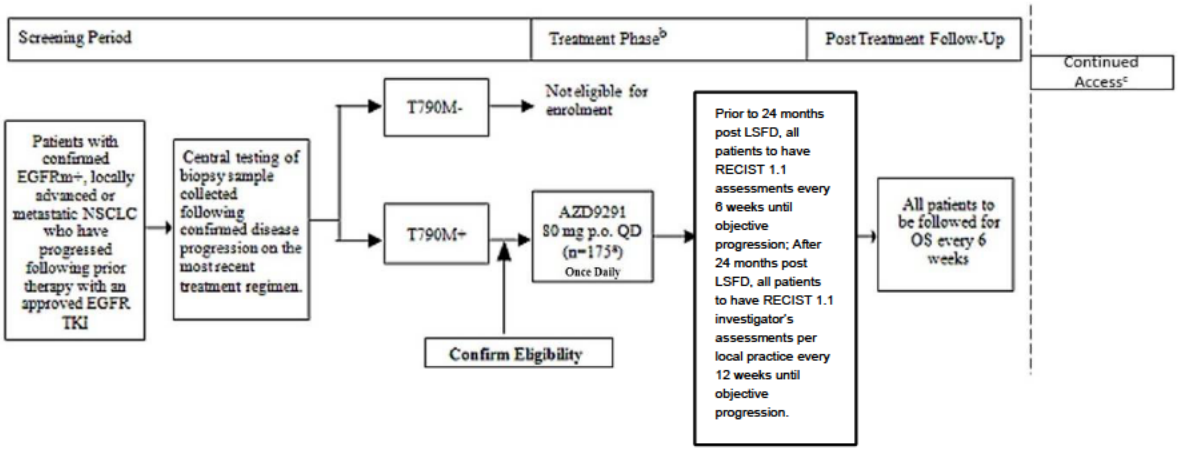
The remaining 25 patients are from other countries. It is expected to enroll patients in a similar ratio between the 2 cohorts as that of the Chinese patient group, e.g. approximately 8 patients from 2nd line and 17 patients from 3rd line or beyond. Patients who have prior neo-adjuvant or adjuvant chemotherapy treatment within 6 months of starting 1st EGFR TKI treatment will be treated as 3rd line patients.

The study size has been selected in order to make an accurate assessment of safety/tolerability and to estimate ORR with 95% confidence intervals that are within +/- 8%. The sample size of the Chinese group of each cohort has been selected in order to provide acceptable precision of the estimation of ORR (ORR 50%, +/-11% for multiple therapies; +/-13% for previous TKI only). Enrolment to individual cohorts may be closed separately. Sites will be informed in advance of cohort closure timelines.

A mandatory biopsy will be needed for central testing of T790M mutation status following confirmed disease progression on the most recent treatment regimen. The T790M mutation status of the patient's tumour must be determined by the designated central laboratory using the cobas® EGFR Mutation Test - and/or the ADx-EGFR test.

Patients should continue on treatment with AZD9291 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 show clinical benefit, as judged by the investigator.

Figure 1.5 Study Flow Chart



[a] 175 patients will be enrolled to this study. The approximately 150 patients from China will compose 2 cohorts: approximately 50 patients with T790M+ NSCLC who have progressed following 1st line EGFR-TKI treatment but who have not received further treatment and approximately 100 patients with T790M+ NSCLC who have progressed following prior therapy with an EGFR-TKI and a platinum-based doublet chemotherapy and Patients may have also received additional lines of treatment. The remaining 25 patients are from other countries. It is expected to enroll patients in similar ratio between the 2 cohorts as that of the Chinese patient group, e.g. approximately 8 patients from 2nd line and 17 patients from 3rd line or beyond.

[b] Patients should continue on treatment with AZD9291 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 show clinical benefit, as judged by the investigator.

[c] Patients receiving AZD9291 at the time of study reaches to final DCO (i.e., after final data cut-off date) may continue to receive AZD9291, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment, the period is defined as continued access.(Please refer to section 4.4and section 7.8)

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To assess the efficacy of AZD9291 by assessment of Objective Response Rate (ORR).	ORR according to RECIST 1.1 by an Independent Central Review (ICR). Sensitivity analysis of ORR using investigators assessments of RECIST 1.1.

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To further assess the efficacy of AZD9291 in terms of: - Progression Free Survival (PFS) - Duration of Response (DoR) - Disease Control Rate (DCR) - Tumour shrinkage - Overall Survival (OS)	PFS, DoR, DCR, and tumour shrinkage according to RECIST 1.1 using assessments performed by an ICR. Sensitivity analysis of PFS, DoR, DCR and tumour shrinkage using investigators assessments of RECIST 1.1. Description of OS.
To assess the safety and tolerability profile of AZD9291.	- Adverse events (graded by CTCAE v4) - Clinical chemistry, haematology and urinalysis - Vital signs, Physical Examination, Weight - Digital ECG - WHO Performance Status - Echocardiogram/MUGA (for LVEF)
To assess the impact of AZD9291 on patients' disease-related symptoms and health related quality of life (HRQoL).	EORTC QLQ-C30: Questionnaire consisting of 30 items measuring patients' general cancer symptoms and functioning. EORTC QLQ LC13: A complementary questionnaire measuring lung cancer symptoms and side effects from conventional chemo- and radiotherapy.

2.3 Exploratory objectives

Results from such analyses outlined below may be reported separately from the Clinical Study Report (CSR).

Exploratory Objective:	**Outcome Measure:**
To explore the impact of AZD9291 treatment and disease state on health state utility.	The EQ-5D-5L health state utility index will be used to derive health state utility based on patient reported data.
To describe and evaluate resource use associated with AZD9291 treatment and underlying disease.	Health resource utilization measures including hospitalization, outpatient visits, or emergency department visits.
To further characterise AZD9291 effects on survival, including impact of baseline prognostic factors, post progression treatments and the course of disease (further progression and changes in symptoms).	Baseline potentially prognostic variables (eg, tumour stage, performance status, sex, baseline LDH), time from enrolment to second progression (referred to as PFS2), time to subsequent treatments, change in symptoms.
To collect and store tumour samples and plasma for potential exploratory research into factors that may influence susceptibility to/development of NSCLC/cancer and/or response to AZD9291 (where response is defined broadly to include efficacy, tolerability or safety).	Analysis of key genetic and proteomic markers to include, but not limited to, EGFR mutations, HER2 & CMET expression and/or amplification. Collection of plasma samples to include, but not be limited to, extraction of circulating tumour DNA (ctDNA) for investigation of biomarkers. Samples may be analysed retrospectively. Any biomarker data generated may be reported separately and may also form part of a pooled analysis with other AZD9291 studies.
To collect and store additional tumour tissue taken following confirmed disease progression on the most recent treatment regimen, for use by a 3rd party diagnostics partner to undertake necessary technical studies for companion diagnostic development and approval.	Technical performance verification studies and clinical reproducibility testing to support the regulatory package for pre-market approval of a companion diagnostic test.
To collect, and store plasma for isolation of ctDNA. Extracted ctDNA will be assessed for the presence of genetic aberrations including, but not limited to, EGFR mutations (T790M, L858R, etc). These samples may be shared with a diagnostic partner for development of a ctDNA test for T790M detection.	Retrospective/real-time analysis of EGFR (and other) mutations in ctDNA from all study patients. More than one method may be used during the course of this study.

Exploratory Objective:	Outcome Measure:
To assess adverse events by patient self-reporting of specific CTCAE symptoms.	Collection of approximately 28 PRO-CTCAE symptoms via an electronic device solution.
To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response to AZD9291, (ie, safety and efficacy) and/or susceptibility to/development of cancers	Correlation of polymorphisms with variation in pharmacodynamic, safety or response observed in patients treated with AZD9291 Data generated may be reported separately and may also form part of a pooled analysis with other AZD9291 studies
To collect and store residual CSF for potential exploratory research of factors that may influence development of NSCLC and/or response to AZD9291 (where response is defined broadly to include efficacy, tolerability or safety).	Collection of CSF for the concentration of AZ9291 and its metabolites (AZ5104 and AZ7550) and/or biomarkers. Samples may be analysed retrospectively.

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

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

3.1 Inclusion criteria

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

1. Provision of informed consent prior to any study specific procedures, sampling and analyses. If a patient declines to participate in any voluntary exploratory research and/or genetic component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

2. Male or female, aged at least 18 years. Patient from Asia Pacific will be enrolled only.

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 on the last treatment administered prior to enrolling in the study:

- following 1st line EGFR TKI treatment but who have not received further treatment

OR

- following prior therapy with an EGFR TKI and a platinum-based doublet chemotherapy regardless the sequence of treatment. Patients may have also received additional lines of treatment.

6. 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).

7. Patients must have central confirmation of tumour T790M mutation positive status from a biopsy sample taken after confirmation of disease progression on the most recent treatment regimen.

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

9. At least one lesion, not previously irradiated and not chosen for biopsy during the study screening period, that can be accurately measured at baseline as ≥10mm in the longest diameter (except lymph nodes which must have short axis ≥15mm) with computerised tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements. If only one measurable lesion exists, it is acceptable to be used as long as it has not been previously irradiated, and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed.

10. Females should be using adequate contraceptive measures, 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 amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments
    - Women under 50 years old would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution
    - Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation

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

12. For inclusion in the **optional genetics research** study patients must:

- Provide informed consent for genetic research

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

3.2 Exclusion criteria

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

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

2. 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 washout time has not occurred due to schedule, an alternative appropriate washout time based on known duration and time to reversibility of drug related adverse events could be agreed upon by AstraZeneca and the Investigator).
   - Any cytotoxic chemotherapy, investigational agents or 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 EGFR TKIs (eg, CO-1686)
   - Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study treatment
   - Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation 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 study treatment) medications or herbal supplements known to be potent inhibitors or inducers of CYP3A4 (Appendix E)
   - Treatment with an investigational drug within five half-lives of the compound

3. 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.

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

5. 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. However, for patients participating biomarker/genetic research and from outside of China, HBV, HCV and HIV tests are needed for sample shipment purpose, and results should be negative.

6. 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.

7. Any of the following cardiac criteria:

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

8. 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.

9. Inadequate bone marrow reserve or organ 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.

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

11. Males and females of reproductive potential who are not using and effective method of birth control and females who are pregnant or breastfeeding or have a positive (urine or serum) pregnancy test prior to study entry.

12. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

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

13. Prior allogeneic bone marrow transplant.

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

15. Other co-existing malignancies or malignancies diagnosed within the last 5 years, with the exception of basal cell carcinoma or cervical cancer in situ.

Procedures for withdrawal of incorrectly enrolled subjects see Section 3.4.

3.3 Subject enrolment

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

The Investigator(s) will:

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

2. Assign potential subject a unique 7-digit enrolment number obtained through the IVRS/IWRS in the following format ECCNNXXX: CC being the country code, NN being the centre number and XXX being the patient enrolment code at the centre.

   If a subject is re-screened, a new E-code will always be assigned. Any repeated tests and/or procedures will be performed as per documented local standards. Subjects will reconfirm their consent to participate in the study by resigning and dating their original consent form(s), next to their initial signature and date. A subject with a valid negative T790M result cannot be re-screened.

3. Determine subject eligibility. See Section 3.

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

4. Perform a drug dispensing call in IVRS/IWRS.

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

3.4 Procedures for handling incorrectly enrolled subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is started on treatment in error, the investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 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 6 weeks 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 4 months. Male patients should avoid procreation for 4 months after completion of trial treatment. Patients should refrain from donating sperm from the start of dosing until 4 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 E).

4. If medically feasible, patients taking regular medication, with the exception of potent inducers of CYP3A4 (see above), should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon BCRP and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving AZD9291. Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (see Appendix E).

   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

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

5. 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.

3.6 Discontinuation of investigational product

Subjects may be discontinued from investigational product (IP) in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event (eg, Risk to patients as judged by the investigator and /or AstraZeneca)
- Pregnancy
- Severe non-compliance with the study protocol as judged by the investigator and/or AstraZeneca

- Patient incorrectly initiated on investigational product
- Objective disease progression or subject is no longer receiving clinical benefit
- Subject loss to follow-up

3.6.1 Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue investigational product or withdraw from the study (ie, investigational product and assessments – see Section 3.7), without prejudice to further treatment. A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Section 6); and all study drugs should be returned by the subject.

Any subject who discontinues study treatment for reasons other than objective disease progression should have tumour assessments performed as scheduled in the protocol (See Table 1 and Table 2) until objective disease progression is documented or death occurs, unless consent is withdrawn. Study procedures related to PROs, SAEs and anti-cancer treatment must be captured until the subject no longer has RECIST 1.1 assessments (disease progression or permanent withdrawal from the study).

3.7 Withdrawal from the study

The term withdrawal from the study refers to both discontinuation from study treatment and study assessments.

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

- Screen failure
- Death
- Withdrawal of consent

If a patient wishes to withdraw their consent to both treatment and study assessments, they should be asked if they are willing to continue with survival follow-up (which can be conducted by telephone – see Section 4.3.4). If a patient wishes to withdraw their consent to further participation in the study entirely, including survival follow-up this should be clearly documented in the patient notes and in the clinical study database.

Withdrawn patients will not be replaced.

3.7.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not receive AZD9291. These patients should have the reason for study withdrawal recorded as “Ineligible” (ie, patient does not meet the required inclusion/exclusion

criteria). This reason for study withdrawal is only valid for screen failures (not patients who have received AZD9291).

3.7.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

Patients may withdraw from any aspects of the voluntary research (see Sections 3.7, 5.4 and 5.5) at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. The patient will return electronic PRO (ePRO) devices and unused study drug.

