AstraZeneca

Revised Clinical Study Protocol	
Drug Substance	AZD9291
Study Code	D5164C00001
Edition Number	6.0
Date	09 August 2023

A Phase III, Double-blind, Randomised, Placebo-Controlled Multi-centre, study to assess the efficacy and safety of AZD9291 versus Placebo, in Patients with Epidermal Growth Factor Receptor Mutation Positive Stage IB-IIIA Non-small Cell Lung Carcinoma, following Complete Tumour Resection With or Without Adjuvant Chemotherapy (ADAURA)

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

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	17 November 2016		
2	01 August 2019		
3	02 July 2020		
4	25 January 2021		
5	09 August 2023		

Administrative change No.	Date of Administrative Change	Local Administrative change No.
1	22 June 2015	

Redacted for Public Disclosure

VERSION HISTORY

CSP Version 6.0; 09 August 2023: Changes to the protocol (all considered as non-substantial) are summarised below:		
Section # and Name	**Description of Change**	**Brief Rationale**
Title page	The name and address of the AstraZeneca global study leader were deleted.	These details are not required to be on the title page in the most recent AstraZeneca protocol template.
Synopsis	Changes were made in line with changes made in the main protocol.	For consistency throughout the CSP.
Section 1.6 Study design	CSP edition 6.0 has introduced a further optional long-term OS follow-up. All patients in survival follow-up will be offered the opportunity to participate in the long-term OS follow-up. Patients who consent to participate will be followed yearly for survival until approximately 10 years after the randomisation of the last patient to capture long-term OS data in the study extension. Safety data (all serious or non-serious events of ILD/pneumonitis and cardiac failure, and all SAEs) will continue to be collected for patients who are treated with open-label osimertinib.	To allow the longer-term survival follow-up of patients in the ADAURA trial to further characterise long-term patient outcomes in the adjuvant setting.
	The following sentences were removed: • "Should there be any remaining patients on study drug at the time of data cut-off for the final OS analysis, they will be able to continue study treatment until completion or a treatment discontinuation criterion is met." • "Patients still receiving study drug after the final analysis will be monitored in accordance with the Investigator's standard clinical practice or national product label. Drug accountability information will be recorded in the source documents."	Final OS analysis has occurred. All patients have had the opportunity to complete the 3 years of planned study treatment and as such there are no patients on IP at this time. Any patient on active treatment is receiving open-label osimertinib. See Section 4.4, Section 4.5, and Section 7.3.3.

CSP Version 6.0; 09 August 2023: Changes to the protocol (all considered as non-substantial) are summarised below:		
Section # and Name	**Description of Change**	**Brief Rationale**
	The instructions for collecting information about SAEs, overdose, and pregnancy were updated.	To provide details of how this information will be collected if the EDC system is not available.
Section 1.7 Study extension for long-term OS follow-up	New section.	To provide details and rationale for the long-term OS follow-up.
Figure 1 Study design	Footnote added.	To include details of the long-term OS follow-up.
Section 3.3 Eligibility for post-recurrence open-label osimertinib	Changes were made to criteria #5 and #7: Criterion #5: Patients must not receive any other systemic anti-cancer therapies **(other than osimertinib)** between the discontinuation of study treatment and the start of treatment with open-label osimertinib. Criterion #7: Patients with recurrence eligible for open-label osimertinib should have completed imaging modalities for chest, abdomen (including liver and adrenal glands) and brain with contrast at **the** time of recurrence~~, as required at recurrence visit.~~	For clarification.
Section 3.11 Criteria for withdrawal from study	Included the long-term OS follow-up.	To provide details for the long-term OS follow-up.
Section 4 Study plan and timing of procedures	Added Table 3 Study plan for the study extension post final OS analysis and up to long-term OS analysis.	To provide details for the long-term OS follow-up.
Section 4.1.1.1 Written informed consent for the long-term OS	New section.	To provide details for the long-term OS follow-up.

