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

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1	30 June 2015		
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1	18 May 2015		

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This Real World Treatment Study Protocol has been subject to an internal review process according to AstraZeneca Standard procedures. The Real World Treatment Study 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.

PROTOCOL SYNOPSIS

Open Label, Multinational, Multicenter, Real World Treatment Study of Single Agent AZD9291 for Patients with Advanced/Metastatic Epidermal Growth Factor Receptor (EGFR) T790M Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) Who Have Received Prior Therapy with an EGFR Tyrosine Kinase Inhibitor (EGFR-TKI)

Objective

The primary objective of this study is to assess the efficacy and safety of single agent AZD9291 in a real world setting in adult patients with advanced or metastatic, epidermal growth factor receptor (EGFR) T790M mutation-positive Non-Small Cell Lung Cancer (NSCLC), who have received prior EGFR-tyrosine kinase inhibitor (TKI) therapy.

Study site(s) and number of patients planned

Approximately 600 patients will be enrolled (dosed) in Europe. The recruitment will be increased beyond that as the study will expand in other regions of the world (America, Asia). Total recruitment for all regions (including China) is expected to be approximately 3500 patients, depending on recruitment speed and national reimbursement timelines

Study period

Estimated date of first patient enrolled	Q3 2015
Estimated date of last patient completed	Q2 2020*

*depends on the date the last country obtains national reimbursement plus 90 days or 18 months after the last patient is enrolled.

Study Design

This will be an open-label, single-arm, multinational, multicenter, real world treatment study.

Target patient population

Adult patients (fulfilling the definition of “age of majority” per local regulations) with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC with confirmed T790M mutation, who have received prior EGFR-TKI therapy.

Investigational product (IP), dosage, and mode of administration

AZD9291 is an oral, potent, selective, irreversible inhibitor of both EGFR-TKI sensitising and resistance mutations in NSCLC with a significant selectivity margin over wild-type EGFR. AZD9291 will be administered orally as one 80 mg tablet once a day.

Duration of IP administration

Patients may continue to receive AZD9291 as long as they continue to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria (see section 4.3).

Enrolment will be closed within 6 months of market license approval in that country or at national reimbursement, whichever is sooner.

The study will be closed in each participating country as soon as possible following national reimbursement of AZD9291 in that country (up to a max of 90 days post reimbursement).

Patients withdrawing from the treatment prior to national reimbursement will be followed up as part of this study until death or lost to follow-up.

At national reimbursement patients still on treatment will be transitioned to commercial supply as long as the patient is benefitting from treatment as per investigator assessment, and in accordance with national regulations in the countries where the study is conducted.

In the event that national reimbursement should not be granted following a reasonable time after market license approval in the country, the study will be closed in a maximum period of 18 months after the last patient is enrolled in that country. Contingencies will be made locally to ensure continued drug supply for patients who are still deriving benefit from AZD9291 at that time.

If applicable, timelines for conversion to commercial drug will be agreed with local bodies which may include regulatory agencies, ethics committees, and institutions.

Study measures

Data collected will include patient demographics, information needed to determine patient eligibility (including medical history, past and current disease characteristics, and tumor EGFR mutational status), AZD9291 exposure (including starting dose, dose adjustments or discontinuations), investigator-reported efficacy (including tumor response and disease progression), overall survival (OS), and safety (including serious adverse events [SAEs], adverse events leading to dose modification, and adverse events of special interest [interstitial lung disease/pneumonitis-like events, and QTc prolongation events]).

Statistical methods

As the objective of the study is to collect physician-reported real world efficacy and safety data while offering access to AZD9291 to patients with significant unmet medical need, a total pre-defined recruitment target of treated patients is not applicable for this study.

All data will be presented for the overall full analysis set, and also by cohorts defined by number and type of previous treatment lines for the advanced disease. 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. OS, time to treatment discontinuation (TTD) and progression-free survival (PFS) will be summarized using Kaplan-Meier estimates of the median event time and quartiles together with their 95% confidence intervals.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse Event of Special Interest
AZ	AstraZeneca
CI	Confidence Interval
CNS	Central nervous system
CRF	Case Report Form (electronic/paper)
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P450
CT	Computer Tomography
DCO	Data cut-off
DLT	Dose limiting toxicity
ECG	Electrocardiogram
EGFR	Epidermal Growth Factor Receptor
EGFRm	EGFR Mutation positive; EGFR Sensitizing Mutation positive
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ILD	Interstitial Lung Disease
ICMJE	International Committee of Medical Journal Editors
IP	Investigational Product
IVRS/IWRS	Interactive Voice Response System/ Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective response rate

Abbreviation or special term	Explanation
OS	Overall Survival
PFS	Progression Free Survival
PT	Preferred Term
QT	Interval on the electrocardiogram representing the duration of depolarization and repolarization of the heart
QTc	The QT interval corrected for heart rate
QTcF	QT interval corrected per Fredericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	Serious adverse event
SOC	System Organ Class
SmPC	Summary of Product Characteristics
T790M	An amino acid substitution at position 790 in EGFR, from a Threonine (T) to a Methionine (M). Presence of T790M
TKI	Tyrosine Kinase Inhibitor
TTD	Time to treatment discontinuation
US	United States
WBDC	Web based data capture
WHO	World Health Organization

1. INTRODUCTION

1.1 Current non-small cell lung cancer (NSCLC)-related treatment patterns

Lung cancer has been the most common cancer in the world for several decades, and by 2012, there were an estimated 1.8 million new cases, representing 12.9% of all new cancers. It was also the most common cause of death from cancer, with 1.59 million deaths (19.4% of the total) ([GLOBOCAN 2012](#)). Non-small Cell Lung Cancer (NSCLC) represents approximately 80% to 85% of all lung cancers. At the time of diagnosis approximately 70% of patients with NSCLC already have locally advanced or metastatic disease not amenable to surgical resection. Patients presenting with unselected advanced NSCLC have a median overall survival (OS) of 10 to 12 months ([Bonomi 2010](#)).

The development of epidermal growth factor receptor (EGFR)-targeted tyrosine kinase inhibitors (TKI) have led to significant advances in patients with tumours harbouring EGFR mutations (EGFRm). Such types of mutations are seen in 10 to 15% of patients with NSCLC in the Western world and 30 to 40% in Asia. As a result of first-line studies comparing a TKI versus chemotherapy in EGFRm patients (IRESSA Pan-Asia Study [IPASS] and EUROpean TARceva versus Chemotherapy [[Mok et al 2009a](#), [Rosell et al 2012](#)]), the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) currently recommend treatment with an EGFR-TKI (e.g., erlotinib, gefitinib, or afatinib) in the front-line setting for those patients with documented EGFRm.

In patients with sensitizing mutations of EGFR, response rates of 50 to 80% have been reported with first-line TKI treatment, compared with less than 30% with conventional chemotherapy. Patients ultimately develop acquired resistance to these agents with progression of disease after approximately 9 to 13 months ([Engelman et al 2008](#), [Pao et al 2005](#), [Nguyen et al 2009](#), [Mok et al 2009b](#), [Rosell et al 2012](#)).

For patients whose tumors have progressed after treatment with an EGFR-TKI, the median OS rate is up to 2 years ([Wang et al 2012](#), [Wu et al 2010](#), [Fukuoka et al 2011](#)). Although EGFR-TKI (e.g., erlotinib, afatinib, gefitinib) are established therapies for patients with NSCLC known to have sensitising mutations in EGFR, the emergence of T790M mutation in patients treated with an EGFR-TKI agent has been described as the major route of development of resistance to this class of therapy ([Pao et al 2005](#), [Kobayashi et al 2005](#), [Yu et al 2013](#)).

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](#)). No targeted therapy is currently approved for this specific disease setting.

Re-treatment with an EGFR-TKI (eg, switching to erlotinib following failure of gefitinib) confers response rates of around 10% and median progression-free survival (PFS) of 1.7 to

6.2 months (Lee et al 2013, Watanabe et al 2011). Afatinib, a second-generation EGFR-TKI, has shown similar efficacy (LUX-Lung 1 trial; Miller et al 2012), with a 7% response rate, 2-month improvement over placebo in PFS (median 3.3 versus 1.1 months) and no OS benefit shown; a similar 8% response rate and 4.4 months PFS was seen in the LUX-Lung 4 trial (Katakami et al 2013).

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).

1.2 Background and rationale for AZD9291

AZD9291 is a potent irreversible inhibitor of both the single mutant EGFRm (TKI sensitivity conferring mutation) and double mutant EGFRm/T790M (TKI resistance conferring mutation) receptor forms of EGFR with a significant selectivity margin over wild-type EGFR (Collett 1994, Cross et al 2014). AZD9291 can effectively block EGFR signalling both in EGFR single mutant cells with sensitising EGFR mutations and in double mutant cells bearing both the primary EGFR sensitising and secondary resistance T790M mutation (Collett 1994, Cross et al 2014). Preliminary data from an ongoing phase I study (D5160C00001) in EGFRm/T790M NSCLC patients has shown good evidence of anti-tumour activity while administration of AZD9291 has shown good tolerability across a range of doses (Ranson et al, Janne et al 2014).

In the clinical programme, at the data cut-off (DCO) of 1 August 2014, a total of 253 patients had received at least one dose of AZD9291 in study D5160C00001 (31 in the dose escalation cohorts and 222 in the dose expansion cohorts). A total of 138 patients had tumour harbouring the T790M mutation as assessed by central testing. The median age was 60 years and 62% of patients were female, 62% of patients were Asian and 36% were Caucasian, and 60% of patients had received immediate prior EGFR-TKI therapy. For all evaluable patients, confirmed Response Evaluation Criteria In Solid Tumours (RECIST 1.1) responses were observed at all dose levels (20–240 mg once daily). For the 78 patients with centrally tested T790M tumours and confirmed response, the longest duration of response is ongoing at >11 months. Preliminary median duration of response at 80 mg was 8.2 months. Preliminary median progression-free survival was 9.6 months (30% maturity, 41/138 events) (Yang et al 2014).