3.8 Termination of the study

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

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

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

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

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Plan - Prior to 24 months post LSFD

Visit	Screening	Treatment Period (further treatment cycles as per Cycle 7)							Treatment Discontinuation	Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+		28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[a]/ Day		C1 D1	C1 D8	C1 D15	C2 D1	C3 D1	C4-6 D1	C7[b]+D1	NA	NA	NA	NA	
Day	-28 to 1	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)[z]	NA	0	±2	±2	±7	±7	±7	±7	0	±7	±7	±7	SECTION:
Informed consent[c]	X												3.3 & 4.1
Submit mandatory tumour tissue sample for mutation analysis[d]	X												4.1 & 5.6
Submit tumour tissue for diagnostic development (optional)[e]	X												4.1 &5.6
Optional tumour biopsy for exploratory research									X[u]		X[u]		5.6
Archival tumour tissue[f]	X												5.6

Table 1 Study Plan - Prior to 24 months post LSFD

Visit	Screening	Treatment Period (further treatment cycles as per Cycle 7)							Treatment Discontinuation	Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+		28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[a]/ Day		C1 D1	C1 D8	C1 D15	C2 D1	C3 D1	C4-6 D1	C7[b]+D1	NA	NA	NA	NA	
Day	-28 to 1	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)[z]	NA	0	±2	±2	±7	±7	±7	±7	0	±7	±7	±7	SECTION:
Demography & baseline characteristics	X												4.1
Medical/surgical history	X												4.1
Inclusion/exclusion criteria[x]	X												3
Physical examination, including weight[g]	X	X[g]			X	X	X	X	X				5.2.3 & 5.2.6.2
Height	X												5.2.6.2
WHO Performance status[g]	X	X			X	X	X	X	X				4.1
Pregnancy test (pre-menaopausal females only)	X												5.2.1

Table 1 Study Plan - Prior to 24 months post LSFD

Visit	Screening	Treatment Period (further treatment cycles as per Cycle 7)							Treatment Discontinuation	Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+		28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[a]/ Day		C1 D1	C1 D8	C1 D15	C2 D1	C3 D1	C4-6 D1	C7[b]+D1	NA	NA	NA	NA	
Day	-28 to 1	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)[z]	NA	0	±2	±2	±7	±7	±7	±7	0	±7	±7	±7	SECTION:
Ophthalmolgic assessment	X	← as clinically indicated →											5.2.7.1
Vital signs[g]	X	X	X	X	X	X	X	X	X				5.2.6
Clinical chemistry[y]/ Haematology/Urinalysis[g]	X	X[h]	X	X	X	X	X	X	X				5.2.1
Digital ECG	X	X			X	X	X	X	X				5.2.4
Echocardiogram/MUGA	X		← every 12 weeks(±1 week) relative to first dose →										5.2.5
Plasma sample for ctDNA[g]	X[i]	X	X	X	X	X	X	← every 6 weeks in line with RECIST assessments[j] →					4.3.3 & 5.6.2
Optional genetic consent and sample	X[k]												5.5
Optional CSF sample					X (once only)[l]								5.4.1

Table 1 Study Plan - Prior to 24 months post LSFD

Visit	Screening	Treatment Period (further treatment cycles as per Cycle 7)							Treatment Discontinuation	Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+		28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[a]/ Day		C1 D1	C1 D8	C1 D15	C2 D1	C3 D1	C4-6 D1	C7[b]+D1	NA	NA	NA	NA	
Day	-28 to 1	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)[z]	NA	0	±2	±2	±7	±7	±7	±7	0	±7	±7	±7	SECTION:
Tumour assessments (RECIST v1.1)[m]	X[v]	every 6 weeks(±1 week) relative to first dose until disease progression											4.2 & 5.1.1
EORTC QLQ-C30 and EQ-5D-5L (by electronic device)		X[g]	every 6 weeks(±1 week) relative to first dose						X		X[n]	X[n]	5.3.2.1 & 5.3.2.2
EORTC QLQ LC13 (by electronic device)		X[g]	Weekly(±2days) relative to first dose				every 3 weeks(±3 days) relative to first dose		X		X[o]	X[o]	5.3.2.1
PRO-CTCAE (by electronic device)[p]		X[g]	weekly(±2 days) for first 18 weeks of treatment					X[q]	X		X[o]	X[o]	5.3.2.3
Healthcare Resource Use													5.3.2.5
Dispense study medication		X			X	X	X	X[b]					3.3 & 7.2

Table 1 Study Plan - Prior to 24 months post LSFD

Visit	Screening	Treatment Period (further treatment cycles as per Cycle 7)							Treatment Discontinuation	Follow-up Period			For details see Protocol Section
	1	2	3	4	5	6	7-9	10+		28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[a]/ Day		C1 D1	C1 D8	C1 D15	C2 D1	C3 D1	C4-6 D1	C7[b]+D1	NA	NA	NA	NA	
Day	-28 to 1	1	8	15	22	43	64-106	127+	NA	NA	NA	NA	
Window (days)[z]	NA	0	±2	±2	±7	±7	±7	±7	0	±7	±7	±7	SECTION:
Dose with AZD9291		← Daily dosing →											7.2
Concomitant medication & procedures	←							→					7.7
Adverse events[w]	←							→			X[r]	X[r]	6.3 & 6.4
Survival Status												X[s]	4.3.4
Anti-cancer treatment	X										X	X[s]	4.3.3, 4.3.4
Subsequent response /progression data												X[t]	5.8

[a] A cycle is defined as 21-day treatment period.
[b] Visit schedule changes after Cycle 7 Day 1 from every 21 days (3 weeks) to every 42 days (6 weeks).
[c] Consent may be taken prior to 28-day window if required,
[d] Taken following progression on the latest line of therapy. The collection of this tumour tissue sample for central mutation analysis is not included in the 28-day screening period.
[e] The optional second tumour tissue sample can be taken as part of the same procedure as the mandatory screening biopsy for mutation analysis.
[f] Archival tumour sample only to be submitted after T790M positive status confirmed by central testing. Not required for T790M negative patients.

[g] To be completed pre-dose.
[h] If screening assessments are not done at Visit 2, but have been done at Visit 1 and have been performed within 14 days window prior to starting study treatment, with no change in condition and no clinical indication to do so, they do not have to be repeated on Visit 2 if subject's condition has not changed. (except for fasting glucose).
[i] To be taken at the same time as the screening biopsy is taken or prior to mutation screening. All plasma samples are required by AstraZeneca, regardless of the outcome of the mutation screening.
[j] Collect every 6 weeks up to and including progression (corresponding with the RECIST assessments – and continuing after treatment discontinuation in absence of disease progression).
[k] If for any reason the sample is not drawn prior to first dose it may be taken at any visit until the last study visit.
[l] To be obtained at one time point at any time from Cycle 2 Day 1 onwards
[m] If only one measurable lesion exists, it is acceptable to be used as long as it has not been previously irradiated, and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed.
[n] Assess every 6 weeks relative to first dose until end of study (including survival follow-up period) and at the time of progression.
[o] Assess every 3 weeks relative to first dose until end of study (including survival follow-up period) and at the time of progression.
[p] PRO-CTCAE will only be administered in those countries where a linguistically validated version exists.
[q] Assessed at Cycle 7 Day 1 then every 3 weeks relative to first dose thereafter until end of study (including survival follow-up period) and at the time of progression.
[r] Following AZD9291 discontinuation, SAEs considered related to study procedures should continue as outlined in Table 6.
[s] Survival status including anti-cancer treatment to be performed every 6 weeks (relative to first dose) following disease progression or withdrawal from treatment.
[t] Record subsequent response/progression data every 6 weeks until first confirmed disease progression on a subsequent treatment.
[u] Discontinuation biopsy can be taken at discontinuation or progression, whichever comes first
[v] If the patient has received CT/MRI scan before signing the ICF, and within 28 days prior to treatment, the assessment can still be acceptable if the scan meets the RECIST 1.1 criteria.
[w] A photograph with proper identification cover may be taken by site and shared with Sponsor if the patient has a rash, or changes to eyelashes, skin or eyes during the study.
[x] For patients participating biomarker/genetic research and from outside of China, HBV and HIV tests are needed for sample shipment purpose, and results should be negative.
[y] Fasting glucose during Cycle 1 only (3 visits, C1D1, D8 and D15). And from cycle 2 onwards (visit will occur only on Day 1 for each cycle) random glucose will be collected
[z] Visit windows are always calculated in relation to Cycle 1, Day 1.

Table 2 Study Plan - After 24 months Post LSFD until Final DCO[a]

Visit	Treatment post 24 months every 84 days (12 weeks)	Treatment Discontinuation	Follow-up Period			For details see Protocol Section
	10+		28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[b]/ Day	**D1**	**NA**	**NA**	**NA**	**NA**	
Window (days)	**±7**	**0**	**±7**	**±7**	**±7**	**SECTION:**
Optional tumour biopsy for exploratory research		X		X		5.6
Physical examination, including weight	X	X				5.2.3 & 5.2.6.2
WHO Performance status	X	X				4.1
Pregnancy test (pre-menopausal females only)	as clinically indicated					5.2.1
Ophthalmologic assessment	← as clinically indicated →					5.2.7.1
Vital signs[c]	X					5.2.6
Digital ECG	X	X				5.2.4
Echocardiogram/MUGA	every 12 weeks (±1 week) related to first dose					5.2.5
Clinical chemistry/ Haematology/Urinalysis[c]	X	X				5.2.1
Echocardiogram/MUGA	X					5.2.5
Plasma sample for ctDNA[c]	X					4.3.3 & 5.6.2

Table 2 Study Plan - After 24 months Post LSFD until Final DCO[a]

Visit	Treatment post 24 months every 84 days (12 weeks)	Treatment Discontinuation	Follow-up Period			For details see Protocol Section
	10+		28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[b]/ Day	**D1**	**NA**	**NA**	**NA**	**NA**	
Window (days)	**±7**	**0**	**±7**	**±7**	**±7**	**SECTION:**
Optional genetic consent and sample	X[d]					5.5
Optional CSF sample	X (once only)[e]					5.4.1
Tumour assessments (RECIST v1.1)	X (every 12 weeks until disease progression)[f] ← →					4.2 & 5.1.1
EORTC QLQ-C30 and EQ-5D-5L (by electronic device)	X (every 6 weeks until end of study and at the time of progression)relative to first dose ← →					5.3.2.1 & 5.3.2.2
EORTC QLQ LC13 (by electronic device)	X (every 3 weeks until end of study and at the time of progression) relative to first dose ← →					5.3.2.1
PRO-CTCAE (by electronic device)	X (every 3 weeks until end of study and at the time of progression) relative to first dose ← →					5.3.2.3
Healthcare Resource Use	← →					5.3.2.5
Dispense study medication	X					3.3 & 7.2
Dose with AZD9291	Daily dosing					7.2
Concomitant medication & procedures	← →					7.7

Table 2 Study Plan - After 24 months Post LSFD until Final DCO[a]

Visit	Treatment post 24 months every 84 days (12 weeks)	Treatment Discontinuation	Follow-up Period			For details see Protocol Section
	10+		28-day follow-up	Progression follow-up	Survival follow-up	
Cycle[b]/ Day	D1	NA	NA	NA	NA	
Window (days)	±7	0	±7	±7	±7	SECTION:
Adverse events	←	←	←	X[g]	X[g]	6.3 & 6.4
Survival Status					X[h]	4.3.4
Anti-cancer treatment				X	X[h]	4.3.3, 4.3.4
Subsequent response /progression data					X[i]	5.8

[a] Table 2is applicable for subject who is still receiving treatment or in follow up period after 24 months post last subject first dosing until final DCO (eg. when approximately 95 OS events have been observed out of all enrolled subjects).
[b] Visit schedule changes after Cycle 7 Day 1 from every 21 days (3 weeks) to every 42 days (6 weeks).
[c] To be completed pre-dose.
[d] If for any reason the sample is not drawn prior to first dose it may be taken at any visit until the last study visit.
[e] To be obtained at one time point at any time from Cycle 2 Day 1 onwards
[f] After 24 month Post LSFD the sites will continue to perform tumour investigator's assessments every 12 weeks(±1 week) per local practice until disease progression. No data will be collected into study database.
[g]. Following AZD9291discontinuation, SAEs considered related to study procedures should continue as outlined in Table 6
[h]. Survival status including anti-cancer treatment to be performed every 6 weeks (relative to first dose) following disease progression or withdrawal from treatment.
[i] Record subsequent response/progression data every 6 weeks until first confirmed disease progression on a subsequent treatment.

4.1 Screening period

It is recommended the screening assessments be performed in a stepwise process beginning with the confirmation of T790M mutation status as determined by the designated central laboratory. However, screening assessments may be done in parallel to the T790M mutation assessment, as appropriate. Procedures will be performed according to the Study Plan (See Table 1). 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 the study treatment.

At screening, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects who do not meet these criteria must not be enrolled in the study. Demographic data and other characteristics will be recorded and will include date of birth or age, gender, smoking history, race and/or ethnicity according to local regulations.

Patients will be considered in screening period until all Visit 1 assessments are completed and eligibility is confirmed. Patients will be considered enrolled and in the treatment period once AZD9291 therapy has been initiated.

Mandatory screening tumour biopsy sample for mutation analysis:

Tumour sample must be formalin fixed and paraffin embedded (FFPE) and must be biopsied following progression on the latest line of therapy. Samples may be collected from primary or metastatic tumour deposits. Bone samples (including soft tissue tumoural masses emerging from the bone) cannot be accepted for testing. Sites should ship the FFPE tumour sample to the testing laboratory as soon as it is available. Tissue should be less than 60 days old from date of sectioning to date of testing. Blocks must be provided wherever possible. If this is not possible, 12-20 slides of freshly prepared unstained 5-micron sections from this screening tumour block may be provided. See Section 5.6.

