Clinical Study Protocol

Drug Substance AZD9291 (Osimertinib)

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Phase II study of osimertinib in NSCLC patients with EGFR exon 20 insertion mutation

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

PROTOCOL SYNOPSIS

Phase II study of osimertinib in NSCLC patients with EGFR exon 20 insertion mutation

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Study site(s) and number of subjects planned

This study will be conducted at approximately 10 sites in South Korea with approximately 30 patients enrolled and dosed and at least 27 evaluable patients required (evaluable for the primary analysis). All patients will be recruited from South Korea.

Study period	Phase of development
Estimated date of first subject enrolled	Q2 2017
Estimated date of last subject completed	Q2 2019

Study design

This is a single-arm, non-randomized multicentre phase 2 study in NSCLC patients with EGFR exon 20 insertion mutation, whose disease has progressed on standard chemotherapy. Patients will have bi-weekly clinic visits for the first 4 weeks (1st cycle); thereafter visits will be every 4 weeks. Safety and efficacy assessments will be collected. Patients' medical care will be performed according to local clinical practice.

Objectives

Primary Objective Outcome Measure

To determine the efficacy of osimertinib in patients with advanced or metastatic NSCLC with EGFR exon 20 insertion mutation who show disease progression on standard chemotherapy. Investigator-assessed objective response as defined by RECIST version 1.1

Secondary Objectives Outcome Measure

To evaluate the safety and tolerability of osimertinib AEs/SAEs as defined by NCI CTCAE version 4.0

To evaluate progression-free survival (PFS) PFS as defined by RECIST version 1.1

To evaluate overall survival (OS)

To evaluate the efficacy based on subtypes of EGFR exon 20 insertion mutation

To evaluate PFS based on subtypes of EGFR exon 20 insertion mutation

Target subject population

Adult patients at age ≥ 19 years with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC with confirmed EGFR exon 20 insertion mutation, who have received prior standard chemotherapy.

Duration of treatment

Patients may continue to receive osimertinib as long as they continue to show clinical benefits, as judged by the investigator, and in the absence of discontinuation criteria.

Investigational product, dosage and mode of administration

Osimertinib is an oral, potent, selective, irreversible inhibitor of both EGFR tyrosine kinase inhibitor (TKI)-sensitizing and -resistant mutations in NSCLC with a significant selectivity margin over wild-type EGFR. Osimertinib at 80mg dose will be administered orally once daily.

Statistical methods

The primary endpoint of this study is to evaluate the proportion of patients who achieved an objective response as assessed by the investigator according to RECIST version 1.1. Up to 30 patients will be enrolled and dosed in order to obtain at least 27 evaluable patients according to Simon's minimax two-stage design as follows: objective response, P0=0.05 and P1=0.20; type 1 error 5%, power 80%, and confidence limit 95%; stage 1 (objective response ≥1/13) plus stage 2 (objective response ≥4/27). All data will be presented for the overall full analysis set, and also by cohorts defined by subtypes of EGFR exon 20 insertion mutations (C-helix vs. loop following C-helix). 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 and 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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Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
cfDNA	Circulating free deoxyribonucleic acid
CR	Complete response
CRF	Case Report Form (electronic/paper)
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computerised tomography
CTC	Circulating tumour cell
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off date
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
EGFR	Epidermal growth factor receptor

EMEA European Medicines Agency

EORTC European Organisation for Research and Treatment of Cancer

FTIP First Time in Patients

GCP Good Clinical Practice

HIV Human immunodeficiency virus

IB Investigators Brochure

ICH International Conference on Harmonisation

LVEF Left ventricular ejection fraction

MedDRA Medical Dictionary for Regulatory Activities

MRI Magnetic resonance imaging

MRT Mean residence time

MTD Maximum tolerated dose

MUGA Multi gated acquisition scan

NE Not evaluable

NOAEL No Observed Adverse Effect Level

NSCLC Non Small Cell Lung Cancer

NTL Non-target lesion

OAE Other significant adverse event

PAD Pharmacologically Active Dose

PD Progression of disease

PK Pharmacokinetics

PR Partial response

PRO Patient Reported Outcomes

QT ECG interval measured from the onset of the QRS complex to the end of the T wave

QTc QT interval corrected for heart rate

RAC	Accumulation ratio
RBC	Red blood count
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Stable disease
SRC	Safety Review Committee
TL	Target lesion
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
WBDC	Web Based Data Capture
WHO	World Health Organisation

1. Introduction

1.1 Background and rationale for conducting this study

EGFR exon 20 insertion mutations are typically located after the C-helix of the tyrosine kinase domain of EGFR1 and account for up to 4% of all EGFR mutations.2 EGFR exon 20 insertion-mutant NSCLC cells are generally resistant to 1st-generation EGFR TKIs (gefitinib, erlotinib) as well as 2nd-generation EGFR TKIs (neratinib, afatinib, and dacomitinib). Clinically, overall response rates were 0% and 8.7% for NSCLC patients with EGFR exon 20 insertion mutation who received gefitinib/erlotinib3 and afatinib,4 respectively.