For further clinical details please refer to the AZD9291 Investigator's Brochure (IB).

1.3 Rationale for dose selection

The selected AZD9291 starting dose of 80 mg is the recommended phase II dose, as defined from study D5160C00001 (AZD9291 IB). This is not the maximum tolerated dose (MTD) as AZD9291 was administered up to 240 mg daily with no dose-limiting toxicity (DLT) observed. In the phase III registration study, the same dose of 80 mg AZD9291 is used.

1.4 Benefit/risk and ethical assessment

1.4.1 Nonclinical data

In a modified embryofetal development study in the rat, AZD9291 caused embryoletality when administered to pregnant rats prior to embryonic implantation, at a maternally tolerated dose of 20 mg/kg (approximately 1.4x the recommended human dose of 80 mg daily). It is not known whether AZD9291 is excreted in human milk. Women of childbearing potential and men must use adequate contraception prior to study entry, for the entire duration of study participation. Women who are breast feeding are excluded from the study. Both women and men must be fully informed of the reproductive toxicity testing, and women must have a negative pregnancy test prior to enrolment (refer to inclusion criteria 8 and 9).

For further preclinical detail please refer to the AZD9291 IB.

1.4.2 Clinical data

At the time of this protocol writing, one phase I study (study D5160C00005) was completed and 15 studies are ongoing. A total of 945 subjects were exposed to AZD9291, including 93 subjects exposed to a combination of AZD9291 plus another treatment and 45 healthy volunteers exposed to a single dose of AZD9291 20 mg. Dose levels of AZD9291 ranged from 20 to 240 mg, with exposure ranging from 1 to 609 days. The emerging safety profile is based on preliminary data from studies with AZD9291 using a DCO of 16 January 2015.

The key efficacy findings from the clinical programme at the DCO of 01 Aug 2014 are summarised below:

- Treatment with AZD9291 has resulted in tumour shrinkage (including an effect on brain metastases) with objective response rates (ORRs) for the dose cohorts in the D5160C00001 study ranging from 43% to 58% for the population of $\geq 2^{\text{nd}}$ line patients as a whole.
- Patients with tumors harboring the T790M appeared to have improved responses (ORRs in these patients ranged from 50% to 70%) compared with responses in patients with tumors without the presence of T790M.
- Responses were durable, with the preliminary median duration of response calculated as 8.2 months for the 80 mg dose in patients with tumors harboring the T790M. Preliminary median PFS was 9.6 months in patients with centrally tested T790M+ NSCLC (30% maturity, 41/138 events) and 2.8 months in patients with centrally confirmed T790M negative NSCLC (71% maturity, 44/62 events).
- The most commonly reported adverse events (AEs) were rash, diarrhoea, pruritus and nausea. The most common SAEs by System Organ Class (SOC) were respiratory, thoracic and mediastinal disorders, gastrointestinal disorders, metabolism and nutrition disorders, and blood and lymphatic system disorders (Table 1).
- A total of 23 deaths were reported across all studies with AZD9291, for which the cause of death was not attributed by the Investigator to their underlying disease. Of

these, 1 death was considered by the Investigator to be related to AZD9291 treatment (an event of respiratory failure/left lung interstitial lung disease (ILD) reported in the D5160C00002 study). A further 62 patients died while participating in studies with AZD9291, but for whom the cause of death was attributed to their underlying disease; of these deaths, 2 were considered by the Investigator to be related to AZD9291 treatment by the Investigator (an event of sepsis/pneumonia/lung cancer and an event of ILD, both reported in the D5160C00001 study).

Table 1 shows the most common SAEs observed at safety DCO in the ongoing clinical studies considered to be related to AZD9291 treatment by the Investigators, by Medical Dictionary for Regulatory Activities (MedDRA) SOC and Preferred Term (PT).

Table 1 Most common (≥ 2) SAEs observed to date in the ongoing AZD9291 clinical studies considered related to AZD9291 treatment

MedDRA SOC and PT	Number of events
Respiratory, thoracic and mediastinal disorders	15
Pneumonitis	8
Interstitial lung disease	4
Pulmonary embolism	2
Gastrointestinal disorders	9
Diarrhoea	5
Nausea	2
Metabolism and nutrition disorders	6
Decreased appetite	3
Dehydration	2
Blood and lymphatic system disorders	3
Thrombocytopenia	2
Infections and infestations	3
Investigations	3
Nervous system disorders	2
General disorders and administration site conditions	2
Skin and subcutaneous tissue disorders	2

Abbreviations: MedDRA Medical Dictionary of Regulatory Activities; PT preferred term; SOC system organ class.

1.4.2.1 Study D5160C00005

A total of 32 healthy male volunteers were enrolled in this study: 16 subjects in Part A (the relative bioavailability part of the study) and 16 subjects in Part B (the food effect part of the study). All healthy volunteers received a single dose of 20 mg AZD9291, either as an oral solution, tablet, or capsule formulation. Part B of the study was conducted using the tablet formulation only. There were no deaths or SAEs reported during the study. There were no events leading to discontinuation during Part A of the study. One healthy volunteer had an

event of alanine aminotransferase increased of mild intensity which led to discontinuation during Part B of the study; this event was considered to be related to AZD9291.

In Part A, 10 out of the 16 healthy volunteers (62.5%) reported at least one AE. The most commonly reported AEs were in the SOC “infections and infestations” (5 AEs); within this SOC, the most commonly reported PT, was influenza (3 out of 16 healthy volunteers [18.8%]). All other PTs were reported in 1 healthy volunteer only. A similar pattern of AEs was observed in Part B, where 6 out of 16 volunteers (37.5%) reported at least one AE. In Part B, the most commonly reported AEs were also in the SOC “infections and infestations” with 2 AEs (PT upper respiratory tract infections). All other PTs were reported in 1 healthy volunteer only.

1.4.2.2 Study D5160C00001

Phase I (dose escalation and expansion)

The following data are based upon the phase I database lock performed on December 2014. No new or relevant safety data have been reported in patients receiving AZD9291 in this phase I study subsequent to this time point. Exposure ranged from 2 to 609 days. The MTD of AZD9291 in patients with advanced NSCLC was not established as the DLT criteria were not met at doses as high as 240 mg. Although a DLT was not identified as defined in the protocol, dose interruptions, dose reductions and EGFR wild type effects were observed at higher frequencies at the 160 mg and 240 mg dose levels. Adverse events were reported in 97% of patients, SAEs were reported in 24% (87/362) of patients. The majority of AEs were mild to moderate in intensity (Common Terminology Criteria for Adverse Event [CTCAE] Grade 1 or 2), and 37.8% (137/362) of patients reported CTCAE Grade ≥ 3 events. In the overall study population, a total of 11 fatal AEs were reported, only one of which (pneumonia) was considered by the Investigator to be related to AZD9291.

Phase II (extension phase)

In the Phase II study, at the safety DCO, 201 patients had received treatment with 80 mg AZD9291. A pre-planned preliminary database lock was performed on November 2014 and safety data are based upon this database lock. No new or relevant safety data has been reported in patients receiving AZD9291 in this phase II study subsequent to this time point. Exposure ranged from 0.1 to > 6.0 months, with 55.5% (111/201) of patients receiving treatment for a total duration of 3 to 6 months. Adverse events were reported in 87% (174/201) of patients, severe AEs (CTCAE Grade ≥ 3) were reported for 13.5% (27/201) of patients. The majority of AEs were mild to moderate in intensity (CTCAE Grade 1 or 2). The most commonly reported AEs (in >5% of patients) were diarrhoea, rash, and paronychia. These AEs are consistent with the most frequently reported AEs in the Phase 1 study. Serious AEs were reported in 10.5% (21/201) of patients on study treatment. A total of 4 patients had fatal AEs, 1 fatal AE of interstitial lung disease considered by the Investigator to be related to AZD9291 and 3 others fatal AEs were attributed to disease progression. The reported AEs infrequently led to AZD9291 dose modification or permanent discontinuation, with 1.5 % (3/201) of reported AEs resulting in permanent discontinuation of AZD9291.

1.4.2.3 Study D5160C00002

In study D5160C00002, at the DCO of January 2015, 210 patients had been exposed to 80 mg AZD9291 daily. Safety data are based on a pre-planned database lock (December 2014), and no new or relevant safety data have been identified from the study D5160C00002 subsequent to this time point. Exposure ranged from 0 to 5.7 months with the majority of patients receiving AZD9291 for a total duration of 3 to 6 months. Adverse events were reported in approximately 79% (166/210) of patients and were infrequently severe (12.9%, [26/210] of AEs were CTCAE \geq Grade 3). The majority of AEs were mild to moderate in intensity (CTCAE Grade 1 or 2). The most commonly reported AEs (in \geq 5% of patients) were diarrhoea, rash and dry skin. The types of AEs were consistent with the known safety profile of AZD9291. Serious AEs were reported in 9.4% (19/210) of patients on study treatment. One fatal AE occurred (dyspnoea) which was not considered to be related to AZD9291 or attributed to disease progression by the Investigator. The reported AEs infrequently led to AZD9291 dose modification or permanent discontinuation, with permanent discontinuation of AZD9291 due to AEs reported in <2% of patients.

1.4.2.4 Study D5160C00003

At the DCO of January 2015, 23 patients with advanced NSCLC had been exposed to AZD9291 in the study D5160C00003. A single case of pneumonitis was reported in one patient enrolled in the study D5160C00002 prior to dosing with AZD9291.

For further clinical detail please refer to the AZD9291 IB.

1.4.3 Conclusions

Based on the identified and potential risks associated with AZD9291 treatment, this clinical study protocol incorporates safety monitoring procedures and guidance to assist with early diagnosis and rapid management of potential AZD9291 drug-related symptoms. Dose modification algorithms are also included in this clinical study protocol.