The mandatory screening tumour biopsy must not be taken from a previously irradiated lesion (Please refer to Inclusion criterion number 9 for details). This biopsy sample is not subject to the 28-day screening window; if tissue is already available from a biopsy taken since confirmation of disease progression on the most recent treatment regimen then there is no need for a further biopsy as this sample can be submitted for T790M mutation status. If the first biopsy is not confirmed as T790M mutation positive due to test failure (i.e. an invalid result or invalid run occurred), testing will be repeated and an additional biopsy sample may be requested. If the T790M mutation is not detected in the first biopsy (and the cobas® EGFR Mutation Test indicates a valid result), no additional testing for the subject will be performed for this study and an additional biopsy sample WILL NOT be accepted.

Optional second tissue sample for diagnostic development:

The optional second tissue sample (FFPE) may be provided to facilitate diagnostic development and pre-market approval of the diagnostic test. This should be obtained at the same time and as part of the same procedure as the mandatory screening biopsy.

Written informed consent/Assignment of subject enrolment number:

Each potential subject will provide informed consent prior to starting any study specific procedures (see Section 10 of this Clinical Study Protocol for Ethics and Regulatory Requirements). All subjects will be required to provide consent to supply a new tumour biopsy sample entry into this study. This consent is included in the main subject informed consent form. However, please note that patients are asked to provide separate consent for provision of optional tumour biopsy samples, if willing (see Section 5.6).

Once consent has been signed, the PI or delegate, will contact IVRS/IWRS to have the subject assigned a unique enrolment number.

WHO Performance Status:

Performance status will be assessed at the visits indicated in the Study Plan (see Table 1 and Table 2) according to WHO criteria as follows:

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

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

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

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

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

4.2 Treatment period

A cycle of treatment is defined as 21 days of once daily AZD9291 treatment. After Cycle 7 Day 1, the duration between study visits will change from every 21 days (3 weeks) to every 42 days (6 weeks).

If a patient continues to receive treatment with AZD9291 beyond RECIST 1.1 defined progression they must continue to follow the Treatment visit schedule and assessments excluding study specific RECIST 1.1 assessments.

Descriptions of the procedures for this period are included in the Study Plan (see Table 1 and Table 2).

After final DCO (i.e. after final data cut-off date), patients may continue to receive AZD9291, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment, the period is defined as continued access. (see Section 4.4 and Section 7.8)

4.3 Follow-up period

4.3.1 Discontinuation visit

A Discontinuation Visit will be performed at the time AZD9291 is permanently stopped. Refer to Table 1 and Table 2 for full details.

4.3.2 28 Day follow-up

As a minimum, telephone contact should be made with the patient 28 days (+/-7 days) following the discontinuation of AZD9291 to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy). Refer to Section 6.3 for full details on AE recordings during follow-up.

4.3.3 Progression follow-up

Patients who discontinue AZD9291 for reasons other than progression will continue RECIST 1.1 assessments every 6 weeks (relative to first dose of AZD9291) for objective progression prior to RECIST modules freeze time (24 months post LSFD). The last tumour assessment data at 24 months post LSFD should be entered into RAVE per eCRF entering guidance. In addition to RECIST 1.1 assessments, the following assessments are also required during this follow-up period as detailed in the Study Plan (see Table 1):

Prior to RECIST modules freeze time:

- EORTC QLQ-C30 and EQ-5D-5L every 6 weeks and at the time of progression.
- EORTC QLQ LC13 and PRO-CTCAE every 3 weeks and at the time of progression.
- Plasma for ctDNA collected every 6 weeks up to and including progression (corresponding with the RECIST 1.1 assessments – and continuing after treatment discontinuation if this is in absence of progression)
- Adverse event collection detailed in Table 6
- Anti-cancer therapy collected every 6 weeks.

Change after RECIST modules freeze time:

- After RECIST modules freeze time, the sites will continue to perform tumour investigator's assessments every 12 weeks according to their local practice, both central imaging scans and investigator assessment data will not be collected into eCRF. Please refer to Table 2.
- Plasma for ctDNA collected every 12 weeks up to and including progression (corresponding with the RECIST 1.1 assessments – and continuing after treatment discontinuation if this is in absence of progression). Please refer to Table 2.

4.3.4 Survival follow-up

- Assessments for survival should be made every 6 weeks (relative to first dose) following objective disease progression or withdrawal from treatment. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. In addition to the survival status, the following assessments are also required post progression as detailed in the study plan (see Table 1 and Table 2):
- EORTC QLQ-C30 and EQ-5D-5L every 6 weeks.
- EORTC QLQ LC13 and PRO-CTCAE every 3 weeks.
- Anti-cancer therapy collected every 6 weeks.
- Subsequent response/progression data every 6 weeks until the first confirmed disease progression on a subsequent treatment.

Survival data will be collected up to the time of the final OS analysis. Patients should be contacted in the 2 weeks following the data cut-off for the final survival analyses to provide complete survival data.

The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patients general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

4.4 Patient management in the continued access period (post final DCO)

The final analysis of the study will be performed based upon a DCO when approximately 95 death events (55% maturity) for the overall survival is reached.

At this time point, the clinical study database will close to new data. Patients are, however, permitted to continue to receive study treatment beyond the closure of the database if in the opinion of the investigator they are continuing to receive benefit from treatment. Dispensing of study treatment post final OS analysis DCO will be recorded outside of IWRS/IVRS. Patients who remain on study treatment after this time point will be monitored according to routine clinical practice as defined by the investigator. At routine clinic visits, patients will return the unused medication, and a thorough drug accountability assessment will be performed at the site.

For patients who do continue to receive treatment beyond the time of this data cut off, investigators will continue to report all SAEs, overdose and pregnancies to AstraZeneca via paper and emailed (preferably) or faxed directly to TCS in accordance with section 6.4, 6.5

and 6.6. All SAEs, overdoses and pregnancies would be reported until 30 days after last dose. 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 casually related to the IP, the investigator should notify AstraZeneca (see Section 6.4). Additionally, as stated in section 6.3, any SAE or non-serious AE that is ongoing at the time of this DCO, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up.

Study would be open until last patient treated. Final Last Subject Last visit will be defined as the last visit after last patient's treatment discontinuation.

If study drug would be approved on market for use in disease under study indication, patients may be discontinued and switched to market product. Drug supply options can be available depending on the country and would be proposed to patient when found as best way to continue treatment by both AZ and investigator.

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

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

5.1 Efficacy assessments

5.1.1 RECIST 1.1

All imaging assessments including unscheduled visit scans should be collected on an ongoing basis and sent to an AstraZeneca (AZ) appointed Clinical Research Organisation (CRO) to enable independent central analyses prior to RECIST modules freeze time (24 months post LSFD).

For both Independent Central Review (ICR) and investigator review RECIST 1.1 criteria will be used to assess each patient's tumour response to treatment and allow calculation of ORR, PFS, DCR, DoR, and assess tumour shrinkage. The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria [CR (complete response), PR (partial response), SD (stable disease) or PD (progression of disease)] are presented in Appendix C. For ORR, a visit response of CR or PR must be confirmed by a later scan conducted at least 4 weeks after the initial response is observed. See Section 4 for considerations related to RECIST 1.1 assessments.

The methods used at baseline for assessment of tumour burden [CT or MRI scans of chest and abdomen (including liver and adrenal glands)] must be used at each subsequent follow-up assessment. Any other areas of disease involvement should be additionally investigated based on the signs and symptoms of individual patients. CT/MRI scan of the brain should be performed in patients with known or suspected brain metastases. The baseline assessment should be performed within 28 days prior to treatment start. Assessments to be performed every 6 weeks relative to first dose until objective disease progression. It is important to follow the assessment schedule as closely as possible. If scans are performed outside of the scheduled visit ±1 week window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Any other sites at which new disease is suspected should also be appropriately imaged.

If the investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesions (NTLs) or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient’s status. If repeat 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 substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

Categorisation of objective tumour response assessment at each visit will be based on the RECIST 1.1 criteria of response: CR, PR, SD and PD. Target lesion (TL) 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.

After 24 month post LSFD, tumour investigator's assessment will be performed following RECIST criteria 1.1 in accordance with local clinical practice every 12 weeks, both scans and data will no longer be collected in eCRF.

5.1.2 RECIST 1.1 Independent Central Review assessment

The primary analysis for this study will be based on ORR using Independent Central Review (ICR) of patients with measurable disease at baseline as assessed by the ICR, according to RECIST 1.1. All scans from all patients (with both progressive and non-progressive disease by investigator assessment), used in the assessment of tumours using RECIST 1.1 will be conducted. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed CRO to enable central analysis. Results of this independent review will not be communicated to Investigators and the management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the Investigator.

Prior to RECIST modules freeze time, tumour assessment will be performed in accordance with clinical practice every 6 weeks until disease progression. The last tumour assessment data at 24 months post LSFD should be entered into RAVE per eCRF entering guidance.

After RECIST modules freeze time, tumour investigator's assessment will be performed in accordance with local clinical practice every 12 weeks until disease progression or final DCO and scans will no longer be collected as well as data will not be collected into study database.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken pre-dose at the times indicated in the Study Plan Table 1 and Table 2). If clinical chemistry, haematology and urinalysis screening assessments have been performed within 14 days prior to staring study treatment they do not have to be repeated on Visit 2 if the patient's condition has not changed (no new treatment during this period of time, no new complication or aggravation).

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

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. The number of samples/blood volumes is therefore subject to site-specific change.

The following laboratory variables will be measured:

Table 3 Laboratory Safety Variables

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[b]	Monocytes
S/P-Lactate dehydrogenase (LDH)[a]	Basophils
S/P-Magnesium	Eosinophils
S/P-Potassium	B-Platelet count
S/P-Sodium	B-Reticulocytes
S/P-Urea nitrogen or Blood urea nitrogen	**Urinalysis**
	U-Glucose
	U-Protein
	U-Blood

[a] LDH is an additional variable collected at Visit 1 only.
[b] Fasting glucose samples during Cycle 1 only (3 visits, C1D1, D8 and D15). And from cycle 2 onwards (visit will occur only on Day 1 for each cycle) random glucose will be collected.

Additionally, at the Screening Visit, a pregnancy test (blood or urine tests are acceptable based on the site's standard clinical practice) will be collected for women of childbearing potential only (See Section 3.1).

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at

centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

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

5.2.2 Volume of blood

Total mandatory blood volume in first 9 weeks is 160 mL.

Visit	Safety (mL)[a]	Plasma (mL)	PGx (mL)
Screening	15	20	10 (optional)
Cycle 1	45	30	
Cycle 2	15	10	
Cycle 3 (onwards)	15	10	
TOTAL (mandatory)	**90**	**70**	**0**

[a] For safety, assumes 6 mL clinical chemistry and 9 mL haematology per visit.

5.2.3 Physical examination

A physical examination will be performed and include an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

5.2.4 ECG

All patients will have 12-lead digital ECGs performed at the study visits indicated in Table 1 and Table 2. Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to times indicated and should be recorded at 25 mm/sec. All ECGs should be recorded with the patient in the same physical position. For each time point three ECG recordings should be taken within an approximate 5 minute period. Digital ECG recordings will be collected, analyzed and stored by a central ECG vendor. A standardized ECG machine should be used and the patient should be examined using the same machine throughout the study if possible.

Resting 12-lead ECG

Twelve-lead ECG will be performed at the visit indicated in the Study Plan (see Table 1 and Table 2).

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

1. Screening

2. On Day 1 of each subsequent Cycle; one assessment at any time during day

3. On occurrence of any cardiac AE

4. Discontinuation visit

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

After ECGs have been recorded as digital ECG files, a print-out will be made and 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 (baseline) is considered to be clinically significant by the investigator, it should be reported as a concurrent medical history condition. If there is a clinically significant abnormal ECG findings during the treatment period, this should be recorded on the AE CRF, according to standard adverse events collection and reporting processes.

5.2.5 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 (±1 week window interval) relative to first dose. The modality of the cardiac function assessments must be consistent within a patient ie, 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.

5.2.6 Vital signs

5.2.6.1 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 1 and 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.

5.2.6.2 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.

5.2.7 Other safety assessments

5.2.7.1 Ophthalmologic exam

Full ophthalmic assessment, including slit lamp examination, should be performed at screening and if a patient experiences any visual symptoms (including blurring of vision),

with additional tests if clinically indicated. Ophthalmology examination results should be collected in the eCRF.

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

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

5.3 Other assessments

5.3.1 Baseline characteristics

Baseline demographics, disease history, previous treatments and EGFR mutation information will be collected.

5.3.2 Patient reported outcomes

Patient reported outcomes (PROs) is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical trials. The following PROs will be administered: EORTC QLQ-C30, QLQ LC13, EQ-5D-5L and PRO-CTCAE (see Appendix F).

5.3.2.1 EORTC QLQ-C30 and QLQ LC13

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group 1993. It consists of 30 items and measures cancer patients' functioning (HRQoL) and symptoms (Aaronson et al 1993) for all cancer types. Questions can be grouped into 5 multi-item functional scales (physical, role, emotional, cognitive and social); 3 multi-item symptom scales (fatigue, pain, nausea and vomiting); a 2-item global HRQoL scale; 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation, diarrhoea) and 1 item on the financial impact of the disease.

The QLQ LC13 is a well-validated complementary module measuring lung cancer associated symptoms and side effects from conventional chemotherapy and radiotherapy (Bergman et al 1994). Refer to Appendix F The QLQ LC13 includes questions assessing cough, haemoptysis, dyspnoea and site specific pain (symptoms), sore mouth, dysphagia, peripheral neuropathy and alopecia (treatment-related side effects) and pain medication.

5.3.2.2 EQ-5D-5L

The EQ-5D is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group 1990). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.

The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty (EuroQol Group 2013).

Since 2009, the EuroQol group has been developing a more sensitive version of the EQ-5D (the EQ-5D-5L) which expands the range of responses to each dimension from 3 to 5 levels of increasing severity (Herdman et al 2011). Preliminary studies indicate that the 5L version improves upon the properties of the 3L measure in terms of reduced ceiling effect, increased reliability and an improved ability to differentiate between different levels of health (Pickard et al 2007, Janssen et al 2008, Janssen et al 2008b).