AZD9291 is an oral, potent, irreversible EGFR-TKI selective for sensitizing EGFR and EGFRT790M resistance mutations with a significant selectivity margin against wild-type EGFR. As a result, AZD9291 can effectively block EGFR signaling both in EGFR single mutant cells with activating EGFR mutations and in double mutant cells bearing the resistance EGFRT790M mutation. AZD9291 is currently under investigation as a treatment option in: 1) Patients with advanced EGFRT790M-positive NSCLC who have previously failed an EGFR-TKI; 2) Patients with advanced EGFR-mutant NSCLC who are treatment naïve; 3) In combination with novel agents for patients with EGFR TKI-

resistant NSCLC.

In the phase 1 dose escalation study of AZD9291 (D5160C00001, AURA1), no dose-limiting toxicities were reported in any of the dose escalation cohorts (20, 40, 80, 160, and 240mg) and a non-tolerated dose has not been defined. Based on the totality of the safety, pharmacokinetic and preliminary efficacy data, 80 mg once daily was selected as the recommended phase II dose.5 Data from the ongoing phase I AURA study (D5160C00001) in patients with EGFRT790M-positive NSCLC who were previously treated with EGFR TKI, have achieved promising efficacy with AZD9291; 61% (95% CI, 52-70%) of subjects achieved a response, 95% (95% CI, 90-98%) achieved disease control, medium duration of response of 12.4 months (95% CI, 8.3-not reach) and median PFS based on 38% maturity of data was 13.5 months (95% CI, 8.3-not reach), as assessed by blinded independent central review. Confirmatory phase 2 study of AZD9291 (AURA2) revealed 70% (95% CI, 64-77%) of patients achieved objective response in patients with EGFRT790M-positive NSCLC.6 In addition, AZD9291 had significantly greater efficacy than platinum-doublet chemotherapy in patients with EGFRT790M-positive NSCLC (AURA3).7 Promising evidence of efficacy has also observed in patients with treatment-naïve EGFR-mutant NSCLC treated with AZD9291 as first line EGFR TKI.8

Although disease progression was observed in one NSCLC patient with EGFR exon 20 insertion mutation who received AZD9291 40mg once daily,5 its efficacy had not been well studied in a homogenous patient population with EGFR exon 20 insertion mutation. In addition, although in vitro efficacy of AZD9291 against EGFR exon 20 insertion mutation (H773_V774HVdup) was initially disappointing,9 AZD9291 was potent with a wide therapeutic window in Ba/F3 cells with EGFR exon 20 insertion mutations: IC50, 44-333 nM for A763_Y764insFQEA, Y764_V765insHH, A767_V769dupASV, and D770_N771insNPG in one study10; IC50, 3.6-128.2 nM for A763_Y764insFQEA, V769_D770insASV, D770_N771insNPG, D770_N771insSVD, P772_H773insPR, H773_V774insNPH, H773_V774insH, and H773_V774insAH (unpublished data). Therefore, this study will be performed to investigate the efficacy of AZD9291 in NSCLC patients with EGFR exon 20 insertion mutation.

Clinical experience with AZD9291 is described in the current version of the AZD9291 IB.

1.2 Rationale for study design, doses and control groups

This open-label, single-arm, non-randomized phase 2 study has been designed to evaluate the efficacy of AZD9291 80mg once daily in NSCLC patients with EGFR exon 20 insertion mutation who

failed to standard chemotherapy.

In the phase 1 dose escalation study of AZD9291 (D5160C00001, AURA1), once daily doses of 20, 40, 80, 160, and 240mg of AZD9291 were evaluated.5 Based on the totality of the safety, pharmacokinetic and preliminary efficacy data, 80 mg once daily was selected as the recommended phase II dose. Please refer to the AZD9291 IB for additional details. No dosage adjustment is required due to patient age, body weight, gender, ethnicity and smoking status.