All trials of AZD9291 exclude patients with clinically significant toxicities related to prior treatments in addition to specifically excluding patients with a history of any of the following:

- Clinically active interstitial lung disease
- Current or concurrent risk factors for severe arrhythmias

Given the clinical activity noted to date with AZD9291, the acceptable safety profile demonstrated thus far, and the inclusion/exclusion criteria stipulated in this study protocol, it is reasonable and appropriate to make AZD9291 available to patients with NSCLC no longer responding to previous EGFR-TKI and whose tumors harbor the T790M mutation.

Cumulative summary tabulations of exposure by age/sex and by racial group are presented in [Table 2](#) and [Table 3](#), respectively.

Table 2 Estimated cumulative subject exposure to AZD9291 from completed and ongoing clinical trials by age and sex

Age range (years)	Number of subjects		
	Male	Female	Total
<18	0	0	0
18-65	415	212	627
66-75	143	69	212
76-85	42	31	73
86-95	5	2	7
>95	0	1	1
Total	605	315	920

Data from completed and ongoing clinical trials as of 16 January 2015.

Table 3 Estimated cumulative subject exposure to AZD9291 from completed and ongoing clinical trials by racial group

Racial group	Number of subjects
Asian	515
White	359
Black or African American	48
Other	13
American Indian or Alaska Native	4
Native Hawaiian or other Pacific Islander	2
Unknown	2
Total	945

Data from completed and ongoing clinical trials as of 16 January 2015.

The difference of 25 subjects between [Table 2](#) and [Table 3](#) is due to subjects with missing age and/or race data. These 25 subjects had dosing information and thus were considered to have received AZD9291 while enrolled in the study. However, due to missing age and/or race information these patients are counted in a different table (i.e., [Table 3](#)).

2. STUDY OBJECTIVE

The primary objective of this study is to assess the efficacy and safety of single agent AZD9291 in a real world setting in adult patients with advanced or metastatic, epidermal growth factor receptor (EGFR) T790M mutation-positive Non-Small Cell Lung Cancer (NSCLC), who have received prior EGFR-tyrosine kinase inhibitor (TKI) therapy.

The primary efficacy outcome is OS, with secondary efficacy outcomes including investigator assessed response rate, investigator assessed PFS and Time to Treatment Discontinuation (TTD).

3. PATIENT SELECTION

Each patient must meet all of the applicable inclusion criteria and none of the exclusion criteria for this Real World Treatment Study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study patients must fulfill the following criteria:

1. Provision of signed and dated written informed consent by the patient or legally acceptable representative prior to any study-specific procedures
2. Adults (according to each country regulations for age of majority)
3. Locally advanced (stage IIIB) or metastatic (stage IV) EGFRm NSCLC, not amenable to curative surgery or radiotherapy, with confirmation of the presence of the T790M mutation
4. Prior therapy with an EGFR-TKI. Patients may have also received additional lines of treatment
5. World Health Organization (WHO) performance status 0-2
6. Adequate bone marrow reserve and organ function as demonstrated by complete blood count, biochemistry in blood and urine at baseline
7. ECG recording at baseline showing absence of any cardiac abnormality as per exclusion criterion #6
8. Female patients of childbearing potential must be using adequate contraceptive measures (see Restrictions, Section 4.2), must not be breast feeding, and must have a negative pregnancy test prior to start of dosing. Otherwise, they must have evidence of non-childbearing potential as defined below:
 - a. Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments
 - b. Women under 50 years would be consider post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal

- treatments and with luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution
- c. Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
9. Male patients must be willing to use barrier contraception, i.e., condoms (see Restrictions, Section 4.2)

3.2 Exclusion criteria

Patients will not be enrolled in this study if any of the following exclusion criteria are met:

1. Previous (within 6 months) or current treatment with AZD9291
2. Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of AZD9291) any treatment known to be potent inhibitors or inducers of cytochrome P450 (CYP) 3A4 (Appendix B)
3. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, active infection* including hepatitis B, hepatitis C and human immunodeficiency virus, or significantly impaired bone marrow reserve or organ function, including hepatic and renal impairment, which in the investigator's opinion would significantly alter the risk/benefit balance.

* active infection will include any patients receiving intravenous treatment for any infection and patients with hepatitis B or C surface antigen (+) – Patients receiving oral antiviral suppressive therapy for hepatitis B or C will be permitted to enrol in the study.

4. Patient with symptomatic central nervous system (CNS) metastases who is neurologically unstable or has required increasing doses of steroids to manage CNS symptoms within the 2 weeks prior to start AZD9291 administration
5. Past medical history of ILD, drug-induced ILD, radiation pneumonitis requiring steroid treatment, or any evidence of clinically active ILD
6. Any of the following cardiac criteria:

- a. Mean resting corrected QT interval (QTcF) > 470 ms using Fredericia's formula :

$$QT_{cF} = \frac{QT}{\sqrt[3]{RR}}$$

- b. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block, second degree heart block)
- c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events

7. Any unresolved toxicity from prior therapy CTCAE \geq grade 3 at the time of starting treatment
8. History of hypersensitivity to excipients of AZD9291 or to drugs with a similar chemical structure or class to AZD9291

4. STUDY CONDUCT

The following section outlines the study implementation plan, details on the study measures that will be collected as part of it are provided in Section 5.

4.1 Study Plan

This study has been subject to an internal review according to AstraZeneca standard procedures.

Concomitant treatments, other than anti-cancer treatments, should be taken according to local medical practice. There are no restrictions on concomitant use in this study except per exclusion criteria. However, it is advised that those medical products and other products known to have interactions with AZD9291 should be avoided (see [Appendix B](#)).

The latest version of the IB and any subsequent updates will be supplied to the investigator. Investigators need to become familiar with the content of the IB and appendices associated with this protocol.

[Table 4](#) below outlines data collection measures that are considered for this study:

Table 4 Study Plan

	Screening/ Enrolment visit		Treatment visit	Treatment Discontinuation	30 day follow up ^(c)	Progression Follow-up (e)	Survival follow up ^(g)
	-28 days	Day 1	(every 6 weeks)			(every 6 weeks)	(every 6 weeks)
Windows (days)			+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days
Informed Consent	X						
Inclusion/Exclusion criteria check	X						
Complete enrolment form	X						
Confirm T790M mutation	X ^(d)						
Patient demographics	X						
Medical history	X						
Disease characteristics	X						
Cancer treatment history	X						
Concomitant medications	X	X	X	X			
Complete blood count	X		If clinically indicated or per institutional standard of care	If clinically indicated or per institutional standard of care			
Biochemistry in blood and urine	X		If clinically indicated or per institutional standard of care	If clinically indicated or per institutional standard of care			
Pregnancy test	X ^(h)						
Physical examination	X			X			
WHO Performance status	X		X	X			
Weight	X		X	X			
ECG recording	X		If clinically indicated or per institutional standard of care	If clinically indicated or per institutional standard of care			
Visual test (slit-lamp)	X		If clinically indicated or per institutional standard of care	If clinically indicated or per institutional standard of care			
Dispense AZD9291 (IVRS/IWRS)		X AZD9291 start-dose	X AZD9291 re-supply				
AZD9291 dosing (daily): - current dose; dose adjustment;			X				

	Screening/ Enrolment visit		Treatment visit	Treatment Discontinuation	30 day follow up ^(c)	Progression Follow-up (e)	Survival follow up ^(g)
interruption/discontinuation reason for change							
Drug accountability			X				
Investigator-reported efficacy			X	X		X	
SAE, including overdose and pregnancy reporting ^{(a)(f)}		X	X	X	X	X	
Adverse event of special interest ^(b) AEs leading to dose modification including drug discontinuation			X	X	X	X	
Reason for withdrawal				X			
Survival status							X

- (a) Following AZD9291 discontinuation, SAEs considered related to study procedures should continue to be collected until disease progression
- (b) ILD/pneumonitis-like event; cardiac event (see section 6.6.1 and 6.6.2).
- (c) A 30 day post last dose follow up contact (visit or by telephone) should be made with the subject to collect new SAEs, andAESI and to follow up on any ongoing SAEs andAESI.
- (d) Before initiating treatment with AZD9291 the T790M mutation status after progression needs to be known. T790M mutation test may have been done per routine practice earlier than 28 days prior to day 1 as long as this was obtained following the progression on prior TKI therapy (patients may also have received additional lines of treatment).
- (e) For subjects withdrawn from treatment but who had not progressed at the time of AZD9291 discontinuation. Follow up to be performed every 6 weeks (± 1 week) relative to the date of enrolment until end of study (including survival follow-up period).
- (f) Pregnancy test to be performed in accordance with local standards
- (g) Survival status to be performed every 6 weeks (± 1 week) relative to the date of enrolment until end of study

Patient enrolment:

1. The investigator will determine patient eligibility based on criteria outlined in Section 3.1 and 3.2.
2. The investigator will inform the patients about the study, AZD9291, the potential benefits and risks, AE reporting, as well as other information collected within the scope of the study. Subsequently, the investigator will obtain signed informed consent from the potential patient or legally acceptable representative, as appropriate per local regulations

Each patient will be assigned a unique identifier through the Interactive Voice Response System (IVRS)/ Interactive Web Response System (IWRS) in the following format ECCNN3XX: CC being the country code, NN being the centre number and 3XX being the subject enrolment code at the centre into the study.

In the event of a patient having an SAE delaying the start of treatment, the screening assessments will need to be performed within 28 days prior to treatment and entered in the CRF in the extended screening visit.

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

3. The investigator will provide a completed enrolment form

The laboratory report describing the test and specimen used to confirm the presence of T790M mutation must be available on site. Before initiating treatment with AZD9291 the tumor's T790M mutation status after progression with an EGFR TKI needs to be known. The test will be performed via a local laboratory wherever possible, and always in an accredited, certified or quality assured clinical laboratory as required by country-specific guidelines, using an appropriately validated test. If T790M mutation status is not known, a new sample following progression on the latest line of therapy may need to be obtained to be sent to a suitable local laboratory or a designated central laboratory (*) for analysis. In that circumstance the patient will be requested to provide consent prior to carrying out this procedure.