The patient will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the patient will be asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state (see Appendix F**).**

5.3.2.3 PRO-CTCAE

The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) system has been developed by the National Cancer Institute (NCI). The PRO-CTCAE will only be administered in those countries where a linguistically validated version exists, currently English, Japanese, German and Spanish. PRO-CTCAE is an item-bank of symptoms experienced by patients while undergoing treatment of their cancer. It was developed in recognition that collecting symptom data directly from patients using PRO tools can improve the accuracy and efficiency of symptomatic AE data collection. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate symptom onset, frequency, and severity in comparison with patient ratings (Sprangers et al 1992; Litwin MS et al 1988-1992; Basch et al 2009). To date, 81 symptoms of the CTCAE (version 4) have been identified to be amenable to patient reporting. These symptoms have been converted to patient terms (eg, CTCAE term “myalgia” converted to “aching muscles”). For several symptoms, like fatigue and pain, additional questions are asked about symptom frequency, severity, and interference with usual activities. For other symptoms like rash, additional questions focus on the presence on the body. The items included in the PRO-CTCAE have undergone extensive qualitative review among experts and patients. These items and the additional questions for some of the symptoms have been extensively evaluated by cancer patients, using cognitive testing methods, to be clear, comprehendible, and measure the symptom of interest. Not all items are administered in any one clinical trial. The intention is to only ask patients to complete those items which are considered relevant for the trial, site of cancer, and cancer treatment (see Appendix F).

5.3.2.4 Administration of electronic PROs

Patients will complete the PRO assessments using a handheld electronic device (ePRO). The following best practise guidelines should be followed when collecting PRO data via an electronic device:

- Explain the value and relevance of participation to patients that we are asking these questions because we are interested in hearing directly from them how they feel. The research nurse or appointed site staff should also stress that the information is confidential. Therefore, if the patient has any medical problems he/she should discuss them with the doctor or research nurse separately from the ePRO assessment.

- Remind patients that there are no right or wrong answers, avoid bias by not clarifying items.

- Train the patient on how to use the ePRO device using the materials and training provided by the ePRO vendor. Also provide guidance on whom to call if there are problems with the device.

Monitor compliance: minimizing missing data is a key aspect of study success. Compliance must be checked at each study visit and should be checked more frequently to identify problems early. If compliance drops below 85% a check-in call from the site to ask the patient if he/she has any difficulties is highly recommended.

5.3.2.5 Healthcare resource use

Healthcare resource use assessment will be completed by the Investigator at all unscheduled visits (ie, excluding routine follow up clinic visits associated with the clinical trial but including both planned and unplanned admissions) during the treatment period and at the 28-day follow-up.

For the purposes of economic evaluation it is necessary to capture healthcare resource use related to the treatment and the underlying disease. Within the study the following resource use will be captured:

- Hospital episodes including the type of contact (hospitalisations, outpatient, day case), reason, length of stay (including intensive care unit) and concomitant medications and procedures

- Treatment related to AEs (including the method of delivery of the treatment)

- Treatment not related to the study.

The above resource use data will mainly come from the patient's medical record and will be captured by site staff using WBDC.

5.4 Pharmacokinetics (Optional)

5.4.1 Collection of cerebrospinal fluid (CSF)

If the patient agrees an optional sample of CSF will be obtained at one time point taken at any time from Cycle 2 Day 1 onwards, preferably on Cycle 2 Day 1 or Cycle 3 Day 1, for the

determination of AZD9291, AZ5104 and AZ7750 concentration in CSF. Samples will be collected, labelled and stored and shipped as detailed in the laboratory manual.

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

5.4.2 Determination of drug concentration

Samples for determination of AZD9291 (and metabolite) concentrations in CSF will be analysed by on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, 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.

Full details of the analytical method used will be described in a separate bioanalytical report.

5.4.3 Storage and destruction of pharmacokinetic samples

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

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

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

Any residual PK samples may be used for future exploratory biomarker research (in this case, residual PK samples will be shipped to AstraZeneca Biobank; see details in the Laboratory Manual).

5.5 Pharmacogenetics

If a patient agrees to participate in the host pharmacogenetics research component of the study a blood sample will be collected.

AstraZeneca intends to perform genetic research in the AZD9291 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD9291.

The benefits of being able to explore associations between genes and clinical outcomes within the AZD9291 programme are potentially many and include:

- analysis of genes that may affect efficacy, safety and tolerability (for example, but not limited to, drug metabolising enzymes and drug transporters)
- genetic research into genes that my contribute to the risk of NSCLC (for example, but not limited to, mutations in the gene encoding EGFR)

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

5.5.1 Collection of pharmacogenetic samples

The subject's consent to participate in the pharmacogenetic research components of the study is optional.

The single blood sample (10 mL) for genetic research will be obtained from the subjects prior to the first administration of AZD9291 in the study. If for any reason the sample is not drawn prior to dosing it may be taken at any visit until the last study visit. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event. Such patients would be important to include in any genetic analysis. Only one sample should be collected per subject for genetics during the study.

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

5.5.2 Storage, re-use and destruction of pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

Refer to Appendix G for details of the optional (DNA) genetic research.

5.6 Exploratory Research

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

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

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

5.6.1 Collection of tumour biopsy samples

5.6.1.1 Archival tumour

All patients eligible for the study will be asked to supply a sample of their archival tumour, if a sample taken at the time of diagnosis is available (blocks preferred, slides acceptable). Any archival biopsy samples taken following previous lines of therapy are also requested, if available. In each case the prior treatment must be clearly indicated for each sample provided. This sample will be used to support exploratory biomarker analyses (see Section 5.6.3.1)

5.6.1.2 Optional tissue collection at screening

Patients will be asked to consent to provide additional tumour tissue at screening, which can be collected at the same time as the mandatory screening tumour biopsy (see Section 4.1), where appropriate to do so. This biopsy will be used to support the development of the diagnostic test for approval by CFDA (China) and/or for exploratory biomarker analyses (see Section 5.6.3.1).

5.6.1.3 Discontinuation Biopsy

Patients will also be asked to consent to a further optional biopsy, to be collected at discontinuation of investigational product. This sample will be used to support exploratory biomarker analyses (see Section 5.6.3).

For timings of all tumour biopsy samples requested see Table 4 below.

Table 4 Tumour biopsy samples

Time relative to dose	Requirement
Archival	M*
Screening	M+O
Discontinuation **or progression**[1]	O

[1] To be taken at discontinuation or progression, whichever occurs first.

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

Tumour samples should be provided in the form of a formalin fixed paraffin embedded block (tissue derived from the diagnostic tumour or a metastatic site). If this is not possible, the following may be provided:

- 10-20 slides of freshly prepared unstained 5-micron sections from the mandatory screening FFPE tumour block may be provided (minimum 10 slides is required)
- 10-20 slides of freshly prepared unstained 5-micron sections from the archival tumour block may be provided.

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

5.6.2 Collection of plasma for exploratory analyses

All patients will be required to provide a series of plasma samples. The Screening Visit sample is to be taken at the same time as the screening biopsy is taken or prior to T790M mutation analysis. All plasma samples from screening visit are required by AstraZeneca, regardless of the T790M mutation results. All samples from Visit 2 onward are to be drawn pre-dose as described in the Study Plan (Table 1, Table 2and Table 5) below. These samples will be used primarily, but not exclusively, for the extraction and analysis of circulating tumour DNA (ctDNA). The ctDNA samples will be used to further explore EGFR (and other gene) mutation status and may be used to develop a plasma-based diagnostic test. Plasma samples collected on the trial may also be used (in an exploratory fashion) as a pharmacodynamics measure of drug activity.

Table 5 Plasma for exploratory analyses[2]

Visit (sample taken pre dose)	ctDNA collection
Screening	X
Cycle 1 Day 1	X
Cycle 1 Day 8	X
Cycle 1 Day 15	X
Cycle 2 Day 1	X
Cycle 3 Day 1	X
Cycle 4 Day 1	X
Cycle 5 Day 1	X
Cycle 6 Day 1	X
Cycle 7 Day 1 (and every 6 week onwards)[1]	X

Table 5 Plasma for exploratory analyses[2]

Visit (sample taken pre dose)	ctDNA collection
Treatment Discontinuation	X
Progression Follow-up (every 6 weeks)[2]	X
Time of Progression[1]	X

[1] Plasma for ctDNA are only collected according to above schedule prior to RECIST modules freeze time (24 months post LSFD), after RECIST modules freeze time, ctDNA plasma will be collected every 12 weeks up to and including progression, until final DCO.
[2] For patients who discontinue treatment prior to progression.

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

5.6.3 Exploratory Analyses

5.6.3.1 Exploratory Biomarker Analyses

Biological samples (eg, plasma, serum, archived and study-obtained tumour, etc) will be collected and may be analysed for exploratory research into factors that may influence susceptibility to/development of NSCLC/cancer and/or response to AZD9291.

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

- EGFR
- MET
- HER2
- MAPK
- AKT
- PDL-1

5.6.3.2 Exploratory analyses to support companion diagnostic development

The mutation test being used to select T790M mutation positive patients for this study is being developed for approval as a companion diagnostic for AZD9291. An optional second screening tissue sample (see Section 5.6.1.2), and some residual tissue from the mandatory screening biopsy may be used to support the diagnostic development of this assay.

ctDNA samples collected during the study may be used to develop a plasma-based diagnostic test.

5.7 Management of Biological Samples

5.7.1 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

5.7.2 Labelling and shipment of biological samples

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

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

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

5.7.3 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 subjects 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 during the entire life cycle.

5.7.4 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, 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 Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca

- Ensures that biological samples from that subject, 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 subject 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 and the action documented and returned to the study site.

AstraZeneca ensures that biological samples are destroyed at the end of a specified period as described in the informed consent.

5.8 Post progression outcomes

The date of second progression up to RECIST modules freeze time (24 months post LSFD) will be recorded by an investigator and defined according to local standard clinical practice and may involve any of; objective radiological or symptomatic progression or death. Second progression status up to RECIST modules freeze time (24 months post LSFD) will be reviewed every 6 weeks following the progression event used for the primary variable PFS (the first progression) and status recorded. To support PFS2, the time to start of subsequent treatment will be recorded up to RECIST modules freeze time.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An 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.

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

For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected. Any deterioration of the disease targeted in the study and associated symptoms should not be regarded as an adverse event**.**

6.2 Definitions of serious adverse event

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

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

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from time of signature of informed consent throughout the treatment period and including the safety 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).

Following discontinuation of AZD9291, SAEs considered related to study procedures should continue to be collected as outlined in Table 6

After the final DCO, there may be some patients remaining on study treatment. For these patients who are continuing to receive AZD9291 AstraZeneca will collect information (during the treatment period and for 30 days safety follow up after last dose) on SAEs, deaths (including those due to disease progression), pregnancy, overdose, discontinuation due to AEs/SAEs and drug accountability only.

Table 6 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 but prior to progression (if applicable)	Post 28-day Follow-up visit and post progression (survival follow-up period)
Collect all new AEs in CRF	Yes	Yes	No	No
Collect all ongoing AEs in CRF	Yes	Yes	Yes	Yes
Collect all study procedure-related SAEs in CRF	Yes	Yes	Yes	Yes
Death due to AE, or unknown cause[a]	Yes	Yes	No	No

[a] For example, death not due to disease progression, refer to Section 6.3.10

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved 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) /SAE(s) at the end of the study, if judged necessary.

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

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date 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

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, rash that covers >30% of the body may be considered severe but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

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

6.3.4 Causality collection

The Investigator will assess causal relationship between 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 procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as ‘yes’.

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

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or care provider or reported in response to the open question from the study personnel: ‘Have you had any health problems since the previous visit/you were last asked?’, or revealed by observation will be collected and recorded

in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

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

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 or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

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

6.3.7 Hy's law

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

Details of identification of PHL cases and actions to take are detailed in Appendix D.

6.3.8 Disease progression

Disease progression can be considered as a worsening of a subject'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, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.3.9 New cancers

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

Progression of the malignancy under study, including signs and symptoms progression, should not be reported as a serious adverse event. Hospitalization due to signs and symptoms of disease progression should not be reported as serious adverse event.

6.3.10 Handling of deaths

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

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

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

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

6.4 Reporting of serious adverse events

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

Note at the time of study completion (i.e. after final OS DCO date), the WBDC system will be decommissioned and SAE data will be collected via paper and emailed (preferably) or faxed directly to TCS (also known as AZ DES), which will be responsible for processing all SAEs onto the AZ global safety database. Drug accountability information will be stored in the patient notes at site.

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

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

For fatal or life-threatening 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 within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

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

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

The reference document for definition of expectedness is the IB for the AstraZeneca drug AZD9291 and the EU Summary of Product Characteristics (SPC) for the active comparator product (including any AstraZeneca comparator).

6.5 Overdose

Investigators are advised that any patient who receives a higher dose than intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

Such overdoses should be recorded as follows:

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

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

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

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

For replacement of a missing dose, please refer to section 7.2.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca during the course of the study (including the continued access) and within 6 weeks of the last dose of AZD9291.

6.6.1 Maternal exposure

If a subject 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 all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study or within 28 days of the final dose of the investigational product, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Pregnancy of the subject's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented. To capture information about a pregnancy from the partner of a male subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome; the male subject should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 4 months after dosing should be followed up and documented.

6.7 Management of Investigational Product related toxicities

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

If the toxicity resolves or reverts to ≤CTCAE grade 2 within 3 weeks of onset, treatment with AZD9291 may be restarted at the same dose (80 mg) or a lower dose (40 mg) using the rules below for dose modifications (Table 7) and with discussion and agreement with the AstraZeneca Study 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 permanently discontinue the study treatment and be observed until resolution of the toxicity.

Table 7 Dose interventions

Intervention	AZD9291 Dose
Starting Dose	80 mg
Reduced Dose –1	40 mg

On resolution of toxicity within 3 weeks:

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

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.