1.3 Benefit/risk and ethical assessment

This study is designed to assess the primary objective for AZD9291 efficacy while minimizing the number of patients exposed to AZD9291 based on Simon's minimax two-stage design. Pre-clinical and emerging clinical tolerability data from patients indicate that AZD9291 is generally well tolerated by patients with advanced cancer. At least 1,258 subjects have been exposed to study treatment (AZD9291 alone or AZD9291 in combination with another treatment) in the ongoing osimertinib clinical programe (excluding healthy volunteers who only received single doses of osimertinib, and excluding patients treated with osimertinib in the ongoing Studies D5160C00003, D5160C00007 and D5165C00001). The safety data from AURA extension and AURA2, supported by consistent data from AURA Phase I, indicate that osimertinib 80 mg has an acceptable safety and tolerability profile in terms of the type, frequency and severity of events, for use in patients with NSCLC.5,6 The most common AEs reported with osimertinib were consistent across AURA extension and AURA2 and in line with the expected profile of an EGFR TKI. AEs of decreased appetite, fatigue, and nausea occurred at an incidence of >10%, but were mostly mild in nature and non-serious. These non-specific AEs represent a range of symptoms related to NSCLC and its treatment and were reported frequently in the past medical history of this patient population (decreased appetite [12.9-16.9%], fatigue [15.7-18.4 %], nausea [6.7-9.0%]). Across all cohorts and dose levels, there were 12 patients who died due to an AE; the most frequently reported AE that led to death was pneumonia (6 patients). No other AE that led to death was reported in more than 1 patient. Taken together, AZD9291 is well tolerated and active in patients with EGFRT790M-positive NSCLC, suggesting that clinical benefits exceed the risk.

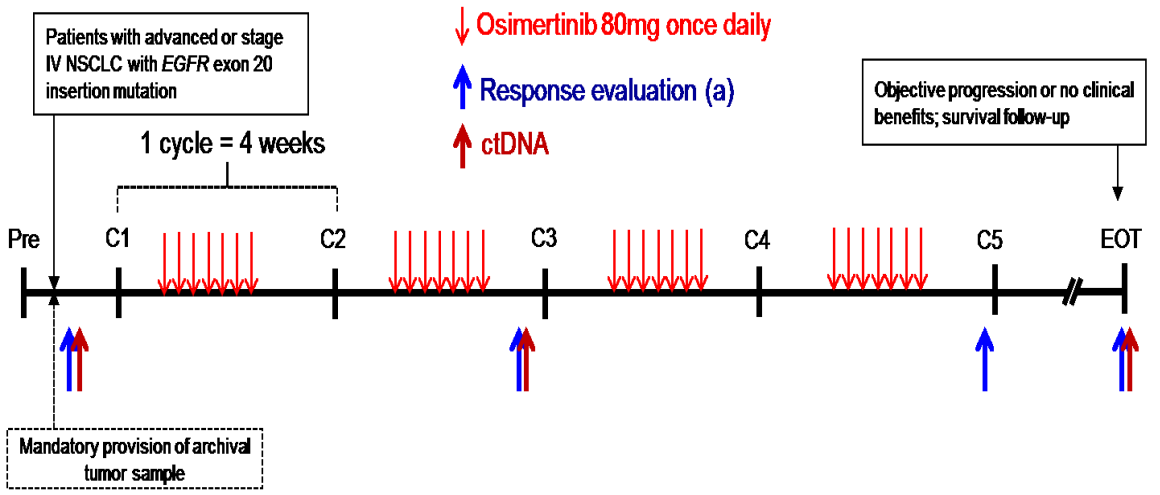
However, there has been no approved targeted agent for NSCLC patients with EGFR exon 20 insertion mutation who show disease progression on standard chemotherapy (platinum doublet

chemotherapy, etc). Based on the totality of the safety and pharmacokinetic data as well as in vitro efficacy data, AZD9291 80mg once daily might be safe and beneficial in patients with NSCLC with EGFR exon 20 insertion mutation. Please refer to the AZD9291 IB for details.

1.4 Study Design

This is a single-arm, non-randomized multicentre phase 2 study in NSCLC patients with EGFR exon 20 insertion mutation, whose disease has progressed on standard chemotherapy. Full details of the assessments conducted at each visits are shown in Table 1.

Figure 1 Study flow chart



(a) Patients will continue to receive osimertinib until objective disease progression (according to RECIST 1.1) or for as long as they are receiving clinical benefit in the opinion of the Investigator unless any of the criteria for treatment discontinuation are met first. Patients who discontinue study treatment for reasons other than disease progression must continue tumour assessments as per the protocol schedule until progression.