CSP Version 6.0; 09 August 2023: Changes to the protocol (all considered as non-substantial) are summarised below:		
Section # and Name	**Description of Change**	**Brief Rationale**
follow-up in the study extension		
Section 4.3.5 Survival follow-up in the study extension for long-term OS analysis	New section.	To provide details for the long-term OS follow-up.
Section 4.4 Study plan for patients eligible for open-label osimertinib	Updated to include the long-term OS follow-up.	To provide details for the long-term OS follow-up.
Section 4.5 Study plan for the study extension for long-term OS analysis	New section.	To provide details for the long-term OS follow-up.
Section 5.1.3 Overall survival	Updated to include the long-term OS follow-up.	To provide details for the long-term OS follow-up.
Section 5.1.3.1 Overall survival - long-term OS survival	New section.	To provide details for the long-term OS follow-up.
Section 6.3.1 Time period for collection of adverse events in the eCRF	The following text was deleted: "After the final database lock, there may be some patients remaining on study treatment. For these patients who are continuing to receive AZD9291, AstraZeneca will collect information, during the treatment period and for 28 days after last dose, on SAEs, deaths (including those due to disease recurrence), discontinuation due to AEs/SAEs and drug accountability only.".	There are no patients remaining on study drug at this time.

CSP Version 6.0; 09 August 2023: Changes to the protocol (all considered as non-substantial) are summarised below:		
Section # and Name	**Description of Change**	**Brief Rationale**
Section 6.5 Reporting of serious adverse events post OS final analysis	The following text was deleted: "For patients who do continue to receive treatment beyond the time of this data cut off, investigators will continue to report all SAEs, overdoses and pregnancies to AstraZeneca via paper and emailed (preferably) or faxed directly to TCS (also known as AZ DES) in accordance with Section 6.4."	There are no patients remaining on study drug at this time.
	Included instructions for patients receiving open-label osimertinib. Included instructions for patients continuing on open-label osimertinib after the completion of the long-term OS follow-up.	For clarification.
Section 6.9.2 Skin reactions	Updated to include toxic epidermal necrolysis.	To align with the latest PSSR (v28).
Section 6.9.3 Aplastic anaemia	New section.	To align with the latest PSSR (v28).
Section 7.3.3 Patients receiving open-label osimertinib post final OS analysis/during study extension for long-term OS analysis	New section.	To provide details for the long-term OS follow-up and to include standard PTAP text.
Section 8.4.1.2 OS	Updated to include the long-term OS follow-up.	To add the long-term OS follow-up.
Section 8.7 Further analysis post IDMC7	The heading was revised: "~~Future~~ **Further** analysis **post IDMC7**". An introductory paragraph was added.	For clarification.
Section 8.8 Long-term OS analysis - study extension	New section.	To provide details for the long-term OS follow-up.

CSP Version 6.0; 09 August 2023: Changes to the protocol (all considered as non-substantial) are summarised below:		
Section # and Name	**Description of Change**	**Brief Rationale**
Section 9.3 Study timetable and end of study definition	Updated to include the long-term OS follow-up.	To provide details for the long-term OS follow-up.
Section 9.4 Data management	Indicated that an alternative vendor may be used for data management.	For clarification.
Throughout	Updates were made to include mandatory text from the recently released Late Development Oncology CSP Template (based on the AstraZeneca CSP TransCelerate Template TMP-0010225); applies to Section 6.6, Section 6.8, Section 9.2.3, Section 9.3, and Section 10. Minor administrative changes for clarification and to correct typographical errors.	To harmonise the content to meet the EU CTR requirements. Minor, therefore have not been summarised.

CSP Version 5.0; 25 January 2021:
Changes incorporated in the revised Clinical Study Protocol v. 5.0 dated 25 January 2021 are summarised in the Version History section of Clinical Study Protocol v. 5.0.

CSP Version 4.0; 02 July 2020:
Changes incorporated in revised Clinical Study Protocol v. 4.0 dated 02 July 2020 are summarised in the Version History section of Clinical Study Protocol v. 4.0.