Patients with QTcF prolongation to >500 msec should have study treatment interrupted and regular ECGs performed until resolution to <481 msec or recovery to baseline if baseline

QTcF is ⩾ 481 msec; and then restart at a reduced dose of 40mg. If there are signs/symptoms of serious arrhythmia, or if the toxicity does not resolve to grade ≤ 1(i.e. QTcF <481 msec), or to baseline QTcF within 21 days, the patient will permanently discontinue the study treatment.

Patients experiencing any of the following will not be permitted to restart study treatment:

- Corneal ulceration
- Interstitial Lung Disease (ILD)
- QTc interval prolongation with signs/symptoms of serious arrhythmia

6.7.1 Skin reactions

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

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

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

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

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.

6.7.2 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.

6.8 Study governance and oversight

6.8.1 Steering Committee

A Steering Committee comprising of the principal investigators for study D5160C00017 in addition to principal investigators from the other AZD9291 pivotal studies will provide advice on any aspect of the study design or conduct based on requests from the sponsor and assure consistency across the entire AZD9291 pivotal programme.

No Data Monitoring Committee (DMC) is planned, as this study is an open-label non-randomised phase II study. In addition the safety profile of AZD9291 from the ongoing phase 1 trial in a similar NSCLC patient population is modest, predictable with no reported life-threatening adverse events. There is therefore no requirement for pre-planned specified expert independent safety reviews in this study.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

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

7.2 Dose and treatment regimens

AstraZeneca will supply AZD9291 as tablets for oral administration as a single daily dose of 80 mg. 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 1 and Table 2) and Section 5.2.1.

At each dispensing visit, sufficient AZD9291 for 21 days treatment, plus overage, will be dispensed. Prior to the final DCO, individual bottles will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS. Dispensing of study treatment post final DCO will be completed outside of IVRS/IWRS.

Patients should swallow one AZD9291 80 mg tablets once daily, commencing on Cycle 1 Day 1. Tablets should be taken whole with water.

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

Doses should be taken approximately 24 hours apart at the same timepoint each day. On ctDNA sampling days, the doses should be delayed until instructed to take by site personnel. 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.

Prior to the final DCO, any change from dosing schedule, dose interruptions, dose reductions should be recorded in the eCRF. Post the final DCO, drug accountability information will be stored in medical records at site.

Tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. 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.

Additional information about the Investigational product may be found in the Investigators' Brochure.

7.3 Labelling

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

7.4 Storage

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

7.5 Compliance

The administration of all study drugs should be recorded in the appropriate sections of the Case Report Form.

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

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the subject.

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.

7.7 Concomitant and other treatments

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study, with reasons for the treatment, will be recorded in the Case Report Form (CRF). Guidance on medications that require close monitoring is given in Section 3.5 and Appendix E

Prohibited Medication/Class of drug:	**Usage:**
Other anticancer agents, investigational agents and radiotherapy	Should not be given while the patient is on study treatment.

Rescue/Supportive Medication/Class of drug:	Usage:
Pre-medication will be allowed after, but not before the first dose of study treatment.	To be administered as directed by the investigator. This includes management of diarrhoea, nausea and vomiting.
Blood transfusions	Allowed at any time during the study.
Granulocyte colony stimulating factors	Should not be used prophylactically during 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.

7.7.1 Other concomitant treatment

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

7.8 Post study access to study treatment

Patients receiving AZD9291 at the time of study reaches to final DCO (i.e., after final data cut-off date) may continue to receive AZD9291, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment. Such patients will continue to be monitored and all safety assessments that may be related to IP and drug dispensing/accountability, until AZD9291 is permanently discontinued. For Pregnancy reporting during continued access, see Section 6.6 (Pregnancy). These patients will then be followed up for a period of 30 days after the last AZD9291 dose is administered for any new treatment-related serious adverse events, in accordance with Section 6.4 (Reporting of serious adverse events). All SAEs, overdoses and pregnancies would be reported until 30 days after last dose.

If study drug would be approved on market for use in disease under study indication, patients may be discontinued and switched to market product. Drug supply options can be available depending on the country and would be proposed to patient when found as best way to continue treatment by both AZ and investigator. Study would be open until last patient treated. Final Last Subject Last visit will be defined as last patient's treatment discontinuation.

Data collected for patients who continue to receive AZD9291 after study completion will only be recorded in the source documents; these data will neither be entered into the study database nor reported as an addendum to the CSR.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first subject enrolled. All Analyses will be performed by AstraZeneca or its representatives. Additional details relating to the Independent Central Review will be detailed in the Independent Central Review Charter.

The data cut-off for the primary analysis of ORR will take place 18 weeks after the last subject enrolled, to allow opportunity for all patients to complete two RECIST follow-up assessments. At this time, DoR and safety/tolerability will also be summarised. The primary analysis CSR will report the analysis of ORR supported by duration of response, and safety and tolerability data.

The full CSR will report the analysis of all primary and secondary endpoints (including updated ORR and DoR, DCR, tumour shrinkage, PFS, OS, Safety and HRQoL) and summarise the exploratory endpoint of patient reported adverse events (PRO-CTCAE). The data cut-off for this analysis will take place approximately 12 months after the last subject has been enrolled, to allow responding patients to have a DoR greater than 6 months.

All patients will continue to be followed up in order to capture the reliable overall survival data based on a final data cut-off when approximately 95 OS events (about 55% maturity) have been observed out of all enrolled. The final analyses will include the analysis for OS PRO and Safety data at this DCO. Analysis for RECIST related endpoints (ORR, DoR, tumor shrinkage, DCR and PFS) cut-off at RECIST modules freeze time will be also performed at final analysis.

8.2 Sample size estimate

The study will recruit approximately 175 patients with EGFRm+ and T790M+ mutation positive locally advanced or metastatic NSCLC, whose disease has progressed following either one prior therapy with an EGFR-TKI (chemotherapy-naïve, 33%) or following treatment with both EGFR-TKI and a platinum-based doublet chemotherapy (Patients may have also received additional lines of treatment, 67%). With 175 patients the precision of the estimation of ORR in the overall study population will be within +/-8% (e.g. ORR 40%, 95% CI 33.0%, 47.4%; ORR 50%, 95% CI 42.1%, 57.4%). In Chinese patients subgroup and for ORR 50%, the precision of the estimation of ORR will be within +/-14% in the 50 patient cohort who have only received previous EGFR-TKI treatment and within +/-10% in the 100 patient cohort who have received previous treatment with both an EGFR-TKI and a platinum-

based doublet chemotherapy. The study will also provide an adequate number of patients in which to assess the safety and tolerability of AZD9291; if zero events are observed in the 175 patients, there is 95% confidence that the true event rate is less than 2.2%.

8.3 Definitions of analysis sets

8.3.1 Full analysis set

The full analysis set is defined as all patients enrolled who received at least one dose of investigational product.

Safety data summaries and analyses will be produced based on the full analysis set.

8.3.2 Evaluable for response analysis set

The evaluable for response analysis set will be all patients who have received at least one dose of treatment and have measurable disease at baseline according to the independent review of baseline imaging data.

The primary analysis of ORR, and other RECIST-based outcomes by independent central review will be produced based on the evaluable for response analysis set. All other efficacy variables will be summarised using the full analysis set.

To support the primary analysis, demographic data will also be summarised for the evaluable for response analysis set.

8.3.3 Chinese patient set

Patients in the Full Analysis Set who are recruited from a site located in mainland China of Chinese ethnicity.

8.4 Outcome measures for analyses

Independent Central Review of RECIST based assessments

The Independent Central Review of all radiological imagining data will be carried out using RECIST version 1.1. All radiological scans for all patients (including those at unscheduled visits, or outside visit windows) will be provided to the ICR. Prior radiotherapy reports for patients (at baseline) and information on biopsied lesions will also be provided to the ICR to allow the selection of appropriate target lesions. The imaging scans will be reviewed by two independent radiologists using RECIST 1.1 criteria and will be adjudicated if required. For each patient, the ICR will define the overall visit response data (CR, PR, SD, PD or NE) and the relevant scan dates for each time point (ie, for visits where response or progression is/is not identified). 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). Endpoints (ORR, DoR, DCR, PFS) will be derived from the overall visit response date and the scan dates. ORR will only include patients whose response has been confirmed by a second scan at least 4 weeks after

the initial response. The endpoint of tumour shrinkage will be assessed from tumour size measurements based on the primary independent radiologist assessment.

Further details of the Independent Central Review will be documented in the Independent Review Charter.

Investigator RECIST based assessments

From the investigators review of the imagining scans, the RECIST tumour response data will be used to determine each subject's visit response according to RECIST version 1.1. It will also be used to determine the endpoints ORR, DoR, DCR and PFS from the overall visit response and scan dates.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD depending on the status of their disease compared with baseline and previous assessments. 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).

Please refer to Appendix C for the definitions of CR, PR, SD and PD.

Overall Response Rate (ORR)

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

In the case where a subject has two non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the subject will be defined as a responder. Similarly, if a subject has visit responses of CR, NE, CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

Duration of Response (DoR)

Duration of response will be defined as the time from the date of first documented response, (that is subsequently confirmed) until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If the response is not confirmed, it will not be included.

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

Disease control rate (DCR)

Disease control rate is defined as the percentage of patients who have a BoR of CR or PR or SD.

Tumour Shrinkage

Tumour shrinkage will be assessed using RECIST tumour response. The absolute change and percentage change from baseline in sum of tumour size at each assessment will be calculated. The best change in tumour size will include all assessments prior to progression or start of subsequent anti-cancer therapy.

Progression Free Survival (PFS)

PFS is defined as the time from enrolment until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from study therapy or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment.

However, if the patient progresses or dies after three or more missed RECIST assessments visits, the patient will be censored at the time of the latest evaluable RECIST assessment. If the patient has no evaluable visits or does not have baseline data they will be censored at 0 days unless they die within two visits of baseline.

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression
- When censoring a patient for PFS the patient will be censored at the latest of the dates contributing to a particular overall visit assessment

Overall Survival

Overall survival is defined as the time from the date of first dose until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Patients should be contacted in the 2 weeks following the data cut-off for the final survival analyses to provide complete survival data

HRQoL & Symptoms

Patient reported outcomes will be assessed using the EORTC QLQ-C30 and QLQ LC13 questionnaires. The QLQ-C30 consists of 30 questions which can be combined to produce 5

functional scales (Physical, Role, Cognitive, Emotional, Social), 3 symptom scales (Fatigue, Pain, Nausea/vomiting), 5 individual items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea) and a global measure of health status. The QLQ LC13 is a lung cancer specific module comprising 13 questions to assess lung cancer symptoms (cough, haemoptysis, dyspnoea and site-specific pain), treatment related side-effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication. With the exception of a multi-item scale for dyspnoea, all are single items.

An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, the functional scales and the global health status scale in the QLQ-C30 and for each of the symptom scales/items in the QLQ LC13 according to the EORTC QLQ-C30 Scoring Manual and EORTC QLQ LC13 instructions.

Higher scores on the global health status and functioning scales indicate better health status/function. Higher scores on the symptoms scales indicate greater symptom burden.

The primary PRO outcome measures will be patient-reported lung cancer symptoms assessed using the EORTC QLQ LC13, namely

- dyspnoea (multi-item scale based on 3 questions: were you short of breath when you rested; walked; climbed stairs)
- cough: 1 item (how much did you cough?)
- haemoptysis: 1 item (did you cough up blood?)
- pain: 3 individual items (Have you had pain in your chest; your arm or shoulder; other parts of your body?)

Definition of clinically meaningful changes

Changes in score compared to baseline will be evaluated. A minimum clinically meaningful change is defined as a change in the score from baseline of ≥5 for scales/items from the QLQ LC13 and ≥10 for scales/items from the QLQ-C30 (Obosa et al 1998).

For example, a clinically meaningful deterioration or worsening in chest pain (as assessed by QLQ LC13) is defined as an increase in the score from baseline of ≥5. A clinically meaningful improvement in fatigue (as assessed by QLQ-C30) is defined as a decrease in the score from baseline of ≥10.

At each post-baseline assessment, change in symptoms/functioning from baseline will be categorised as improved, stable or worsening as shown in Table 8.

Table 8 Visit Response for HRQoL and disease-related symptoms

Score	Change from baseline	Visit Response
LC13 symptom scales/items	≥+5	Worsened
	≤-5	Improved
	Otherwise	Stable
C30 symptom scales/items	≥+10	Worsened
	≤-10	Improved
	Otherwise	Stable
C30 functional scales and Global health status	≥+10	Improved
	≤-10	Worsened
	Otherwise	Stable

Time to symptom deterioration

For each of the symptoms scales/items in QLQ LC13, time to symptom deterioration will be defined as the time from enrolment until the date of first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥5) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from study therapy or receives another anticancer therapy prior to symptom deterioration. Death will be included as an event only if the death occurs within two visits of the last PRO assessment where the symptom change could be evaluated.

Patients whose symptoms (as measured by QLQ LC13) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms progress after two or more missed PRO assessments or the patient dies after two or more missed PRO assessments, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a patient has no evaluable assessments or does not have baseline data they will be censored at day 1. The population for analysis of time to symptom deterioration will include a subset of the FAS population who have baseline scores ≤95.

Symptom Improvement Rate

The symptom improvement rate will be defined as the number (%) of patients with two assessments at least 18 days apart (ie, 21 days allowing a visit window of 3 days) which showed a clinically meaningful improvement (a decrease from baseline score >5 for LC13 scales/items or >10 for C30 scales/items) in that symptom from baseline. The denominator

will consist of a subset of the FAS population who have a baseline symptom score ≥5 (LC13 scales/items) or ≥10 (C30 scales/items).