2. Study objectives

2.1 Primary objective

Primary Objective	Outcome Measure
To determine the efficacy of osimertinib in patients with advanced or metastatic NSCLC with EGFR exon 20 insertion mutation who show disease progression on standard chemotherapy.	Investigator-assessed objective response as defined by RECIST version 1.1

2.2 Secondary objectives

Secondary Objectives Outcome Measure

To evaluate the safety and tolerability of osimertinib AEs/SAEs as defined by NCI CTCAE version 4.0

To evaluate progression-free survival (PFS) PFS as defined by RECIST version 1.1

To evaluate overall survival (OS)

To evaluate the efficacy based on subtypes of EGFR exon 20 insertion mutation

To evaluate PFS based on subtypes of EGFR exon 20 insertion mutation

2.3 Exploratory objectives

Exploratory Objective Outcome Measure

To collect and store archival tumour tissues and cell-free DNA (cfDNA) for evaluation of mutant subtypes and disease monitoring Objective response based on genetic subtypes of EGFR exon 20 insertion mutation

3. SUBJECT SELECTION, ENROLMENT, DISCONTINUATION AND WITHDRAWAL

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

3.1 Inclusion criteria

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

1. Provision of informed consent prior to any study specific procedures

2. Male or female must be > 19 years of age.

3. Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy with local confirmation of the presence of the EGFR exon 20 insertion mutation

4. Disease progression while on standard chemotherapy (platinum doublet chemotherapy or single-agent chemotherapy in selected patients)

5. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.

6. Patients must have a life expectancy ≥ 12 weeks

7. Females should be using adequate contraceptive measures, should not be breast feeding and must have a negative pregnancy test prior to start of dosing if of child-bearing potential or

must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

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

8. Male patients should be willing to use barrier contraception (see Restrictions, Section0).

9. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

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

11. Provision of archival FFPE tissue (3 slices of 10μm thickness in EP tube)

12. Provision of informed consent for translational genetic research

3.2 Exclusion criteria

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

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

2. Previous treatment with osimertinib

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

4. Patients currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be potent inhibitors of CYP3A4 (at least 1 week prior) and potent inducers of CYP3A4 (at least 3 week prior) (Appendix A). All patients must try to avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer/inhibitory effects on CYP3A4.

5. Any unresolved toxicities from prior therapy greater than Common Terminology Criteria for

Adverse Events (CTCAE) grade 1 at the time of starting study treatment with the exception of alopecia and grade 2, prior platinum-therapy related neuropathy.

6. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required.

7. Patients with symptomatic CNS metastases who are neurologically unstable; however, those with asymptomatic CNS metastases who do not require steroids for at least 4 weeks prior to start of osimertinib are eligible.

8. Past medical history of ILD, drug-induced ILD, radiation pneumonitis requiring steroid treatment, or any evidence of clinically active ILD

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

Absolute neutrophil count <1.5 x 109/L

Platelet count <100 x 109/L

Haemoglobin <90 g/L

Alanine aminotransferase >2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases

Aspartate aminotransferase >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases

Total bilirubin >1.5 times ULN if no liver metastases or >3 times ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia) or liver metastases

Creatinine >1.5 times ULN concurrent with creatinine clearance <50 ml/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN.

10. Any of the following cardiac criteria:

Mean resting corrected QT interval (QTc using Fredericia's formula) > 470 msec

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)

Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medication known to prolong the QT interval

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

12. History of hypersensitivity to AZD9291 (or drugs with a similar chemical structure or class to AZD9291) or any excipients of these agents

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

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

15. Previous allogeneic bone marrow transplant.

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

3.3 Subject enrolment

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

The Investigator(s) will:

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

2. Assign potential subject a unique enrolment number.

3. Determine subject eligibility. See Sections 0.1 and 3.2.

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

3.4 Procedures for handling incorrectly enrolled or randomized subjects

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

treatment, and must be withdrawn from the study.

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

3.5 Methods for assigning treatment groups (Not applicable)

3.6 Methods for ensuring blinding (Not applicable)

3.7 Methods for unblinding (Not applicable)

3.8 Restrictions

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

1. Females of child-bearing potential should use reliable methods of contraception from the time of screening until 3 months after discontinuing AZD9291. Acceptable methods of contraception include total and true sexual abstinence, tubal ligation, hormonal contraceptives that are not prone to drug-drug interactions (IUS Levonorgestrel Intra Uterine System [Mirena], Medroxyprogesterone injections [Depo-Provera]), copper-banded intra-uterine devices, and vasectomized partner. All hormonal methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse.

2. Male patients should be asked to use barrier contraceptives (i.e., by use of condoms) during sex with all of their female partners during the trial and for a washout period of 3 months. Patients should not father a child for 6 months after completion of AZD9291 treatment. Patients should 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 AZD9291treatment.