(*) Note: No other genetic tests will be performed other than EGFR mutation test and samples will not be retained by the central lab if a central lab needs to be used. The samples provided will be destroyed at the end of the study or returned upon request as per the Laboratory Manual of the designated central laboratory.

4. The study site must receive enrolment confirmation for each patient from AstraZeneca (or designee) prior to drug dispensation

5. Patient visits (e.g. physical exam, laboratory tests, etc.) must be performed according to the institutional standard of care and investigator's best medical judgment. AZD9291 re-supply must always be preceded by a treatment visit per [Table 4](#). Additionally, at each visit:

- a. Drug accountability must be documented in the case report form (CRF) and necessary paper logs.
- b. Patient needs to be screened for reportable safety events outlined in [Section 6](#)
- c. Investigator-reported efficacy measures described in [Section 5](#) needs to be documented in the CRF
- d. Investigators are required to assess the patient's performance status and confirm that the patient continues to be deriving benefit from AZD9291 at the time of study drug re-supply.
- e. If a patient withdraws from the treatment and/or completely from the study, the investigator will record the reason for withdrawal

****Please note that if the reason for withdrawal is an event meeting the definition of SAE, it must be recorded in both the safety and clinical forms****

- f. For patients lost to follow-up, every reasonable effort must be made to establish the survival status and document this in the CRF
6. As an investigational drug, AZD9291 must be stored appropriately and dispensed from a secure storage area (or site pharmacy). Study sites are required to maintain accountability logs for drug receipt, dispensation, destruction and return (as applicable per local regulations).
 - a. AZD9291 may only be used for the specific patient enrolled into the study.
 7. Patients must be followed through the designated follow-up period (30 days post last dose of AZD9291 study medication) to collect SAEs occurring during this period and other required reporting per Section 6 and follow-up on any ongoing SAEs.

Consenting patients who do not fulfil the eligibility criteria must not be enrolled (dosed) into the study and will be discontinued. They will be considered screening failures and only demography data, reason for discontinuation will be recorded. Supporting safety information can be collected in case of SAE, if applicable.

4.2 Restrictions

The following restrictions apply while the patient is receiving AZD9291 and for the specified times before and after:

1. Females of childbearing potential must use reliable methods of contraception from the time of screening until 3 months after discontinuing AZD9291. Acceptable methods of contraception include true abstinence, when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception], tubal ligation, hormonal contraceptives that are not prone to drug-drug interactions (e.g., IUS Levonorgestrel Intra Uterine System, Medroxyprogesterone injections), copper-banded intra-uterine devices, and vasectomized partner. All hormonal methods of contraception should be used in combination with the use of a condom by their male sexual partner(s) for intercourse.
2. Male patients must be asked to use barrier contraceptives (i.e., by use of condoms) during sex with all of their female partners during the trial and for a period of 6 months. Patients should not father a child for 6 months after completion of AZD9291 treatment. Patients must refrain from donating sperm from the start of dosing until 6 months after discontinuing AZD9291 treatment. If male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of AZD9291 treatment.
3. If medically feasible, patients taking regular medication, with the exception of potent inducers of CYP3A4 (see [Appendix B](#)), should be maintained on it throughout the study

period (30 days post-last dose). Patients taking concomitant medications whose disposition is dependent upon CYP3A4 and breast cancer resistance protein and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving AZD9291. Patients taking concomitant medications whose disposition is dependent upon CYP3A4, CYP1A2, CYP2C or p-glycoprotein and which have a narrow therapeutic index should be closely monitored for reduction in therapeutic activity as a result of the reduced exposure of the concomitant medication while receiving AZD9291. Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (see [Appendix B](#)).

Up to 3-fold increase in exposure may occur in statin exposure when co-administered with AZD9291. It is recommended that the starting and maintenance dose of statins should be as low as possible and should be guided by the statin prescribing information.

Patients taking warfarin should be monitored regularly for changes in prothrombin time or international normalized ratio.

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 to by a study doctor, at any time during the study until 1 week after AZD9291 has been permanently discontinued. Patients must consult their investigator promptly if they have any concerns.

4.3 Discontinuation from study treatment

Patients may be discontinued from AZD9291 treatment in the following situations:

- The investigator thinks that it is in the patient's best interest to stop therapy (i.e. disease progression or patient is no longer receiving clinical benefit)
- Patient decision: the patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Confirmed diagnosis of ILD
- Ulcerative ocular events
- QTc interval prolongation with signs/symptoms of serious arrhythmia
- Other manifestation of unacceptable toxicity
- Pregnancy
- Patient incorrectly enrolled or treated on the study
- Patient starts receiving additional anti-cancer therapy

- Lost to follow up (unsuccessful contact with patient despite every effort made by investigator)
- Termination of the study (see Sections 4.4 and 10.2.4)

All unused investigational product (IP) must be returned by the patient or representative (e.g. caregiver, family member).

4.3.1 Procedures for discontinuation of a subject from study treatment

Any subject who discontinues study treatment for reasons other than disease progression should have tumour assessments performed as scheduled in the protocol (see Table 4) until disease progression is documented or death occurs, unless consent is withdrawn.

Patients may continue study treatment beyond disease progression if they are still receiving clinical benefit, as judged by the Investigator, and in the absence of any other discontinuation criteria.

4.4 Patient Withdrawal or Study Termination

At any time, patients are free to discontinue AZD9291 treatment or withdraw from the study without prejudice to further treatment.

Reasons for withdrawal from the study:

- Eligibility criteria not fulfilled
- Death
- Withdrawal of consent.

If a subject 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). If a subject wishes to withdraw their consent to further participation in the study entirely, including survival follow-up, this should be clearly documented in the subject notes and in the CRF.

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

The withdrawal reasons must be documented and SAEs reported appropriately in the CRF. If the patient agrees, the investigator must follow the patient for safety reasons until 30 days post-last dose, and then for survival status (and also for progression status if the subject had not progressed). If patient declines, the investigator will separately follow up and manage any

SAEs as a matter of clinical practice. The patient or representative will return unused AZD9291 tablets.

AstraZeneca reserves the right to terminate the study. The study will be terminated if in the judgment of AstraZeneca, patients are placed at undue risk because of clinically significant findings or AZD9291 received national reimbursement.

The study will be closed in each participating country as soon as possible following national reimbursement of AZD9291 in that country (up to a max of 90 days post reimbursement). Enrolment will be closed within 6 months after market license approval in that country or at national reimbursement, whichever is sooner.

Patients withdrawing from the treatment prior to national reimbursement will be followed up as part of this study.

At national reimbursement, patients still on treatment will be transitioned to commercial supply as long as patient is benefitting from treatment as per investigator assessment and in accordance with national regulations in the countries where the study is conducted.. Once the study is closed no further data will be collected. Reasons for termination or withdrawal must be documented in the CRF. All data, collected as part of the study, that is available at the time of discontinuation from treatment, withdrawal from study or study termination, must be recorded.

5. STUDY MEASURES

The sources of information for all study variables collected for this study will be patient medical records or charts and patients surveys. All data collected will be entered by the investigator into a CRF. All patients participating in the study will be followed from enrolment until completion of the study, discontinuation of AZD9291 administration (determined by investigator due to adverse events, toxicities or other relevant reasons), discontinuation due to disease progression, or death, whichever occurs earlier.

Study measures will be collected at baseline and during the follow-up period. For each patient, physicians will be required to provide date of enrolment, and thereafter during the follow-up visits, the date and outcome of the more recent disease assessment, and date of progression and death (if applicable). The variables described in the following sections will be collected to address the study objectives.

The study measures that will be assessed among patients participating in this study are listed below:

- **Baseline demographic characteristics:** patient characteristics including age, gender, race (if available or allowed by local regulations) will be collected
- **T790M** positive mutation status results and type of test performed and receptors

- **Relevant Medical history:** comorbidities and relevant medical history (this includes any chronic conditions currently requiring medication)
- **Physical examination:** at baseline and at treatment discontinuation
- **Weight:** at each visit
- **Visual test:** at screening, a slit-lamp examination should be obtained. Ophthalmologic exams to be performed as clinically indicated. A 30-day follow-up assessment will be required if an on treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.
- **Disease characteristics:** tumor histology, stage at diagnosis, current stage, presence of leptomeningeal /brain metastases at baseline, WHO performance status at study enrollment and subsequent follow-up visits
- **Cancer treatment history:** first-line therapy type (targeted or non-targeted) and agents received, start and end-dates, subsequent-lines type and start and end-date, radiation therapy (yes/no), surgery (yes/no) received prior to study enrollment must be documented
- **Relevant Concomitant medication:** in case of SAE, AE of special interest, AE leading to dose modification (including study medication discontinuation).
- **AZD9291 dosing:** starting dose, dose adjustments, dose interruptions, dose discontinuation and reason for any dose change.
- **Disease assessment:** as per institutional standard of care, physicians will report in the CRF date, procedure, and best overall response at each follow-up visit time-point as well as if the patient is taking benefit from the study medication (yes/no). In case of disease progression, the physician will assess, date, and document in the CRF the progression and methods (eg CT scan) used as per standard definitions and routine institutional standard of care. Physician will also indicate if the patient progressed with leptomeningeal/brain metastasis.
 - Imaging assessments (CT scans or MRI) from baseline and following visits (where available and provided an Informed Consent is obtained) will be collected from a subset of patients where a T790M positive mutation was identified via the **cobas**[®] EGFR Mutation Test performed on a plasma or tissue specimen,
 - Imaging assessments (CT scans or MRI) from baseline and following visits (where available and provided an Informed Consent is obtained) may also be collected from patients where a T790M positive mutation was identified via other molecular testing methods.
- **Progression follow-up:** after study medication discontinuation for reasons other than disease progression, the patient will continue assessments as per institutional standard of care and the physicians will report in the CRF date, procedure, and best overall response at each follow-up visit.