Time from enrolment to second progression (PFS2) (exploratory)

Time from enrolment to second progression (PFS2) is defined as the time from the date of enrolment to the earliest date of the progression event subsequent to that used for the primary variable PFS or death. The date of second progression will be recorded by the Investigator and defined according to local standard clinical practice and may involve any of; objective radiological or symptomatic progression or death. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression, ie, censored at the last progression assessment date if the patient has not had a second progression or death).

Time to second subsequent anti-cancer therapy or death is defined as the time from the date of enrolment to the earlier of the date of second subsequent anti-cancer therapy start date, or death date. Any patient not known to have had a further second subsequent therapy or death will be censored at the last known time to have not received second subsequent chemotherapy.

8.5 Calculation or derivation of safety variable(s)

Adverse events

Adverse Events (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient.

Any AE occurring before treatment with AZD9291 will be included in the data listings but will not be included in the summary tables of AEs.

Any AE occurring within 28 days of discontinuation of investigational product (ie, the last dose of AZD9291) will be included in the AE summaries. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of AZD9291) will be flagged in the data listings.

A separate data listing of AEs occurring more than 28 days after discontinuation of AZD9291 will be produced. These events will not be included in AE summaries

Other significant adverse events (OAEs)

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. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these could be 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.

Safety Assessments

For change from baseline summaries for vital signs, laboratory data, LVEF, ECGs and physical examination, the baseline value will be the latest result obtained prior to the start of investigational product.

The denominator used in laboratory summaries will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded
- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient need only have 1 post dose-value recorded

The denominator in vital signs data should include only those patients with recorded data.

8.6 Calculation or derivation of health State utility (EQ-5D-5L)

The EQ-5D-5L index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems). A unique EQ-5D health state is referred to by a 5-digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from EQ5D value sets elicited from general population samples (the base case will be the United Kingdom valuation set, with other country value sets applied in scenario analyses). Where values sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied. In addition to the descriptive system, respondents also assess their health on the day of assessment on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately. The evaluable population will comprise the Full Analysis Set (FAS) population.

8.7 Methods for statistical analyses

All data will be presented for the overall full analysis set/evaluable for response set (as appropriate), and also by two cohorts defined by line of treatment; TKI treatment only / previous TKI and a platinum-based doublet chemotherapy (patients may have also received additional lines of treatment).

Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the full analysis set.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of investigational product, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to enrolment.

8.7.1 Analysis of the primary variable(s)

Objective response rate (ORR) by ICR in the evaluable for response analysis set will be presented together with 95% exact (Clopper Pearson) confidence intervals. Summaries of the number of patients with best response in each of the follow categories will be summarised: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) and Non-Evaluable (NE).

The baseline patient characteristics will be summarised, including demographics, EGFR mutation type and prior anti-cancer therapy, including most recent previous treatment.

Additional summaries of ORR will be performed

- ORR by investigator assessment
- ORR summarised for both confirmed and unconfirmed responses
- ORR by EGFR mutation subtype: Exon 19 deletion/L858R/Other.
- ORR in the subgroup of patients who received TKI as last treatment prior to study start and those whose treatment prior to study start was not a TKI
- ORR at week 6 and 12 will also be summarised.

The concordance between ORR as assessed by ICR and by investigator will be presented.

8.7.2 Analysis of the secondary variable(s)

Duration of response

Duration of response in responding patients will be summarised and the number (%) of responding patients with a duration of response >3; >6; >9; >12; >18 and >24 months will be presented. A Kaplan Meier plot and median duration of response with 95% CI (calculated from the Kaplan Meier plot) will be presented. DCR will be summarised. DoR and DCR will be presented based on the ICR, and as a sensitivity analysis they will be present based on the investigator assessment.

Tumour shrinkage

The best absolute change in target lesion tumour size from baseline and percentage change in target lesion tumour size from baseline will be summarized using descriptive statistics and presented at each timepoint.

Tumour size will also be presented graphically using waterfall plots, to present each patient's best percentage change in tumour size as a separate bar, with the bars ordered from the largest increase to the largest decrease. Reference lines at the +20% and –30% change in tumour size levels will be added to the plots, which correspond with the definitions of progression and 'complete or partial' response respectively.

The mean and median best change from baseline in tumour size will be summarized. This will also be summarised for week 6 and week 12 data.

To assess the depth of tumour shrinkage, the proportion of patients who achieve >30%, >50% and >75% reduction in target lesions will be summarised descriptively.

Tumour shrinkage will be presented based on the primary reader ICR data, and as a sensitivity analysis they will be present based on the investigator assessment.

Disease control rate (DCR)

BoR of disease control rate (DCR) by ICR in the evaluable for response analysis set will be presented together with 95% exact (Clopper Pearson) confidence intervals.

Additional summaries of DCR will be performed

- DCR by investigator assessment
- DCR by EGFR mutation subtype: Exon 19 deletion/L858R/Other.
- DCR in the subgroup of patients who received TKI as last treatment prior to study start and those whose treatment prior to study start was not a TKI

The concordance between DCR as assessed by ICR and by investigator will be presented.

Progression Free Survival (PFS)

PFS will be displayed using a Kaplan-Meier plot. The number events, median (calculated from the Kaplan Meier plot), and the proportion of patients without an event at 6, 12, 18 and 24 months summarised. PFS will be presented based on the ICR assessments, and as a sensitivity analysis PFS will be presented based on the investigator assessment.

Overall Survival (OS)

When there is sufficient data (>20 events), OS will be displayed using a Kaplan-Meier plot. The number events, median (calculated from the Kaplan Meier plot), and the proportion of patients without an event at 6, 12 and 18 months will be summarised.

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

HRQoL and symptoms

Time to symptom deterioration

For each of the 6 symptoms scales/items in QLQ LC13 (dyspnoea, cough, haemoptysis, chest pain, arm/shoulder pain, other pain) time to deterioration in symptoms will be presented using a Kaplan-Meier plot. Summaries of the number and percentage of subjects experiencing a clinically meaningful deterioration or death, and the median time to deterioration will be also be provided. The proportion of patients alive and free from symptom deterioration at 3, 6, 12 and 24 months will be summarized using the Kaplan-Meier estimates.

Symptom Improvement Rate

For each of the symptom scales/items in QLQ LC13, a 95% confidence interval for symptom improvement rate will be constructed using the Newcombe-Wilson method. In addition, the change from baseline at each assessment time point (in terms of proportion of patients improved, stable, and worsened as defined in Section 8.4) and the mean change from baseline scores at each time point will be summarised for all symptom scales/items from the QLQ LC13 and QLQ-C30.

Definition of clinically meaningful changes

For each functional scale in the QLQ-C30 (physical, role, emotional, cognitive, social) and for Global Health status, the change from baseline at each assessment time point (in terms of proportion of patients improved, stable, and worsened as defined in Section 8.4) and the mean change from baseline scores at each time point will be summarised.

Safety Assessments

Safety and tolerability data will be presented using summaries and descriptive statistics, as detailed in the SAP.

AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient. The number of patients experiencing each AE will be summarised by CTCAE grade.

Other safety data will be assessed in terms of physical examination, clinical chemistry, haematology, vital signs and LVEFs.

Exposure to AZD9291 will be summarised. Time on study and AZD9291 dose reductions and dose delays will also be summarised.

8.7.3 Subgroup analysis

All data summaries will be made by treatment cohort [previous TKI only/previous TKI and a platinum-based doublet chemotherapy (patients may have also received additional lines of

treatment)]. Summary of Chinese patients will be made combinedly and separately by treatment cohort.

8.7.4 Planned Analyses

No interim analyses are planned for this study.

The primary analysis of ORR will take place after all patients have completed at 18 weeks after the last subject enrolled, to allow opportunity for all patients to completed two RECIST follow-up assessments. At this time, DoR and safety/tolerability will also be summarised. The primary analysis will report the analysis of ORR supported by duration of response, and safety and tolerability data.

The full analysis will report the analysis of all primary and secondary endpoints (including updated ORR and DoR, DCR, tumour shrinkage, PFS, OS, Safety HRQoL) and summarise the exploratory endpoint of patient reported adverse events (PRO-CTCAE). This analysis will take place approximately 12 months after the last subject has been enrolled, to allow responding patients to have a DoR greater than 6 months.

All patients will continue to be followed up in order to capture the reliable overall survival data based on a final data cut-off when approximately 95 OS events (about 55% maturity) have been observed out of all enrolled patients. The final analyses will include the analysis for OS and Safety data at this DCO. Analysis for RECIST related endpoints (ORR, DoR, tumor shrinkage, DCR and PFS) cut-off at RECIST modules freeze time will be also performed at final analysis as presented in the table below.

Table 9 Endpoint for final analysis and related data extraction time

Data extraction time	Endpoints
RECIST modules freeze time (24 months post LSFD)	ORR DoR Tumor shrinkage DCR PFS PFS2* time to subsequent treatment*
Final DCO (when reach approximately 95 OS events)	OS, PRO and safety

*Exploratory analysis

An earlier summary of ORR (before all patients have completed two RECIST follow-up assessments) could be performed at the request of regulatory authorities or AZD9291 Steering Committee.

8.7.5 Sensitivity analysis

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

8.7.6 Exploratory analysis

PRO-CTCAE

PRO-CTCAE data will be presented using summaries and descriptive statistics based on the Full Analysis Set and further details will be provided in the SAP.

Healthcare Resource Use

Healthcare Resource Use data will be presented using summaries and descriptive statistics, based on the Full Analysis Set and further details will be provided in the SAP.

Exploratory analysis of post progression endpoints

Up to RECIST modules freeze time (24 months post LSFD), PFS2 and time to subsequent treatment will be analysed using the same methods as the analysis of PFS and further details will be provided in the SAP.

Exploratory biomarker analysis

The comparison of each T790M status between results from the T790M screening test and the 3rd party kit (if data is available at time of analysis) will be performed and further details will be provided in SAP.

Summaries and analyses for other exploratory objectives will be documented in the study SAP and will be reported within the CSR.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

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

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

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

9.2 Monitoring of the study

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

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

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

9.2.1 Source data

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

9.2.2 Study agreements

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

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

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study is expected to start in Q2 2014 and to end by approximately Q4 2018.

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

The end of the study is defined as 'the last visit of the last subject undergoing the study', this will occur when the last patient receiving treatment as continued access has permanently discontinued AZD9291 and completed 30 days safety follow-up period.

9.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Centre staff, according to the Data Management Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

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

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

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

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

The clinical database of the study will be closed and no further data entered /updates following the final DCO. Data from the continued access period will only be recorded in the source documents; these data will not be entered into the study database, or reported as an addendum to the CSR.

Serious Adverse Event (SAE) Reconciliation

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

Data Management of genotype data

Any genotype data generated in this study will be stored in the AstraZeneca genotyping

Laboratory Information Management System (LIMS) database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples.

Data associated with human biological samples

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

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

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

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

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

10.3 Ethics and regulatory review

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

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

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

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

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

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

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

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

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

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

10.5 Changes to the protocol and informed consent form

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

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

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

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

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

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

10.6 Audits and inspections

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

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APPENDIX A ADDITIONAL SAFETY INFORMATION

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

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

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

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

Examples of such events are:

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

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

APPENDIX B INTERNATIONAL AIRLINE TRANSPORTATION ASSOCIATION (IATA) 6.2 GUIDANCE DOCUMENT

Labelling and shipment of biohazard samples
International Airline Transportation Association (IATA) classifies biohazardous agents into three categories: [http://www.iata.org/whatwedo/cargo/dgr/Documents/DGR52_Infectious Substances (DGR362).pdf]. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- http://www.iata.org/whatwedo/cargo/dgr/Documents/DGR52_PI650_EN.pdf
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.

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

APPENDIX C GUIDELINES FOR EVALUATION OF OBJECTIVE TUMOUR RESPONSE USING RECIST 1.1 (RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS)

1. INTRODUCTION

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

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

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

Measurable lesions

At least one lesion, not previously irradiated and not biopsied during the screening period , that can be accurately measured at baseline as ≥10mm in the longest diameter (except lymph nodes which must have short access ≥15mm) with computered tomograpghy (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements. If only one measurable lesion exists, it is acceptable to be used as long as it has not been previously irradiated, and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed.

Non-measurable lesions

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

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

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

- Lesions chosen for biopsy during the study screening period if still present should be selected as NTL at baseline and follow up as part of the NTL assessment unless they fulfil the criteria for measurability, when there is only one measurable lesion.
- Skin lesions assessed by clinical examination
- Brain metastasis

Special cases

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these non-cystic lesions should be selected as the target lesions (TLs).

Target lesions

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

Non-target lesions

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

3. METHODS OF MEASUREMENT

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

The methods to be used for RECIST assessment are summarised in Table 10 and those excluded for tumour assessments in this study are discussed below, with the rationale provided.

Table 10 Summary of Methods of Assessment

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

3.1 CT and MRI

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

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

3.2 Clinical examination

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

3.3 X-rays

3.3.1 Plain X-ray

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

3.3.2 Chest X-ray

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

3.4 Ultrasound

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

3.5 Endoscopy and laparoscopy

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

3.6 Tumour markers

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

3.7 Cytology and histology

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

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

3.8 Isotopic bone scan

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

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

3.9 FDG-PET scan

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

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

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

Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. CT/MRI scan of the brain should be performed in patients with known or suspected brain metastases. Follow-up assessments should be performed every 6 weeks (±7 days) after the start of treatment until discontinuation of study

treatment or withdrawal of consent. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

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

4.2 Target lesions

4.2.1 Documentation of target lesions

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

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

Special cases:

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.

- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.

- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.

- If a TL splits into two or more parts, then record the sum of the diameters of those parts

- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s)

- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.

- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion

- When a TL has had any intervention eg, radiotherapy, embolisation, surgery etc, during the study, the size of the TL should still be provided where possible

4.2.2 Evaluation of target lesions

Table 11 provides the definitions of the criteria used to determine objective tumour visit response for TLs.