3. If medically feasible, patients taking regular medication, with the exception of potent inhibitors or inducers of CYP3A4 (see above), should be maintained on it throughout the access program period (30 days post-last dose). Patients taking concomitant medications whose disposition is dependent upon CYP3A4 and breast cancer resistance protein (BCRP) and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving AZD9291. Patients taking concomitant medications whose disposition is dependent upon CYP3A4, CYP1A2, CYP2C or p-

glycoprotein and which have a narrow therapeutic index should be closely monitored for reduction in therapeutic activity as a result of the reduced exposure of the concomitant medication while receiving AZD9291. Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (see Appendix A).

Up to 1.5-fold increase in exposure may occur in statin exposure when coadministered with AZD9291. It is recommended that the starting and maintenance dose of statins should be as low as possible and should be guided by the statin prescribing information.

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

4. Patients who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE grade ≤2) while receiving treatment with AZD9291 until at least one week after symptoms have resolved. If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade ≥3) ocular events, they must discontinue wearing their contact lenses until at least one week after treatment with AZD9291 is permanently discontinued. Patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed to by a access program doctor, at any time during the access program until 1 week after AZD9291 has been permanently discontinued. Patients should consult their clinician promptly if they have any concerns.

3.9 Discontinuation of investigational product

Subjects may be discontinued from osimertinib in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance with the study protocol
- Progressive disease or no clinical benefits

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

3.9.1 Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue investigational product or withdraw from the study (i.e., investigational product and assessments – see Section 0), without prejudice to further treatment. A subject that decides to discontinue investigational will always be asked about the reason(s) and the

presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Section 0); and all study drugs should be returned by the subject. If a subject is withdrawn from study, see Section 0.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be treated in the study.

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment. A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The investigator will follow up AEs outside of the clinical study. If a subject withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn subjects will be replaced.

3.11 Discontinuation of the study

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

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

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented. In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

4. Study plan and timing of procedures

Table 1 Study Plan detailing the procedures

Visit

Visit window

Days –28 to 0 for Visit 1

±0 day for Visit 2

±1 day for Visits 3 and 4

±5 days starting at Visit 5 1

Screening	2	3	4	5	6	7	8 (n)	30-day	follow-up
For details see Protocol Section									
Week	0	2	4	8	12	16	20+		Section
Day -	0	14	28	56	84	112	140+	-	
Written informed consent (including tissue samples, pharmacogenetics)								X	
Demographics X									
Physical examination, height, and weight X									
X									
Medical/surgical history X									
Inclusion/exclusion criteria X		X							
Archival tumor tissue	X								
12-lead ECG	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
AZD9291 dispense/return		X		X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X
Adverse event review (AEs and SAEs)				X	X	X	X	X	X
X	X								
Blood samples for haematology and clinical chemistry				X	X	X	X	X	

	X	X	X					
Urinalysis	X	X	X	X	X	X	X	X
Blood sampling for cfDNA			X			X		X

4.1 Enrolment/screening period

Procedures will be performed according to the Study Plan (Table 1). At screening, consenting subjects are assessed to ensure that they meet eligibility criteria (Sections 3.1 and 3.2). Subjects who do not meet these criteria must not be enrolled in the study. All subjects will be required to provide consent to supply a sample of their archival tumor samples for entry into this study. This consent is included in the main subject informed consent form.

4.2 Treatment period

Descriptions of the procedures for this period are included in the Study Plan (Table 1) with exceptions of the following specific requirements for the treatment period: Subjects will receive osimertinib 80mg once daily until disease progression, unacceptable toxicities, or no clinical benefits.

4.3 Follow-up period

Descriptions of the procedures for this period are included in the Study Plan (Table 1) with exceptions of the following specific requirements for the follow-up period: Patients will return to the clinic/hospital for follow-up assessments 30 days (±7 days) after their last dose. If a patient discontinues AZD9291, they will also attend a study treatment discontinuation visit.

5. Study assessments

The investigator will ensure that data are recorded on the electronic Case Report Forms (eCRFs) as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the sponsor agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy assessments

RECIST 1.1 guidelines for measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumour response criteria are present. Baseline CT or MRI assessments of chest and abdomen (including liver and adrenal glands) must be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. Additional imaging may be performed based on individual patient signs and symptoms. The methods of assessment used at baseline should be used at each subsequent follow-up assessment. Follow-up assessments should be performed every 2 cycles (± 7 days) after the start of treatment until objective disease progression as defined by RECIST 1.1. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits whilst the patient remains on study treatment.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 guidelines for response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion progression will be calculated in comparison to when the tumour burden was at a minimum (i.e. smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment. If the investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment and reassess the patient's status at the next scheduled assessment or sooner if clinically indicated. If repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression. To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal disease progression status. It is important to follow the assessment schedule as closely as possible.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan . The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF. The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample

tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Table 2 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
Urinalysis (dipstick)	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Protein/Albumin	S/P-Calcium, total
U-Glucose	S/P-Sodium
	S/P-Creatine kinase (CK)

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section.