- **Survival status:** patient survival status (dead, alive, unknown) at each follow-up must be documented in the CRF. The time from the date of first dose in the study until death will be used to evaluate OS. Lost to follow-up patients will be censored at last documented contact with patient status “alive”.
- **Laboratory assessments:** laboratory parameters will not be collected. If done, they will be assessed by the investigator as normal or abnormal and details about abnormality will be entered in the CRF.
- **Safety** will be assessed by collection of SAEs, AEs leading to dose-modification, AEs of special interest, and on-study deaths.

Central reading of imaging assessments

All imaging assessments from a selected subset of patients (where available and Informed Consent is obtained), including unscheduled visit scans, should be collected and sent to an AstraZeneca appointed Clinical Research Organisation to enable independent central analyses. The central imaging review is required only for this selected subset of patients where a selected T790M positive mutation test was performed on a plasma or tissue specimen. The baseline scan should ideally be performed within 28 days of the start of treatment. The results of this independent review will not be communicated to investigators. The purpose of this review is to assess tumour response according to RECIST 1.1 in order to evaluate the objective response rate in these subsets of patients with various methods of T790M molecular testing.

Further details will be provided in the Statistical Analysis Plan.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The investigator is responsible for reporting all serious adverse events and the other adverse events specifically defined on [Table 4](#) and ensuring that all staff involved in the study is familiar with the content of this section.

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition occurring at any time from signing informed consent, whether or not considered causally related to the investigational drug. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram).

6.2 Definition of serious adverse events

An SAE is an event occurring from the time the patient signs informed consent (as per local regulations) through the end of the post-treatment follow-up visit (30 days post-last dose) or

until disease progression, whichever is the latest, which fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- 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 jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see [Appendix A](#) to the study protocol.

Follow-up of unresolved adverse events

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

6.2.1 Handling of deaths

All deaths that occur during the study or within the follow-up period after the administration of the last dose of AZD9291 (30 days post-last dose) or until disease progression, whichever is the latest, must be reported as follows:

- Death, which is unequivocally due to disease progression, must be reported to the study representative and must be documented in the CRF, but must not be reported as an SAE during the study.
- Where death is not clearly due to progression of the disease being treated as part of the study, the primary and most likely event causing the death must be reported to AstraZeneca's representative as an SAE within 24 hours. The report must contain a comment regarding the co-involvement of progression of disease, if appropriate, and must assign a single primary cause of death together with any contributory causes.
- Deaths with an unknown cause must always be reported as an 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 must be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes.

6.2.2 Hy's Law

Cases where a subject shows an AST or ALT $\geq 3 \times \text{ULN}$ or total bilirubin $\geq 2 \times \text{ULN}$ may need to be reported as SAEs. The investigator is responsible for, without delay, determining whether a subject meets potential Hy's law (PHL) criteria. Details of identification of PHL cases and actions to take are detailed in [Appendix C](#). Those SAE will be collected until 30 days post last dose of study medication.

6.3 Reporting of serious adverse events

All SAEs must be reported through the completion and submission of the SAE report form, from the time of signature of informed consent through 30 days post-last dose, whether or not considered causally related to AZD9291.

If any SAE occurs in the timeframe mentioned above, then the investigator or other site personnel must inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work 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. Investigator or other site personnel must inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The investigator or other study site personnel must report SAEs to the appropriate AstraZeneca representative through the completion and submission of the AstraZeneca SAE report form.

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

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug AZD9291.

6.4 Overdose

There is no definition of what constitutes an overdose. In the Phase I study, 355 patients with advanced NSCLC were administered AZD9291 at single and multiple oral doses ranging from 20 mg to 240 mg daily (as of data cut-off date 02 December 2014). All doses were well tolerated. Experiences of excessive doses (i.e. in excess of the optimal 80 mg indicated dose) in this study did not show any DLTs or acute toxicities.

There is no known antidote. 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 overdose must be recorded in the CRF. If an overdose occurs in the course of the study, then the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca representative through the completion and submission of the overdose report form.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 6.3. For other overdoses, reporting must occur within 30 days.

6.5 Pregnancy

All pregnancies, including partner's pregnancy and outcomes of pregnancy, must be reported to AstraZeneca during the course of the study and within 30 days of the last dose of AZD9291 treatment through completion and submission of the pregnancy reporting form. (for partner pregnancies see Section 6.5.2)

6.5.1 Maternal exposure

If a patient becomes pregnant during the course of the study, AZD9291 treatment must be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the AZD9291 may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages must be reported and handled as SAEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study or within 30 days of the final dose of the AZD9291, the investigator or other site personnel must inform the appropriate AstraZeneca representatives within 1 day, i.e., 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 6.3) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.5.2 Paternal exposure

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal

birth or congenital abnormality) should, if possible, be followed up and documented. If allowed by local regulations, information about a pregnancy from the partner of a male patient can be captured. If so, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 6 months after dosing must be followed up and documented.

6.6 Management of toxicities related to AZD9291

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity (any grade), where the investigator considers the event of concern to be specifically associated with AZD9291 (and not attributable to the disease or disease-related processes for which patient is being treated), 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, daily) or a lower dose (40 mg, daily) using the rules below for dose modifications (Table 5) as per the investigator's evaluation and/or in discussion and agreement with the study Medical Monitor as needed. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption. Once a dose reduction is implemented, the dose of AZD9291 cannot be reverted back to 80 mg.

If the toxicity does not resolve to CTCAE grade ≤ 2 after 3 weeks, then the patient must be withdrawn from the study treatment and kept in observation until resolution of the toxicity.

Table 5 Dose Interventions

Intervention	AZD9291 Dose
Starting Dose	80 mg daily
Reduced Dose	40 mg daily

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

6.6.1 Pulmonary Symptoms

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of interstitial lung disease are observed, the administration of AZD9291 needs to be interrupted and the study Medical Monitor must be informed. 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. The results of the full diagnostic workup (including high-resolution computed tomography, blood and sputum culture, haematological parameters) will be recorded in the CRF by the investigator. Where ILD is suspected, local practice must be followed in discussion with the study Medical

Monitor. In the absence of a confirmed diagnosis of ILD, AZD9291 may be restarted following consultation with the study Medical Monitor. In case of a confirmed diagnosis of ILD, AZD9291 must be permanently discontinued. (refer to “Guidance for the Management of AE in studies using 80mg AZD9291”)

6.6.2 QTc Prolongation (using Fredericia’s formula –QTcF–)

Patients with Grade 3 QTcF with QTcF prolongation (i.e., confirmed QTcF prolongation to > 500 ms absolute or a > 60 ms increase from baseline) should have AZD9291 interrupted and regular ECGs performed until resolution to baseline. If the QTcF interval resolves to Grade 1 (<481 msec), AZD9291 may be restarted at the reduced dose of 40 mg. If the QT prolongation does not resolve to \leq CTCAE grade 1 (<481 msec) after 3 weeks, then the patient will be permanently withdrawn from AZD9291 and observed until resolution of the toxicity.

All QTcF prolongation of >470 ms at any point during the study must be reported to AstraZeneca, and ECGs sent to the Study Team upon request for further analysis. This does not alter the management guidance outlined above.

6.6.3 Corneal Ulceration

Following an ocular event, the results of eye investigation must be recorded in the CRF by the investigator. Patients experiencing corneal ulceration will not be permitted to restart AZD9291 treatment.

6.6.4 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 clinicians.

6.6.5 Diarrhoea

Recommendations for appropriate management of diarrhoea, including uncomplicated CTCAE grade ≤ 2 , and dose-adjustments for AEs of diarrhoea that are of CTCAE grade ≥ 3 or that are clinically significant and/or intolerable and considered by the investigator to be causally related to AZD9291, will be provided to participants in the study.

For further guidance on skin reactions and diarrhoea, please refer to “Guidance for the Management of Adverse Events in Studies using 80 mg AZD9291”

6.7 Study governance and oversight

An Executive Steering Committee will be set up. It will involve 7 experts with the relevant knowledge and experience required for the study. This Executive Committee will have the executive oversight and supervision of the study. It will also be involved in the publication strategy of the study.

7. DATA MANAGEMENT

7.1 Collection, monitoring, processing of data and archiving

Data management will be performed by PAREXEL staff according to the Data Management Plan.

Data collected will include descriptive patient demographics, information needed to determine patient eligibility (including medical history, past and current disease characteristics, and tumor EGFR mutational status), AZD9291 exposure (including starting dose, dose adjustments or discontinuations), investigator-reported efficacy (including tumor response and disease progression), OS, and safety (including serious adverse events, adverse events leading dose-modification, and adverse event of special interest [interstitial lung disease/pneumonitis-like events, and QTc prolongation events]).

Data will be entered in the web-based data capture (WBDC) system at the Investigator's site. The Investigator (or delegate) will be responsible for entering data into the WBDC system and according to the Investigator Instructions Manual. The Investigator Instructions Manual will also provide the study site with data entry instructions.

Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered, reviewed and edited, the Investigator will be notified to sign the CRF electronically as per the agreed project process. A copy of the CRF will be archived at the Investigator's site.

7.2 Reporting and publication of data

AstraZeneca will prepare a Study Report within 12 months after database lock or completion of the study. AstraZeneca is obliged to analyse and report all study data as described in the protocol.

In accordance with the Declaration of Helsinki, both authors and publishers have ethical obligations. In publication of the results of this study, the authors are obliged to preserve the accuracy of the results. AstraZeneca endeavours to publish the results of this study and is committed to ensure that the data are reported in a responsible and coherent manner.

AstraZeneca seeks to ensure that publications in biomedical journals follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and published in its *Uniform Requirements of Manuscripts Submitted to Biomedical Journals*.

AstraZeneca is committed to ensuring that authorship for all publications must comply with the criteria defined by the ICMJE. These state that: "*Each author must have participated sufficiently in the work to take public responsibility for the content.*"

AstraZeneca believes that participation solely in the collection of data or drafting the manuscript does not justify authorship. These conditions apply equally to external investigators and to AstraZeneca employees.

Other members of the group should be listed in the acknowledgments as appropriate.