Table 11 Overall Visit Response for Target Lesions

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

4.3 Non-Target lesions

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator. Table 12 provides the definitions of the criteria used to determine and record overall response for NTLs at the investigational site at each visit.

Table 12 Overall Visit Response for Non-Target Lesions

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

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

4.4 New Lesions

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

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

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

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

4.5 Symptomatic deterioration

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

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

4.6 Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table 13.

Table 13 Overall Visit Response

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

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

5. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

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

5.1 CT Scan

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

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

Anatomic coverage

Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease

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

Intravenous contrast administration

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

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

Slice thickness and reconstruction material

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

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

5.2 MRI Scan

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

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

5.3 FDG-PET scans

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

5.3.1 PET/CT scans

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

6. REFERENCES

Eisenhauer et al 2009

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

APPENDIX D ACTIONS REQUIRED IN CASES OF COMBINED INCREASE OF AMINOTRANSFERASE AND TOTAL BILIRUBIN - HY'S LAW

1 INTRODUCTION

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

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

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

2. DEFINITIONS

Potential Hy's Law (PHL)

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

Hy's Law (HL)

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

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

- ALT ≥3x ULN
- AST ≥3x ULN
- TBL ≥2x ULN

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

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

4. FOLLOW-UP

4.1 Hy's Law Criteria not met

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

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

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

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

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

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

If Yes:

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

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

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

8. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

APPENDIX E GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

Guidance regarding potential interactions with concomitant medications

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

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

AZD9291 is metabolised by CYP3A4 and CYP3A5 enzymes.

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

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

Table 14 Drugs inducing CYP3A4

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

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

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

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

Table 15 Exposure, pharmacological action and toxicity may be increased by AZD9291

Warning of possible interaction	Advice
Rosuvastatin	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD9291.
Sulfasalazine doxorubicin, daunorubicin, topotecan	

3. DRUGS THAT MAY PROLONG QT INTERVAL

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

3.1 Drugs known to prolong QT interval

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

Table 16 Drugs prolonging QT interval

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

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

3.2 Drugs that may possibly prolong QT interval

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

Table 17 Drugs that may prolong QT interval

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

APPENDIX F PATIENT REPORTED OUTCOMES: EORT-QLQ-C30, EORT-QLQ-LC13, PRO-CTCAE AND EQ-5D-5L

APPENDIX LIST

1. EORT-QLQ-C30;
2. EORT-QLQ-LC13;
3. PRO-CTCAE;
4. EQ-5D-5L

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: |__|__|__|__|

Your birthdate (Day, Month, Year): |__|__|__|__|__|__|__|__|

Today's date (Day, Month, Year): 31 |__|__|__|__|__|__|__|__|

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

During the past week:

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

14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - LC13

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

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

Appendix F - PRO-CTCAE Items

The RECIPIENT must include the following notification to be included in all distributions and implementations of the PRO-CTCAE

items listed in this Appendix F :

« The PRO-CTCAE items below and information herein were developed by the Division of Cancer Control and Population. Sciences in the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. and are the property of the NATIONAL CANCER INSTITUTE. PRO-CTCAE is experimental in nature; no warranty or guarantee of fitness for any particular use is implied or provided. »

ADD LIST ITEMS BELOW

Cutaneous (9 items): Rash, Skin Dryness, Acne, Hair Loss, Hand-Foot Syndrome, Itching, Nail Loss, Nail Ridging, Nail

Discoloration

Cardio/Circulatory (1 item): Swelling?

Gastro-Intestintal (8 items): Taste Changes, Decreased Appetite, Nausea, Vomiting, Constipation, Diarrhea, Abdominal Pain,

Fecal Incontinence

Sleep/Wake (1 item): Fatigue

Neurological (1 item): Numbness and Tingling

Visual/Perceptual (1 item): Blurred Vision

Oral (3 items): Dry mouth, Mouth/Throat Sores, Cracking at the corners of the mouth (Cheliosis)

Others (4 items): Sensitivity to sunlight, Nose bleed, Bruising, and Chills

Total = 28 items being requested to use in AURA 17

Requested PRO-CTCAE items are being provlded in English, Spanish, German, and Japanese which are all of the language translations available to date.

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English Version of selected PRO-CTCAE items:

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an X in the one box that best describes your experiences over the past 7 days…

RASH	
Did you have any RASH?	
O Yes	O No

DRY SKIN				
What was the SEVERITY of your DRY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

ACNE OR PIMPLES ON THE FACE OR CHEST				
What was the SEVERITY of your ACNE OR PIMPLES ON THE FACE OR CHEST at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

HAIR LOSS				
Did you have any HAIR LOSS?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

HAND-FOOT SYNDROME(A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS, OR PAIN)				
What was the SEVERITY of your HAND-FOOT SYNDROME (A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS OR PAIN) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

ITCHY SKIN				
What was the SEVERITY of your ITCHY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

FINGERNAILS OR TOENAILS	
Did you lose any FINGERNAILS OR TOENAILS?	
O Yes	O No

RIDGES OR BUMPS ON YOUR FINGERNAILS OR TOENAILS	
Did you have any RIDGES OR BUMPS ON YOUR FINGERNAILS OR TOENAILS?	
O Yes	O No

CHANGE IN COLOR OF YOUR FINGERNAILS OR TOENAILS	
Did you have any CHANGE IN COLOR OF YOUR FINGERNAILS OR TOENAILS?	
O Yes	O No

ARM OR LEG SWELLING			
How OFTEN did you have ARM OR LEG SWELLING?			
O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your ARM OR LEG SWELLING at its WORST?			
O Mild	O Moderate	O Severe	O Very severe
How much did ARM OR LEG SWELLING INTERFERE with your usual or daily activities?			
O A little bit	O Somewhat	O Quite a bit	O Very much

PROBLEMS WITH TASTING FOOD OR DRINK				
What was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

DECREASED APPETITE				
What was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

NAUSEA				
How OFTEN do you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

VOMITING				
How OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

CONSTIPATION				
What was the SEVERITY of your CONSTIPATION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

LOOSE OR WATERY STOOLS (DIARRHEA)				
How OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

PAIN IN THE ABDOMEN (BELLY)				
How OFTEN did you have PAIN IN THE ABDOMEN (BELLY)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did PAIN IN THE ABDOMEN (BELLY) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

LOSE CONTROL OF BOWEL MOVEMENTS				
How OFTEN did you LOSE CONTROL OF BOWEL MOVEMENTS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
How much did LOSS OF CONTROL OF BOWEL MOVEMENTS INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

FATIGUE, TIREDNESS OR LACK OF ENERGY				
What was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

NUMBNESS OR TINGLING IN YOUR HANDS OR FEET				
What was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

BLURRY VISION				
What was the SEVERITY of your BLURRY VISION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did BLURRY VISION INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

DRY MOUTH				
What was the SEVERITY of your DRY MOUTH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

MOUTH AND THROAT SORES				
What was the SEVERITY of your MOUTH AND THROAT SORES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did MOUTH AND THROAT SORES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

SKIN CRACKING AT THE CORNERS OF YOUR MOUTH				
What was the SEVERITY of SKIN CRACKING AT THE CORNERS OF YOUR MOUTH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

INCREASED SKIN SENSITIVITY TO SUNLIGHT	
Did you have any INCREASED SKIN SENSIVITY TO SUNLIGHT?	
O Yes	O No

NOSEBLEEDS				
How OFTEN did you have NOSEBLEEDS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your NOSEBLEEDS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

BRUISE EASILY (BLACK AND BLUE MARKS)	
Did you BRUISE EASILY?	
O Yes	O No

SHIVERING OR SHAKING CHILLS				
How OFTEN did you have SHIVERING OR SHAKING CHILLS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your SHIVERING OR SHAKING CHILLS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

Spanish version of selected PRO-CTCAE items

Los pacientes que reciben tratamiento para el cáncer a menudo presentan ciertos síntomas y efectos secundarios. Para cada pregunta, haga una marca o escriba una X en la casilla que mejor describe sus experiencias en los últimos siete días…

SARPULLIDO	
¿tuvo algún SARPULLIDO?	
O Sí	O No

SEQUEDAD DE LA PIEL				
¿cuál fue la INTENSIDAD de la SEQUEDAD DE LA PIEL en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa

ACNÉ O LOS GRANOS EN EL ROSTRO O EN EL PECHO				
¿cuál fue la INTENSIDAD del ACNÉ O LOS GRANOS EN EL ROSTRO O EN EL PECHO en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa

CAÍDA DEL CABELLO				
¿tuvo CAÍDA DEL CABELLO?				
O Nada	O Un poco	O Algo	O Mucho	O Muchísimo

SÍNDROME DE MANO-PIE (UN SARPULLIDO EN LAS MANOS O LOS PIES QUE PUEDE OCASIONAR PIEL AGRIETADA, DESCAMACIÓN, ENROJECIMIENTO O DOLOR)				
¿cuál fue la INTENSIDAD del SÍNDROME DE MANO-PIE (UN SARPULLIDO EN LAS MANOS O LOS PIES QUE PUEDE OCASIONAR PIEL AGRIETADA, DESCAMACIÓN, ENROJECIMIENTO O DOLOR) en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa

PICAZÓN (COMEZÓN) EN LA PIEL				
¿cuál fue la INTENSIDAD de la PICAZÓN (COMEZÓN) EN LA PIEL en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa

UÑA DE LAS MANOS O DE LOS PIES	
¿PERDIÓ ALGUNA UÑA DE LAS MANOS O DE LOS PIES?	
O Sí	O No

LÍNEAS ELEVADAS O PEQUEÑOS BULTOS EN LAS UÑAS DE LAS MANOS O DE LOS PIES	
¿tuvo LÍNEAS ELEVADAS O PEQUEÑOS BULTOS EN LAS UÑAS DE LAS MANOS O DE LOS PIES?	
O Sí	O No

CAMBIO EN EL COLOR DE LAS UÑAS DE LAS MANOS O DE LOS PIES	
¿tuvo algún CAMBIO EN EL COLOR DE LAS UÑAS DE LAS MANOS O DE LOS PIES?	
O Sí	O No

HINCHAZÓN EN LOS BRAZOS O EN LAS PIERNAS				
¿con qué FRECUENCIA tuvo HINCHAZÓN EN LOS BRAZOS O EN LAS PIERNAS?				
O Nunca	O Rara vez	O A veces	O A menudo	O Casi siempre
¿cuál fue la INTENSIDAD de la HINCHAZÓN EN LOS BRAZOS O EN LAS PIERNAS en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa
¿cuánto INTERFIRIÓ la HINCHAZON EN LOS BRAZOS O EN LAS PIERNAS en sus actividades habituales o diarias?				
O Nada	O Un poco	O Algo	O Mucho	O Muchísimo

PROBLEMAS PARA NOTAR EL SABOR DE LAS COMIDAS O LAS BEBIDAS				
¿cuál fue la INTENSIDAD de los PROBLEMAS PARA NOTAR EL SABOR DE LAS COMIDAS O LAS BEBIDAS en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa

DISMINUCIÓN DEL APETITO				
¿cuál fue la INTENSIDAD de la DISMINUCIÓN DEL APETITO en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa
¿cuánto INTERFIRIÓ la DISMINUCIÓN DEL APETITO en sus actividades habituales o diarias?				
O Nada	O Un poco	O Algo	O Mucho	O Muchísimo

NÁUSEAS				
¿con qué FRECUENCIA tuvo NÁUSEAS?				
O Nunca	O Rara vez	O A veces	O A menudo	O Casi siempre
¿cuál fue la INTENSIDAD de las NÁUSEAS en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa

VÓMITOS				
¿con qué FRECUENCIA tuvo VÓMITOS?				
O Nunca	O Rara vez	O A veces	O A menudo	O Casi siempre
¿cuál fue la INTENSIDAD de los VOMITOS en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa

ESTREÑIMIENTO				
¿cuál fue la INTENSIDAD del ESTREÑIMIENTO en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa

HECES O EXCREMENTOS SUELTOS O ACUOSOS (DIARREA)				
¿con qué FRECUENCIA tuvo HECES O EXCREMENTOS SUELTOS O ACUOSOS (DIARREA)?				
O Nunca	O Rara vez	O A veces	O A menudo	O Casi siempre

DOLOR EN EL ABDOMEN (EL VIENTRE)				
¿con qué FRECUENCIA tuvo DOLOR EN EL ABDOMEN (EL VIENTRE)?				
O Nunca	O Rara vez	O A veces	O A menudo	O Casi siempre
¿cuál fue la INTENSIDAD del DOLOR EN EL ABDOMEN (EL VIENTRE) en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa
¿cuánto INTERFIRIÓ el DOLOR EN EL ABDOMEN (EL VIENTRE) en sus actividades habituales o diarias?				
O Nada	O Un poco	O Algo	O Mucho	O Muchísimo

PÉRDIDA DE LA CAPACIDAD PARA CONTENER LAS EVACUACIONES INTESTINALES				
¿con qué FRECUENCIA PERDIÓ LA CAPACIDAD PARA CONTENER LAS EVACUACIONES INTESTINALES?				
O Nunca	O Rara vez	O A veces	O A menudo	O Casi siempre
¿cuánto INTERFIRIÓ la PÉRDIDA DE LA CAPACIDAD PARA CONTENER LAS EVACUACIONES INTESTINALES en sus actividades habituales o diarias?				
O Nada	O Un poco	O Algo	O Mucho	O Muchísimo

AGOTAMIENTO, EL CANSANCIO O LA FALTA DE ENERGÍA				
¿cuál fue la INTENSIDAD del AGOTAMIENTO, EL CANSANCIO O LA FALTA DE ENERGÍA en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa
¿cuánto INTERFIRIERON EL AGOTAMIENTO, EL CANSANCIO O LA FALTA DE ENERGÍA en sus actividades habituales o diarias?				
O Nada	O Un poco	O Algo	O Mucho	O Muchísimo