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

5.2.2 Physical examination

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

systems.

5.2.3 ECG

Patients should be monitored for ECG changes at every cycle. ECGs should be reviewed and any abnormalities noted.

5.2.3.1 Resting 12-lead ECG

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

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

5.2.4 Ophthalmologic exam

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

with additional tests if clinically indicated. Ophthalmology examination results should be

collected in the eCRF.

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

5.2.5 Vital signs

Vital signs will be measured at the times specified in the study plans (Table 1) and recorded in the eCRF. However, the Investigator reserves the right to add extra assessments if there are any abnormal findings or for any other reason the Investigator feels meets this requirement.

5.2.5.1 Pulse and blood pressure

Pulse and blood pressure will be measured at the times specified in the study plans (Table 1).

5.2.5.2 Body temperature

Body temperature will be measured at the times specified in the study plans using a semi-automatic body temperature recording device.

5.2.6 Other safety assessments (Not applicable)

5.3 Other assessments (Not applicable)

5.4 Pharmacokinetics (Not applicable)

5.5 Pharmacodynamics (Not applicable)

5.6 Pharmacogenetics (Not applicable)

5.7 Biomarker analysis

The subject's consent to the use of donated biological samples is mandatory. Biological samples (e.g., archived tumour samples and cfDNA) will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity.

5.7.1 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

5.7.2 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped appropriately.

5.7.3 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle. The Principal Investigator keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival. The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival. The sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of study

sites and auditing of external laboratory providers. Samples retained for further use should be documented and stored during the entire life cycle.

5.7.4 Withdrawal of Informed Consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, the sponsor is not obliged to destroy the results of this research.

The Principal Investigator:

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

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

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., treatment, follow-up), that fulfils one or more of the following criteria:

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

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca in accordance with the agreed process.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from time of signature of informed consent, enrolment throughout the treatment period and including the 30-day follow-up period. SAEs will be recorded from the time of informed consent.

6.3.2 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. The sponsor retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Whether the AE is serious or not

- Investigator causality rating against the Investigational Product (yes or no), comparator/combination drug (yes/no)
- Action taken with regard to investigational product/ comparator/combination agent
- Outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section6.2 . An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section0. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event. For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

6.3.5 Adverse events based on signs and symptoms

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

6.3.6 Adverse events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s). Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.7 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 Disease progression

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

6.3.9 New cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 6.4.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion

of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

6.3.10 Lack of efficacy

When there is deterioration in the condition for which the study treatment(s) is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

6.3.11 Deaths

All deaths that occur during the study, or within the protocol defined 30 day post study follow up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the eCRF but should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within 24 hours (see Section6.3.8 for further details). The report should contain a comment regarding the co involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death eCRF'.

- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca within the usual timeframes.

6.4 Reporting of serious adverse events

Investigators and other site personnel must inform the KFDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AZ. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the KFDA. It is the responsibility of the investigator to compile all necessary information and ensure that the KFDA receives a report according to the KFDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

* A cover page should accompany the MedWatch/AdEERs form indicating the following:

- Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the KFDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number

* Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

* Send SAE report and accompanying cover page by way of fax to AstraZeneca's designated fax line:

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the KFDA.

Serious adverse events that do not require expedited reporting to the KFDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

For all studies of AZD9291, the Sponsor should continue sending SUSARs to AZ in parallel to regulatory authorities as defined per AZ standard minimum requirements for safety data collection; all other SAEs should be sent to AZ on a monthly basis.

In the case of blinded trials, AstraZeneca will request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Non-serious adverse events and SAEs will be collected from the time consent is given, throughout the treatment period and up to and including the 30 day follow-up period. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for 30 calendar days after the last dose of trial drug and/or until event resolution. All new AEs occurring during that period must be recorded (if SAEs, then they must be reported to the FDA and AstraZeneca). All study-related toxicities/ SAEs must be followed until resolution, unless in the Investigator's opinion, the condition

is unlikely to resolve due to the patient's underlying disease.

6.5 Overdose

There is no specific treatment in the event of AZD9291 overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

For overdoses associated with a SAE, the standard agreed reporting timelines apply, see Section6.3.8 .