Publication or presentation of data subsets from individual institutions, regions or countries participating in this global multicentre study may precede the primary manuscript with the approval of the AZ global study team. The AZ global study team will determine if in certain instances publication of institution, regional or country-specific data by the participating country may precede the primary global publication.

8. INVESTIGATIONAL PRODUCT

8.1 Identity and dose of investigational product – AZD9291

AZD9291 will be supplied as tablets for oral administration as a single daily dose of 80 mg. Each bottle will contain sufficient AZD9291 treatment for 21 days, plus overage. 40 mg tablets will be supplied as needed upon request to the AstraZeneca representative.

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

The tablets can be taken with or without food and should be swallowed whole with water. The tablet should not be crushed, split or chewed.

If the patient is unable to swallow the tablet, it may first be dispersed in 50 mL of non-carbonated water. The tablet should be dropped in the water, without crushing, stirred until dispersed and immediately swallowed. An additional half a glass of water should be added to ensure that no residue remains and then immediately swallowed.

If administration via nasogastric tube is required, the same process as above should be followed but using volumes of 15 mL for the initial dispersion and 10 mL for the residue rinses. The total liquid should be administered as per the nasogastric tube instructions with appropriate water flushes

The initial dose of AZD9291 80 mg daily can be reduced to 40 mg once daily under circumstances described in Section 6.6.

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

Any change from dosing schedule, dose interruptions, or dose reductions must be recorded in the CRF.

Tablets will be packed in high-density polyethylene bottles with child-resistant closures. Bottles will be dispensed to patients in the packaging provided. The packaging includes bottles, caps and a label. Bottle tamper must not be broken prior to dispensing AZD9291 to a patient.

Additional information about AZD9291 may be found in the IB.

8.2 Labeling

Labels for AZD9291 will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. Label text will be translated into local language.

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

Patient's leaflet will be inserted if required per local regulations

8.3 Storage

All IP must be kept in a secure place under appropriate storage conditions. The IP label on the bottles specifies the appropriate storage.

8.4 Compliance

The administration of AZD9291 must be documented in the appropriate sections of the CRF. Patients must return all unused IP and empty containers to the investigator.

8.5 Accountability

The IP provided for this study will be used only as directed in the study protocol. The study personnel will account for all IP dispensed to and returned from the patient.

The study personnel at the investigational site will account for all treatments dispensed and for appropriate return or destruction. The site is required to maintain documentation of the delivery, return and destruction of IP. AstraZeneca representatives will review and collect this documentation.

9. STATISTICAL ANALYSES

Statistical analysis and generation of all tables, listings and figures will be performed by using SAS® (SAS Institute, North Carolina), version 9.2 or higher.

The analyses of the data collected within this study will be descriptive only.

9.1 Statistical evaluation-general aspects

A Statistical Analysis Plan (SAP) will be prepared and finalised prior to first subject in (FSI). The aim of the study is to assess efficacy and safety of AZD9291 in a real world setting.

9.2 Description of outcome variables in relation to objectives and hypotheses

Analysis will be conducted to evaluate the following as available in the CRF:

- Baseline characteristics: demographics, relevant medical history, disease characteristics, cancer treatment history.
- Exposure to AZD9291
- Response Rate (RR):
RR is defined as the percentage of patients with a best response of ‘responding’ by investigator assessment as recorded in the CRF.
- Overall Survival (OS):
Overall survival is defined as the time from the date of first dose of AZD9291 in this study until death due to any cause. Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.
- Progression Free Survival (PFS)
PFS is defined as the time from first dose of AZD9291 in this study until the date of disease progression as recorded in CRF or death (by any cause in the absence of progression) regardless of whether the subject withdraws from therapy or receives another anti-cancer therapy prior to progression. Subjects who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment.
- Time to treatment discontinuation (TTD):
TTD is defined as the time from the date of first dose of AZD9291 in this study until the date of AZD9291 discontinuation for any reason including disease progression, treatment toxicity, death or other reason as recorded in CRF. Subjects who are still on treatment at the time of analysis will be censored at the date of last dose received.
- Adverse events
Serious Adverse Events [SAEs], adverse events leading to dose modification, and adverse events of special interest

9.3 Description of analysis sets

Full analysis set (FAS)

The full analysis set will include all subjects who received at least one dose of study treatment.

9.4 Methods for statistical analyses

All analyses will be performed on the FAS population. No statistical tests will be performed, the statistical analyses will be descriptive.

Efficacy analyses will be repeated by cohorts defined by number and type of previous treatment lines and by other pre-defined subgroups of interest as pre-specified in the SAP.

Data will be summarized using descriptive statistics as appropriate. Continuous variables will be summarised by the number of observations (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.

9.4.1 Evaluation of primary efficacy objective

OS will be summarized using Kaplan-Meier (KM) estimates of the median time to death or censoring and quartiles together with their 95% confidence intervals (CIs). KM estimates of the OS rate at appropriate time points (to be defined in SAP) will be presented as well. A plot of the KM overall survival curve will be produced.

9.4.2 Evaluation of secondary efficacy objectives

PFS and TTD will be summarized similarly to OS using KM estimates of the median times to progression or death or treatment discontinuation, and quartiles together with their 95% CIs. KM estimates of the PFS or TTD rate at appropriate time points (to be defined in SAP) will be presented as well. A plot of the KM PFS and TTD curve will be produced.

The response rate will be summarised together with the 95% CI.

9.4.3 Safety analysis

Safety and tolerability will be assessed in terms of AEs. These will be collected for all subjects.

- Adverse events
SAEs and adverse events leading to study drug discontinuation will be summarised by MedDRA preferred terms and CTCAE grade.

Any AE occurring within 30 days of discontinuation of investigational product (ie, the last dose of AZD9291) or until disease progression, whichever is the latest, will be included in the AE summaries.

- Adverse events of special interest
Adverse events of special interest (for example interstitial lung disease/pneumonitis-like events; QTc prolongation events) will be summarised by pre-defined categories described in the SAP.

9.4.4 Interim analysis

Interim analysis of the global data will take place annually for the first three years (i.e. at approximately 12, 24 and 36 months from the start of recruitment) to provide annual updates of key study measures as specified in the SAP. Regional and country level analysis may also be performed at these time points if deemed appropriate.

The final analysis will take place approximately 5 years after the start of recruitment, depending on the date of actual global study closure.

9.5 Determination of sample size

OS is the primary efficacy endpoint of interest for this study. Median OS is assumed to be approximately 21-25 months in patients with Advanced/Metastatic Epidermal Growth Factor Receptor (EGFR) T790M Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) who have received prior therapy with an EGFR Tyrosine Kinase Inhibitor (EGFR-TKI) receiving AZD9291. While the sample size is not known a priori illustrations of the precision with which OS could be calculated from this real world study are given in the table below. These illustrations assume a study length of 58 months with non-uniform accrual over 40 months and that OS is exponentially distributed.

N	21		23		25	
	n events	95% CI median OS*	n events	95% CI median OS*	n events	95% CI median OS*
500	313	18.8-23.5	297	20.5-25.8	283	22.3-28.1
1000	627	19.4-22.7	595	21.2-24.9	566	23.0-27.1
1500	941	19.7-22.4	893	21.5-24.6	800	23.3-26.8
2000	1255	19.9-22.2	1191	21.7-24.3	1133	23.6-26.5
3000	1883	20.1-22.0	1787	22.0-24.1	1700	23.8-26.2
3500	2197	20.1-21.9	2085	22.0-24.0	1983	23.9-26.1

*based on the formula in [Collett 1994](#)

Therefore if 3500 patients enter the study globally and the median OS is 25 months the 95% CI around this survival figure would be approximately 23.9-26.1 months. For Europe, assuming recruitment of 1000 patients the equivalent 95% CI would be approximately 23.0-27.1 months.

10. STUDY MANAGEMENT BY ASTRAZENECA REPRESENTATIVE

10.1 Training of site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the study protocol and related documents with the site personnel and also train them in any protocol-specific procedures.

The investigator will ensure that appropriate training relevant to the study is given to all investigational staff involved in the study.

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

10.2 Monitoring of the study

During the study, an AZ representative will have regular contacts with the study site, including visits, as per local regulations, to verify the conduct of the study.

The AZ representative will be available during the course of the study if the investigator or other staff at the site needs information and advice about the study conduct.

10.2.1 Source data

Study sites will maintain source data in accordance with Good Clinical Practice (GCP) or local regulations.

10.2.2 Study agreements

The site and the investigator at each site must comply with all the terms, conditions, and obligations of the Study Agreement, or equivalent, for this study. In the event of any inconsistency between this study protocol and the Study Agreement, the terms of the protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Study Agreement shall prevail.

Agreements between AstraZeneca (or its delegation) and the investigator/site must be in place before any study-related procedures can take place.

10.2.3 Archiving of study documents

The Investigator must follow the archiving requirements outlined in the Study Agreement.

10.2.4 Timetable and End of Study

The study is expected to start in Q3 2015 and to end by Q2 2020.

The study will be closed in each participating country as soon as possible following national reimbursement of AZD9291 in that country (up to a max of 90 days post reimbursement). Enrolment will be closed within 6 months after market license approval in that country or at national reimbursement, whichever is sooner.

Patients withdrawing from the treatment prior to national reimbursement will be followed up as part of this study.

At national reimbursement, patients still on treatment will be transitioned to commercial supply as long as patient is benefitting from treatment as per investigator assessment and in accordance with national regulations in the countries where the study is conducted. Once the study is closed no further data will be collected.

In the event that national reimbursement should not be granted following a reasonable time after market license approval in the country, the study will be closed in a maximum period of 18 months after the last patient is enrolled in that country. Contingencies will be made locally to ensure continued drug supply for patients who are still deriving benefit from AZD9291 at that time.

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

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

11. ETHICAL AND REGULATORY REQUIREMENTS

11.1 Ethical conduct of the study

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

11.2 Patient data protection

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

AstraZeneca or its representative will not provide patient information to patients, any insurance company, any employer, their family members, general physician or to any other third party, unless required to do so by law.