ADORMECIMIENTO O EL HORMIGUEO EN LAS MANOS O EN LOS PIES				
¿cuál fue la INTENSIDAD del ADORMECIMIENTO O DEL HORMIGUEO EN LAS MANOS O EN LOS PIES en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa
¿cuánto INTERFIRIERON el ADORMECIMIENTO O EL HORMIGUEO EN LAS MANOS O EN LOS PIES en sus actividades habituales o diarias?				
O Nada	O Un poco	O Algo	O Mucho	O Muchísimo

VISIÓN BORROSA				
¿cuál fue la INTENSIDAD de la VISIÓN BORROSA en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa
¿cuánto INTERFIRIO la VISION BORROSA en sus actividades habituales o diarias?				
O Nada	O Un poco	O Algo	O Mucho	O Muchísimo

SEQUEDAD EN LA BOCA				
¿cuál fue la INTENSIDAD de la SEQUEDAD EN LA BOCA en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa

LLAGAS (ÚLCERAS) EN LA BOCA O EN LA GARGANTA				
¿cuál fue la INTENSIDAD de las LLAGAS (ÚLCERAS) EN LA BOCA O EN LA GARGANTA en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa
¿cuánto INTERFIRIERON las LLAGAS (ÚLCERAS) EN LA BOCA O EN LA GARGANTA en sus actividades habituales o diarias?				
O Nada	O Un poco	O Algo	O Mucho	O Muchísimo

GRIETAS EN LAS COMISURAS DE LA BOCA				
¿cuál fue la INTENSIDAD de las GRIETAS EN LAS COMISURAS DE LA BOCA en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa

MAYOR SENSIBILIDAD EN LA PIEL A LA LUZ DEL SOL	
¿tuvo una MAYOR SENSIBILIDAD EN LA PIEL A LA LUZ DEL SOL?	
O Sí	O No

SANGRÓ LA NARIZ				
¿con qué FRECUENCIA le SANGRÓ LA NARIZ?				
O Nunca	O Rara vez	O A veces	O A menudo	O Casi siempre
¿con qué INTENSIDAD le SANGRÓ LA NARIZ en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa

MORETONES (MARCAS NEGRAS Y VIOLETAS) CON FACILIDAD	
¿le salieron MORETONES (MARCAS NEGRAS Y VIOLETAS) CON FACILIDAD?	
O Sí	O No

ESCALOFRÍOS (tiritó o tembló de frío)				
¿con qué FRECUENCIA tuvo ESCALOFRIOS (tiritó o tembló de frío)?				
O Nunca	O Rara vez	O A veces	O A menudo	O Casi siempre
¿cuál fue la INTENSIDAD de los ESCALOFRIOS (tiritó o tembló de frío) en su PEOR momento?				
O Ninguna	O Leve	O Moderada	O Intensa	O Muy intensa

German Version of selected PRO-CTCAE items

German Version of selected PRO-CTCAE items

In the last 7 days, did you have any **rash**: Yes / No	Während der letzten 7 Tage: hatten Sie einen **Hautausschlag**? Ja / Nein
In the last 7 days, what was the SEVERITY of your **dry skin** at its WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage, wie STARK **trocken** war Ihre **Haut** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, what was the SEVERITY of your **acne or pimples on the face or chest** at its WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK hatten Sie **Akne oder Pickel im Gesicht oder auf dem Brustkorb** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, did you have any **hair loss**: Not at all / A little bit / Somewhat / Quite a bit / Very much	Während der letzten 7 Tage: hatten Sie **Haarausfall**? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, what was the SEVERITY of your **hand-foot syndrome (a rash of the hands or feet that can cause cracking, peeling, redness, or pain)** at its WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK war Ihr **Hand-Fuss-Syndrom (ein Hautausschlag der Hände oder Füsse, der Brennen, Abschälen der Haut, Rötung oder Schmerzen machen kann)** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr

In the last 7 days, what was the SEVERITY of your **itchy skin** at its WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK war Ihr Juckreiz im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, did you lose any **fingernails or toenails**: Yes / No	Während der letzten 7 Tage: sind Ihnen **Finger- oder Fussnägel ausgefallen**? Ja / Nein
In the last 7 days, did you have any **ridges or bumps on your fingernails or toenails**: Yes / No	Während der letzten 7 Tage: hatten Sie **Furchen oder Unebenheiten der Finger- oder Fussnägel**? Ja / Nein
In the last 7 days, did you have any **change in the color of your fingernails or toenails**: Yes / No	Während der letzten 7 Tage: hatten Sie **Veränderungen der Farbe von Finger- oder Fussnägeln**? Ja / Nein
In the last 7 days, how OFTEN did you have **arm or leg swelling**: Never / Rarely / Occasionally / Frequently / Almost constantly	Während der letzten 7 Tage: wie HÄUFIG hatten Sie **geschwollene Arme oder Beine**? Nie / Selten / Gelegentlich / Häufig / Fast immer
In the last 7 days, what was the SEVERITY of your **arm or leg swelling** at its WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK **geschwollen** waren Ihre **Arme oder Beine** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, how much did **arm or leg swelling** INTERFERE with your usual or daily activities: Not at all / A little bit / Somewhat / Quite a bit / Very much	Während der letzten 7 Tage: wie sehr haben **geschwollene Arme oder Beine** Sie in Ihren täglichen Aktivitäten GESTÖRT? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr

In the last 7 days, what was the SEVERITY of your **problems with tasting food or drink** at their WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK waren Ihre **Geschmacksveränderungen beim Essen oder Trinken** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, what was the SEVERITY of your **decreased appetite** at its WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK war Ihr **Appetitmangel** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, how much did **decreased appetite** INTERFERE with your usual or daily activities: Not at all / A little bit / Somewhat / Quite a bit / Very much	Während der letzten 7 Tage: wie sehr hat Ihr Appetitmangel Sie in Ihren täglichen Aktivitäten GESTÖRT? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, how OFTEN did you have **nausea**: Never / Rarely / Occasionally / Frequently / Almost constantly	Während der letzten 7 Tage: wie HÄUFIG hatten Sie **Übelkeit**? Nie / Selten / Gelegentlich / Häufig / Fast immer
In the last 7 days, what was the SEVERITY of your **nausea** at its WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK war Ihre **Übelkeit** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, how OFTEN did you have **vomiting**: Never / Rarely / Occasionally / Frequently / Almost constantly	Während der letzten 7 Tage: wie HÄUFIG mussten Sie **erbrechen**? Nie / Selten / Gelegentlich / Häufig / Fast immer

In the last 7 days, what was the SEVERITY of your **vomiting** at its WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK war Ihr **Erbrechen** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, what was the SEVERITY of your **constipation** at its WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK war Ihre **Verstopfung** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, how OFTEN did you have **loose or watery stools (diarrhea)**: Never / Rarely / Occasionally / Frequently / Almost constantly	Während der letzten 7 Tage: wie HÄUFIG hatten Sie **Durchfall**: Nie / Selten / Gelegentlich / Häufig / Fast immer
In the last 7 days, how OFTEN did you have **pain in the abdomen (belly area)**: Never / Rarely / Occasionally / Frequently / Almost constantly	Während der letzten 7 Tage: wie HÄUFIG hatten Sie **Bauchschmerzen**? Nie / Selten / Gelegentlich / Häufig / Fast immer
In the last 7 days, what was the SEVERITY of your **pain in the abdomen (belly area)** at its WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK waren Ihre **Bauchschmerzen** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, how much did **pain in the abdomen (belly area)** INTERFERE with your usual or daily activities: Not at all / A little bit / Somewhat / Quite a bit / Very much	Während der letzten 7 Tage: wie sehr haben **Bauchschmerzen** Sie in Ihren täglichen Aktivitäten GESTÖRT? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, how OFTEN did you **lose control of bowel movements**: Never / Rarely / Occasionally / Frequently / Almost constantly	Während der letzten 7 Tage: wie HÄUFIG konnten Sie Ihren **Stuhlgang nicht kontrollieren oder halten**? Nie / Selten / Gelegentlich / Häufig / Fast immer

In the last 7 days, how much did **loss of control of bowel movements** INTERFERE with your usual or daily activities: Not at all / A little bit / Somewhat / Quite a bit / Very much	Während der letzten 7 Tage: wie sehr wurden Sie in ihren täglichen Aktivitäten GESTÖRT, weil Sie Ihren **Stuhlgang nicht kontrollieren oder halten** konnten? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, what was the SEVERITY of your **fatigue, tiredness, or lack of energy** at its WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK waren Ihre **Müdigkeit, Erschöpfung oder fehlende Energie** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, how much did **fatigue, tiredness, or lack of energy** INTERFERE with your usual or daily activities: Not at all / A little bit / Somewhat / Quite a bit / Very much	Während der letzten 7 Tage: wie sehr haben **Müdigkeit, Erschöpfung oder fehlende Energie** Sie in Ihren täglichen Aktivitäten GESTÖRT? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, what was the SEVERITY of your **numbness or tingling in your hands or feet** at its WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK waren Ihre **Taubheit oder Kribbeln in Händen oder Füssen** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, how much did **numbness or tingling in your hands or feet** INTERFERE with your usual or daily activities: Not at all / A little bit / Somewhat / Quite a bit / Very much	Während der letzten 7 Tage: wie sehr hat Sie Ihre **Taubheit oder Kribbeln in Händen oder Füssen** in Ihren täglichen Aktivitäten GESTÖRT? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, what was the SEVERITY of your **blurry vision** at its WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK **verschwommen** haben Sie im schlimmsten Fall **gesehen**? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr

In the last 7 days, how much did **blurry vision** INTERFERE with your usual or daily activities: Not at all / A little bit / Somewhat / Quite a bit / Very much	Während der letzten 7 Tage: wie sehr hat Sie **verschwommenes Sehen** in Ihren täglichen Aktivitäten GESTÖRT? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, what was the SEVERITY of your **dry mouth** at its WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK war Ihre **Mundtrockenheit** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, what was the SEVERITY of your **mouth or throat sores** at their WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK hatten Sie **wunde oder offene Stellen in Mund oder Hals im schlimmsten Fall**? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, how much did **mouth or throat sores** INTERFERE with your usual or daily activities: Not at all / A little bit / Somewhat / Quite a bit / Very much	Während der letzten 7 Tage: wie sehr haben **wunde oder offene Stellen in Mund oder Hals** Sie in ihren täglichen Aktivitäten GESTÖRT? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, what was the SEVERITY of **skin cracking at the corners of your mouth** at its WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK hatten Sie **rissige Mundwinkel** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, did you have any **increased skin sensitivity to sunlight**: Yes / No	Während der letzten 7 Tage: hatten Sie eine **erhöhte Sonnenempfindlichkeit der Haut**? Ja / Nein
In the last 7 days, how OFTEN did you have **nosebleeds**: Never / Rarely / Occasionally / Frequently / Almost constantly	Während der letzten 7 Tage: wie HÄUFIG hatten Sie **Nasenbluten**? Nie / Selten / Gelegentlich / Häufig / Fast immer

In the last 7 days, what was the SEVERITY of your **nosebleeds** at their WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK war Ihr **Nasenbluten** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr
In the last 7 days, did you **bruise easily (black and blue marks)**: Yes / No	Während der letzten 7 Tage: haben Sie **leicht blaue Flecken bekommen**? Ja / Nein
In the last 7 days, how OFTEN did you have **shivering or shaking chills**: Never / Rarely / Occasionally / Frequently / Almost constantly	Während der letzten 7 Tage: wie HÄUFIG hatten Sie **Schüttelfrost?** Nie / Selten / Gelegentlich / Häufig / Fast immer
In the last 7 days, what was the SEVERITY of your **shivering or shaking chills** at their WORST: None / Mild / Moderate / Severe / Very severe	Während der letzten 7 Tage: wie STARK war Ihr **Schüttelfrost** im schlimmsten Fall? Gar nicht / Ein wenig / Mäßig / Ziemlich / Sehr

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

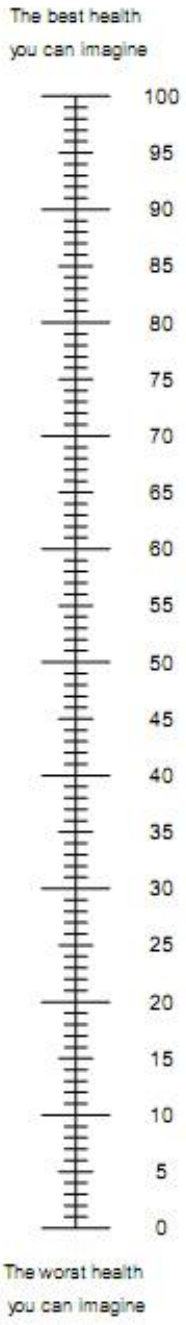
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX G PHARMACOGENETICS RESEARCH

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AE	Adverse events
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
LIMS	Laboratory information management system
PGx	Pharmacogenetics

1. BACKGROUND AND RATIONALE

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

Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD9291 but also susceptibility to the 'response'/disease for which AZD9291 may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD9291.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

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

3.1.2 Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol, Section 3.1.

3.1.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main body of the Clinical Study Protocol, Section 3.2.

3.1.4 Discontinuation of subjects from this genetic research

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

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 3.7 and 3.8 of the main Clinical Study Protocol

3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Visit 1 or after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 1, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

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

3.3 Coding and storage of DNA samples

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

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

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

4. ETHICAL AND REGULATORY REQUIREMENTS

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

4.1 Informed consent

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

4.2 Subject data protection

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

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

5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

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

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

7. LIST OF REFERENCES

None

Document Name:	d5160c00017-csp-v3
Document Title:	D5160C00017 Clicial Study Protocol Version 3
Document ID:	Doc ID-003694074
Version Label:	1.0 Approved CURRENT LATEST

Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)	**Signed By**	**Meaning of Signature**
		Clinical Development Approval
		Biostatistics Approval
		Clinical Operations Approval
		Clinical Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.