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study AZD9291 should be discontinued immediately. Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study. If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day 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 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Pregnancy of the subject's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented. To capture information about a pregnancy from the partner of a male subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome; the male subject should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 6 months after dosing ends should be followed up and documented.

6.7 Management of IP related toxicities

Dose adjustment for adverse events should be in accordance with the following table:

Table 3. AZD9291 dose adjustment information for adverse reactions

Target Organ	Adverse Reactiona	Dose Modification
Pulmonary	ILD/Pneumonitis	Permanently discontinue AZD9291
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold AZD9291 until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg).
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue AZD9291
Other	Grade 3 or higher adverse reaction	Withhold AZD9291 for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of AZD9291 for up to 3 weeks	AZD9291 may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue AZD9291

a Note: The intensity of clinical adverse events graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity (any grade), where the clinician 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. Detailed information on the clinical management of events may be found in Appendix B, "Guidance for the Management of Adverse Events in Studies using 80mg AZD9291."

Patients with QTc prolongation (i.e., confirmed QTc prolongation to >500 msec absolute or a > 60

msec increase from baseline) should have AZD9291 treatment interrupted and regular ECGs performed until resolution to baseline.

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 4). There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption.

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

Table 4. Dose Interventions

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

On resolution of toxicity within 3 weeks:

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 clinician.

6.7.1 Pulmonary Symptoms

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in AZD9291 dosing is recommended, and the AstraZeneca representative should 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.

Where ILD is suspected, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater pneumonitis, followed by corticosteroid taper. Permanently discontinue for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold until resolution for moderate (Grade 2) pneumonitis.

In the absence of a diagnosis of interstitial lung disease AZD9291 may be restarted.

6.7.2 QTc Prolongation

Patients with QTcF prolongation fulfilling the following criteria (i.e., confirmed QTcF prolongation to > 500 msec absolute or a > 60 msec increase from baseline) should have AZD9291 interrupted and regular ECGs performed until resolution to baseline. If the toxicity does not resolve to < grade 1 within 3 weeks the patient will be permanently withdrawn from AZD9291 treatment.

6.7.3 Corneal Ulceration

Patients experiencing corneal ulceration will not be permitted to restart AZD9291 treatment.

6.7.4 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 clinician to be causally related to AZD9291 is provided in Appendix B, Guidance for the Management of Adverse Events in Studies using 80mg AZD9291."

6.7.5 Diarrhea

Recommendations for appropriate management of diarrhea, including dose-adjustments for adverse events of diarrhea that are of CTCAE grade ≥3 or that are clinically significant and/or intolerable and considered by the clinician to be causally related to AZD9291, is provided in Appendix B, "Guidance for the Management of Adverse Events in Studies using 80mg AZD9291."

6.8 Study governance and oversight

An Executive Steering Committee will be set up. It will involve 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. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product (AZD9291)

Investigational product	Dosage form and strength	Manufacturer
AZD9291	40mg Tablets	

80mg Tablets AstraZeneca

AstraZeneca will supply AZD9291 as tablets for oral administration as a single daily dose of 80 mg. AZD9291 will usually be supplied as either bulk or unlabelled bottles for ISS/ESR studies. Additional information about the Investigational product may be found in the Investigators' Brochure.

7.2 Dose and treatment regimens

AZD9291 is administered as 80 mg once daily. AZD9291 can be taken without regard to food.

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 dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their AZD9291, they should not make up for this dose, but should take the next scheduled dose.

The dose of 80 mg AZD9291 daily can be reduced to 40 mg AZD9291 once daily under circumstances described in Section 6.7. Further dose reductions are not possible. Once a dose has been reduced, it should not be re-escalated at future cycles. Any change from dosing schedule, dose interruptions, or dose reductions should be recorded.

7.3 Labelling

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

7.4 Storage

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

7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

7.6 Accountability

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

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

7.7 Concomitant and other treatments

Once enrolled all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known potent inhibitors or inducers of CYP3A4 whenever feasible, but patients may receive any medication that is clinically indicated for treatment of adverse events. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 months after the last dose of AZD9291. All concomitant medications should be captured on the CRF. Guidance on medicines to avoid, medications that require close monitoring and on washout periods is provided (see Appendix A).