Precautions are taken to preserve confidentiality and prevent data being linked to the identity of the patient. Also Regulatory authorities may require access to the relevant files.

11.3 Ethics and regulatory review

An Independent Review Board (IRB)/Ethics Committee (EC) must approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients, as per local regulations. The opinion of the IRB/EC must be given in writing.

AstraZeneca or its representative must approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol must be re-approved by the IRB/EC annually.

Before enrollment of any patient into the study, the final protocol, including the final version of the ICF, is to be approved by the national regulatory authority or a notification to the national regulatory authority is to be done, according to local regulations.

AstraZeneca or its representative will provide Regulatory Authorities, IRB/EC, and investigators with safety updates/reports according to local requirements.

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

11.4 Informed consent

The investigator at each site will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study.
- Ensure each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient or legally acceptable representative provides signed and dated ICF before conducting any procedure specifically for the study.
- Ensure the original, signed ICF(s) is/are stored in the investigator's study file.
- Ensure a copy of the signed ICF is given to the patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB/EC.
- Ensure that the Addendum to the ICF is signed and dated for the subset of patients tested for a T790M positive mutation via the **cobas®** EGFR Mutation Test (or any other molecular testing methods if relevant) before any imaging assessments are collected.

11.5 Changes to the protocol and informed consent form

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

The amendment in the form of a revised protocol is to be approved by the relevant IRB/EC and if applicable, the national regulatory authority needs also to be notified or has to provide approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca or its representative will distribute any new versions of the protocol to each participating investigator. For distribution to IRB/EC, see Section [11.3](#).

If a protocol amendment requires a change to a site's ICF, AstraZeneca (or its representative) and the site's IRB/EC are to approve the revised ICF before the revised form is used.

If required by local regulations, any administrative change will be communicated to or approved by each IRB/EC.

11.6 Audits and inspections

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

12. LIST OF REFERENCES

Bonomi 2010

Bonomi PD. Implications of key trials in advanced non small cell lung cancer. *Cancer* 2010;116:1155-64.

Collett 1994

Collett D. Modelling survival data in medical research Chapman & Hall/CRC 1994

Cross et al 2014

Cross D, Ashton S, Ghiorghiu S, Eberlein C, Nebhan C, Spitzler P, Orme J, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov.* 2014;4:1046-61.

Engelman et al 2008

Engelman J, Jänne P. Mechanisms of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer. *Clin. Cancer Res.* 2008;14:2895–2899.

Fukuoka et al 2011

Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS, Sriuranpong V, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J.Clin.Oncol.* 2011 Jul 20;29(21):2866-2874.

GLOBOCAN 2012

Globocan 2012. Lung cancer – the most common cancer in the world. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.

Goldberg et al 2012

Goldberg SB, Supko JG, Neal JW, Muzikansky A, Digumarthy S, Fidias P, et al. A phase I study of erlotinib and hydroxychloroquine in advanced non-small-cell lung cancer. *J.Thorac.Oncol.* 2012 Oct;7(10):1602-1608.

Gridelli et al 2012

Gridelli C, Ciardiello F, Gallo C, Feld R, Butts C, Gebbia V, et al. First-line erlotinib followed by second-line cisplatin-gemcitabine chemotherapy in advanced non-small-cell lung cancer: the TORCH randomized trial. *J.Clin.Oncol.* 2012 Aug 20;30(24):3002-3011.

Janne et al 2014

Janne PA, Ramalingam SS, Yang JCH, Ahn MJ, Kim DW, Kim SW, et al. Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor-resistant non-small cell lung cancer (NSCLC). *J Clin Oncol* 2014; 32:5s (Suppl; abstr 8009).

Katakami et al 2013

Katakami N, Atagi S, Goto K, et al. LUX-Lung 4: A Phase II Trial of Afatinib in Patients With Advanced Non-Small Cell Lung Cancer Who Progressed During Prior Treatment With Erlotinib, Gefitinib, or Both. *Journal of Clinical Oncology* 2013; 31(27): 3335 – 3342.

Kobayashi et al 2005

Kobayashi S, Boggon TJ, Dayaram T, Janne PA, Kocher O, Meyerson M, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N.Engl.J.Med.* 2005 Feb 24;352(8):786-792.

Langer et al 2012

Langer CJ, Mok T, Postmus PE. Targeted agents in the third-/fourth-line treatment of patients with advanced (stage III/IV) non-small cell lung cancer (NSCLC). *Cancer Treatment Reviews* 2012. [Http://dx.doi.org/10.1016/j.ctrv.2012.05.003](http://dx.doi.org/10.1016/j.ctrv.2012.05.003).

Lee et al 2013

Lee JC, Jang SH, Lee KY & Kim Y. Treatment of non small cell lung carcinoma after failure of epidermal growth factor receptor tyrosine kinase inhibitor. *Cancer Res Treat.* 2013; 45(2): 79 -85.

Maemondo et al 2010

Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N.Engl.J.Med.* 2010 Jun 24;362(25):2380-2388.

Miller et al 2012

Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol.* 2012; 13: 528-538.

Mok et al 2009a

Mok TS, Wu YL, Thongprasert S, et al. (2009) Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 361:947–957.

Mok et al 2009b

Mok T, Wu Y, Zhang L. A small step towards personalized medicine for non-small cell lung cancer. *Discov Med.* 2009;8:227-31.

Nguyen et al 2009

Nguyen KS, Kobayashi S, Costa DB. Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancers dependent on the epidermal growth factor receptor pathway. *Clin Lung Cancer* 2009;10:281–9.

Pao et al 2005

Pao W, Miller VA, Politi KA, Riely GJ, Somwar R, Zakowski MF, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med* 2005, 2(3):e73.

Ranson et al

Ranson M., Pao W., Kim D.W., Kim S.W., Ohe Y., Felip E., et al. Preliminary results from a Phase I study with AZD9291: An irreversible inhibitor of epidermal growth factor receptor (EGFR) activating and resistance mutations in non-small cell lung cancer (NSCLC). *Eur. J. Cancer* 2013 Sep: Vol 49, Supplement 3: LBA 33.

Rosell et al 2012

Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239-246.

Wang et al 2012

Wang M, Zhao J, Zhang LM, Li H, Yu JP, Ren XB, et al. Combined Erlotinib and Cetuximab overcome the acquired resistance to epidermal growth factor receptors tyrosine kinase inhibitor in non-small-cell lung cancer. *J.Cancer Res.Clin.Oncol.* 2012 Dec;138(12):2069-2077.

Watanabe et al 2011

Watanabe S, Tanaka J, Ota T, Kondo R, Tanaka H, Kagamu H, et al. Clinical responses to EGFR-tyrosine kinase inhibitor retreatment in non-small cell lung cancer patients who benefited from prior effective gefitinib therapy: a retrospective analysis. *BMC Cancer* 2011 Jan 1;11:1-2407-11-1.

Wu et al 2010

Wu JY, Wu SG, Yang CH, Chang YL, Chang YC, Hsu YC, et al. Comparison of gefitinib and erlotinib in advanced NSCLC and the effect of EGFR mutations. *Lung Cancer* 2011 May;72(2):205-212.

Yang et al 2014

Yang J-C, Kim D, Planchard D, Ohe Y, Ramalingam SS, Ahn M, Kim S, Su W, Horn L, Haggstrom D, Felip E, Kim J, Frewer P, Cantarini M, Ghiorghiu S, Ranson M, Janne PA. Updated safety and efficacy from a Phase I study of AZD9291 in patients (pts) with EGFR-TKI- resistant non-small cell lung cancer (NSCLC). *Ann Oncol* 2014; 25(Suppl 4): iv149, abs 449PD.

Clinical Study Protocol
Drug Substance AZD9291
Study Code **D5160C00022**
Version **3**
Date **20 October 2016**

Yu et al 2013

Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin.Cancer Res. 2013 Apr 15;19(8):2240-2247.

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

‘Life-threatening’ means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject’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

Outpatient 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 subject 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 jeopardize the subject 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 must be used.

- 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

When making an assessment of causality consider the following factors 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 subject 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?
- De-challenge 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.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of ‘related’ is made if following a review of the relevant data, there is evidence for a ‘reasonable possibility’ of a causal relationship for the individual case. The expression ‘reasonable possibility’ of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as ‘not related’.

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 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 relevant concomitant medications must be recorded in the eCRF.

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 6 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.

Medicines whose exposures may be affected by azd9291 that AstraZeneca considers may be allowed with caution

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

Table 7 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	

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>.

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 8 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
Bepidil, chlorpromazine, halofantrine, haloperidol, mesoridazine	14 days
Levomethadyl, methadone, pimozone	4 weeks
Arsenic trioxide	6 weeks*
Pentamidine	8 weeks
Amiodarone, chloroquine	1 year

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

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 9 Drugs that may prolong QT interval

Drug	Minimum treatment period on medication prior to AZD9291 start
Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, fosfarnet, galantamine, gemifloxacin, isradipine, ketoconazole, levofloxacin, mexiletine, nicardipine, octreotide, ofloxacin, ondansetron, quetiapine, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine, ziprasidone	2 days

Table 9 **Drugs that may prolong QT interval**

Drug	Minimum treatment period on medication prior to AZD9291 start
Amantadine, amitriptyline, amoxapine, clozapine, doxepin, felbamate, flecainide, fluconazole, fosphenytoin, gatifloxacin, granisetron, imipramine, indapamide, lithium, moexipril/HCTZ, moxifloxacin, risperidone, roxithromycin, sertraline, trimethoprim-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 C Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

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.

Definitions

Potential Hy's Law (PHL)

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

Hy's Law (HL)

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

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

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 $\geq 3xULN$
- AST $\geq 3xULN$
- TBL $\geq 2xULN$.

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

- Determine whether the patient meets PHL criteria (see definition within this Appendix for definition) by reviewing laboratory reports from all previous visits

Follow-up

Potential Hy's Law Criteria not met

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

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

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
- 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
- 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

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.