If medically feasible, patients taking regular medication, with the exception of potent inhibitors or inducers of CYP3A4 (see above), should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon CYP3A4,and BCRP and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving AZD9291. Additionally due to the potential CYP450 and p-glycoprotein induction risk exposure of drug that are metabolized by CYP3A4, CYP1A2 or CYP2C or whose deposition is mediated by p-glycoprotein could also be reduced and should also be monitored for reduction in therapeutic activity (especially those which have narrow therapeutic index). Guidance on medications to avoid, medications that require close monitoring and on washout periods should be provided (see Appendix A)

Patients should be advised of the potential reduction in effectiveness of oral hormonal contraceptives (due to CYP3A4 induction) when used with AZD921. A change to a non-oral method of contraception (e.g. IUS Levonorgestrel Intra Uterine System, Medroxyprogesterone injections), or addition of a barrier method (e.g. condoms, diaphragm) to the primary hormonal method, is recommended prior to the commencement of treatment. Up to 1.5-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 label. Monitoring of low- density lipoprotein (LDL) cholesterol levels is advised. If the patient experiences any potentially relevant adverse events suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, the statin should be stopped, creatine kinase (CK) levels should be checked, and any appropriate further management should be taken. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR.

7.7.1 Other concomitant treatment

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

7.8 Post Study Access to Study Treatment (Not applicable)

8. STATISTICAL ANALYSES BY SPONSOR

8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified.
- Analyses will be performed by the Sponsor or its representatives.
- Refer to SAP for details (if such a document exists and more details will be added).

8.2 Sample size estimate

The primary endpoint of this study is to evaluate the proportion of patients who achieved an objective response as assessed by the investigator according to RECIST version 1.1. Up to 30 patients (withdrawal 10%) will be enrolled and dosed in order to obtain at least 27 evaluable patients according to Simon's minimax two-stage design as follows: objective response, P0=0.05 and P1=0.20; type 1 error 5%, power 80%, and confidence limit 95%; stage 1 (objective response ≥1/13) plus stage 2 (objective response ≥4/27). All data will be presented for the overall full analysis set, and also by cohorts defined by subtypes of EGFR exon 20 insertion mutations (C-helix vs. loop following C-helix). 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 and PFS will be summarized using Kaplan-Meier estimates of the median event time and quartiles together with their 95% confidence intervals.

8.3 Definitions of analysis sets

The full analysis sets will include all subjects who received at least one dose of study treatment (safety) and dose patients with a baseline tumour assessment (efficacy).

8.4 Outcome measures for analyses

Outcome measures for analyses are presented in Section 2.

8.5 Methods for statistical analyses

8.5.1 Analysis of the primary variable (s)

The investigator-assessed objective response will be evaluated according to RECIST version 1.1 including 95% confidence intervals.

8.5.2 Analysis of the secondary variable(s)

PFS will be summarized using Kaplan-Meier estimates of the median time to progression. OS will be summarized using Kaplan-Meier estimates of the median time to death or censoring and quartiles together with their 95% confidence intervals.

8.5.3 Subgroup analysis (Not applicable)

8.5.4 Interim analysis (Not applicable)

8.5.5 Sensitivity analysis (Not applicable)

8.5.6 Exploratory analysis (if applicable)

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

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

The principal investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, a sponsor representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being

accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

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

9.2.1 Source data

9.2.2 Study agreements

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

9.2.3 Archiving of study documents

The study site (and the Principal Investigator) will retain essential documents in accordance to ICH GCP.

9.2.4 Deviation from the clinical study protocol

The Investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the Principal Investigator and the IRB approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the subjects or for other compelling medical reasons.

9.3 Study timetable and end of study

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

of treatment will not occur until the LPLV occurs of the patient who was deriving clinical

benefit or when AZD9291 is discontinued. The study is expected to start in Q2 2017 and to end by Q2 2019. The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other

study with AZD9291.

9.4 Data management

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database

and/or the investigational site.

Data Management of genotype data

Any genotype data generated in this study will be stored in the appropriate secure system within principle investigator site.

Data associated with human biological samples

Data associated with biological samples will be transferred from each participating centres to principle investigator site.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and all applicable regulatory requirements.

10.2 Subject data protection

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

10.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff. The opinion of the Ethics Committee should be given in writing. If required by local regulations, the protocol should be re-approved by the Ethics Committee annually. Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory

authority or a notification to the national regulatory authority is done, according to local regulations. Safety updates/reports will be provided to regulatory authorities, ethics committees and Principal Investigators in accordance with local requirements and agreement with AstraZeneca.

10.4 Informed consent

The Principal Investigator(s) at each centre will:

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

10.5 Changes to the protocol and informed consent form

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol). The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

If a protocol amendment requires a change to a centre's Informed Consent Form, the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used. If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

10.6 Audits and inspections

11. LIST OF REFERENCES

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7. Mok TS, Wu YL, Ahn MJ, et al: Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med, 2016

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