Actions required when potential Hy’s law criteria are met before and after starting study treatment

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

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

- Determine if there has been a significant change in the patients’ condition compared with the last visit where PHL criteria were met
 - If there is no significant change no action is required

- If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Potential Hy's law criteria met of this Appendix.

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

Actions required for repeat episodes of potential Hy's law

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

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

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

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Actions Required When Potential Hy's Law Criteria are Met Before and After Starting the Study.

If No: Follow the process described in Potential Hy's Law Criteria Met 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 Potential Hy's Law Criteria Met of this Appendix.

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

Clinical Study Protocol Appendix C
Drug Substance AZD9291
Study Code D5160C00022
Version 3
Date 20 October 2016

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>

VERSION HISTORY

Table 4 (footnote c) was amended:

A 30 day post last dose follow up contact (**visit or by telephone**) should be made with the subject **to collect new SAEs and AESI and to follow up on any ongoing SAEs and AESI-** to clarify the type of contact.

Section 5 Study Measures: was modified to introduce the collection of imaging assessments (CT scans or MRI) from baseline and following visits from a subset of patients where a T790M positive mutation was identified via the **cobas®** EGFR Mutation Test performed on a plasma or tissue specimen. CCI

The collection of imaging assessments (CT scans or MRI) from baseline and following visits has also been added for patients where a T790M positive mutation was identified via other molecular testing methods. - was also added.

Central reading of imaging assessments was added in section 5

All imaging assessments from a selected subset of patients (where available and Informed Consent is obtained), including unscheduled visit scans, should be collected and sent to an AstraZeneca appointed Clinical Research Organisation to enable independent central analyses. The central imaging review is required only for this selected subset of patients where a selected T790M positive mutation test was performed on a plasma or tissue specimen. The baseline scan should ideally be performed within 28 days of the start of treatment. The results of this independent review will not be communicated to investigators. The purpose of this review is to assess tumour response according to RECIST 1.1 in order to evaluate the objective response rate in these subsets of patients with various methods of T790M molecular testing.

Further details will be provided in the Statistical Analysis Plan.

Section 6.4 Overdose was modified to be in line with the AstraZeneca protocol template and SOP.

There is no definition of what constitutes an overdose. In the Phase I study, 355 patients with advanced NSCLC were administered AZD9291 at single and multiple oral doses ranging from

20 mg to 240 mg daily (as of data cut-off date 02 December 2014). All doses were well tolerated. Experiences of excessive doses (i.e. in excess of the optimal 80 mg indicated dose) in this study did not show any DLTs or acute toxicities.

There is no known antidote. 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 overdose must be recorded in the CRF ~~if the overdose is associated with an SAE.~~

Section 11.4 Informed consent was modified and the following paragraph was added:

Ensure that the Addendum to the ICF is signed and dated for the subset of patients tested for a T790M positive mutation via the **cobas®** EGFR Mutation Test (or any other molecular testing methods if relevant) before any imaging assessments are collected.

Version 2.0, 23 June 2016

Is applicable to all participating countries.

Changes to the protocol are summarised below.

Section of protocol affected:

In PROTOCOL SYNOPSIS-

Study site(s) and number of patients planned.

The number of patients enrolled is reduced in Europe (from 1500 to 600) due to lower enrolment than initially planned. The total number of patients is more defined and with the participation of China, the total number of patients expected would be approximately 3500 by the time the study ends in Q4 2020.

Duration of IP administration

Removal of the patient registry after national reimbursement. This means that the data collection for ASTRIS stops at the last patient last visit.

Statistical methods

Addition of the Time to Treatment Discontinuation (TTD) in the secondary endpoints.

In the body of the protocol:

2. Study Objective

Clarification of primary and secondary objectives: **The primary efficacy outcome is OS,**

with secondary efficacy outcomes including investigator assessed response rate, investigator assessed PFS and Time to Treatment Discontinuation (TTD).

3.2 Exclusion criteria

Clarification of exclusion criteria # 3 (with *)

Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, active infection* including hepatitis B, hepatitis C and human immunodeficiency virus, or significantly impaired bone marrow reserve or organ function, including hepatic and renal impairment, which in the investigator's opinion would significantly alter the risk/benefit balance.

*** active infection will include any patients receiving intravenous treatment for any infection and patients with hepatitis B or C surface antigen (+) – Patients receiving oral antiviral suppressive therapy for hepatitis B or C will be permitted to enrol in the study**

Table 4 study plan

Addition in footnote (e): For subjects withdrawn from treatment but who had not progressed at the time of AZD9291 discontinuation. **Follow up to be performed every 6 weeks (± 1 week) relative to the date of enrolment until end of study (including survival follow-up period).**

Addition of footnote (g) **Survival status to be performed every 6 weeks (± 1 week) relative to the date of enrolment until end of study**

Section 4.1 modified

In 3) Laboratory results for T790M meeting still needs to be available at the site but is not faxed anymore with the enrolment form. This is in order to avoid confidentiality issue.

Addition of: **Consenting patients who do not fulfil the eligibility criteria must not be enrolled (dosed) into the study and will be discontinued. They will be considered screening failures and only demography data, reason for discontinuation will be recorded. Supporting safety information can be collected in case of SAE, if applicable.**

Section 4.2 modified

In 3) Removal of the restriction on CYP3A4 inhibitors as Study 12 has shown that CYP3A4 inhibitors have no effect on AZD9291.

Section 4.3 modified

Addition of **QTc interval prolongation with signs/symptoms of serious arrhythmia** as a criteria for discontinuation to be aligned with AstraZeneca Project Specific Safety

Requirements.

Section 4.3.1 modified

Addition: Patients may continue study treatment beyond disease progression if they are still receiving clinical benefit, as judged by the Investigator, and in the absence of any other discontinuation criteria.

Section 4.4: modified

Removal of the patient registry after national reimbursement. This means that the data collection for ASTRIS stops at the last patient last visit.

Section 5 modified

Disease characteristics / Disease assessment: Addition of the collection of information at entry and at progression, about **leptomeningeal /brain metastases** in the CRF. This was missed from the beginning.

Survival status: ~~For patients entering in the registry, the date of death in the follow-up period will be used to evaluate OS.~~

Section 6.7 Study governance and oversight added

An Executive Steering Committee will be set up. It will involve 7 experts with the relevant knowledge and experience required for the study. This Executive Committee will have the executive oversight and supervision of the study. It will also be involved in the publication strategy of the study.

Section 7.2 modified

Publication or presentation of data subsets from individual institutions, regions or countries participating in this global multicentre studies may ~~must not~~ precede the primary manuscript with the approval of the AZ global study team. ~~, and when developed must always reference the primary publication of the entire study.~~ **The AZ global study team will determine if in certain instances publication of institution, regional or country-specific data by the participating country may precede the primary global publication.**

Following a recommendation from the Executive Steering Committee.

Section 9.2 modified

Addition of the definition for **Response Rate (RR): RR is defined as the percentage of patients with a best response of ‘responding’ by investigator assessment as recorded in the CRF.**

Addition of **Time to treatment discontinuation (TTD):**

TTD is defined as the time from the date of first dose of AZD9291 in this study until the

date of AZD9291 discontinuation for any reason including disease progression, treatment toxicity, death or other reason as recorded in CRF. Subjects who are still on treatment at the time of analysis will be censored at the date of last dose received.

Following a recommendation from the Executive Steering Committee.

Section 9.4.2 modified

PFS and TTD will be summarized similarly to OS using KM estimates of the median times to progression or death, treatment discontinuation and quartiles together with their 95% CIs. KM estimates of the **PFS or TTD** rate at appropriate time points (to be defined in SAP) will be presented as well. A plot of the KM **PFS and TTD** curve will be produced.

The response rate will be summarised together with the 95% CI.

Section 9.4.4 Interim analysis added

Interim analysis of the global data will take place annually for the first three years (i.e. at approximately 12, 24 and 36 months from the start of recruitment) to provide annual updates of key study measures as specified in the SAP. Regional and country level analysis may also be performed at these time points if deemed appropriate.

The final analysis will take place approximately 5 years after the start of recruitment, depending on the date of actual global study closure.

Section 9.5 modified

The table illustrating the precision for OS was adapted with a revised patient's distribution and increased study length based on the Collett formula.

Section 11.5 modified

In case of amendment to a protocol, only a revised protocol is prepared to be approved by the relevant IRB/EC. To comply with change in AstraZeneca SOP.

Version 1.0, 30 June 2015

Is applicable to all participating countries. Refer to the Protocol Amendment 1 for details.

Changes to the protocol are summarised below.

Section of protocol synopsis - Study site(s) and number of patients planned- was modified to include America and Asia.

Section of protocol synopsis- Duration of IP administration and Section 10.2.4 Timetable and End of Study were modified to add a clause about study termination in each country.

Section of protocol synopsis - Statistical methods was amended to provide a more detailed and robust description of the statistical evaluations.

Section of protocol affected: Study Plan (Table 4) was amended to provide a more detailed study plan in line with the CRF as well as more details about the enrolment process and clarification about the T790M testing and what will happen to the samples if a central laboratory is used.

Section of protocol affected: 4.2 Restrictions was amended to provide clarity in male patients contraception.

Section 4.3 Discontinuation from study: a new paragraph **'4.3.1 Procedures for discontinuation of a subject from study treatment'** was added to provide details about procedures for discontinuation from study treatment.

Section 4.4 Patient Withdrawal or Study Termination was amended to provide details about what will happen in case of study withdrawal and for the follow-up of overall survival.

Section 5. Study Measures was amended to provide a more detailed list of study measures collection in line with the CRF.

Section 6. Safety reporting and medical management was amended to provide clarity about SAE reporting timeframes and add instructions about follow-up of unresolved adverse events.

Section 6.6.2 QTc Prolongation (using Fredericia's formula –QTcF–) was amended to be aligned with the AZD9291 Core Data Sheet:

Section 8.1 Identity and dose of investigational product – AZD9291 was modified to be aligned with the AZD9291 Core Data Sheet

Section 9 Statistical Analyses was rewritten to provide a more robust description of the statistical evaluations and sample size determination.

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