CSP Version 3.0: 01 August 2019
Changes incorporated in revised Clinical Study Protocol v. 3.0 dated 01 August 2019 are summarised in the Version History section of Clinical Study Protocol v. 3.0.

CSP Version 2.0: 17 November 2016
Revised Clinical Study Protocol v. 2.0 dated 17 November 2016 was created to incorporate all changes that were outlined in Clinical Study Protocol Amendment v 1.0 dated 17 November 2016.

CSP Version 1.0: 22 June 2015
Revised Clinical Study Protocol v. 1.0 dated 22 June 2015 was created to incorporate all changes that were outlined in Clinical Study Protocol Administrative Change v. 1.0 dated 22 June 2015.

Version 1.0: 04 June 2015
Initial creation

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

PROTOCOL SYNOPSIS

A Phase III, Double-blind, Randomised, Placebo-Controlled Multi-centre, study to assess the efficacy and safety of AZD9291 versus Placebo, in Patients with Epidermal Growth Factor Receptor Mutation Positive Stage IB-IIIA Non-small Cell Lung Carcinoma, following Complete Tumour Resection With or Without Adjuvant Chemotherapy (ADAURA)

International Co-ordinating Investigators:

PPD

Smilow Cancer Hospital at Yale, USA

PPD

National Cancer Center Hospital East, Japan

PPD

Guangdong General Hospital, China

This study will be global, with approximately 700 patients to be randomised from an estimated 210 sites over an estimated 28 months. Approximately 10-15% recruitment is anticipated from USA. Approximately 60% recruitment is anticipated to be from Asia.

Study period		**Phase of development**
Estimated date of first subject enrolled	August 2015	Phase 3
Estimated date of last subject completed (OS cut-off)	Q1 2023	Phase 3
Estimated date of last subject completed long-term OS follow-up	Q2 2029	Phase 3

Study Design

This is a phase 3 double-blind, randomised, placebo-controlled, study to assess the efficacy and safety of AZD9291 versus placebo in patients with stage IB-IIIA non-small cell lung cancer (NSCLC) with centrally confirmed, most common sensitising EGFR mutations (Ex19Del and L858R) either alone or in combination with other EGFR mutations as confirmed by a central test, who have had complete tumour resection, with or without post-operative adjuvant chemotherapy. Adjuvant chemotherapy should have consisted of a platinum based doublet given for a maximum of 4 cycles.

Patients will be randomised 1:1, to receive either AZD9291 or placebo. Patients must have sufficiently recovered from surgery and completed any standard of care adjuvant chemotherapy prior to randomisation. Patients must be randomised within 10 weeks following complete surgical resection if adjuvant chemotherapy was not administered, within 26 weeks following surgery if adjuvant chemotherapy was administered.

Accounting for patients who are found to have wild type EGFR, sample attrition and 10% screen fail rate for other reasons, it is estimated that approximately 3200 patients will be screened to randomise approximately 700 patients. It is assumed that approximately 60% of patients will be recruited from Asia and 40% from non-Asian countries. The proportion of patients randomised with stage 1B cancer will be 30% and the proportion of patients randomised with Stage II-IIIA cancer will be 70%. Patients will be stratified at randomisation by stage (IB vs II vs IIIA), mutation type (Ex19Del/L858R either alone or in combination with other EGFR mutations) as confirmed by a central laboratory using a tissue based test, and race (Asian/ non-Asian).

Following complete resection all patients will be required to have a baseline CT scan (chest and abdomen including liver and adrenal glands) within 28 days prior to treatment initiation to confirm that disease is not present.

Patients will undergo safety assessments at baseline, 2 weeks, 4 weeks, 12 weeks, and every 12 weeks until treatment is completed or discontinued. All study patients must have a 28 day follow up visit after treatment is stopped.

Patients will undergo regular CT scan (chest and abdomen including liver and adrenal glands) with additional anatomy imaging, as indicated by signs and symptoms of the patient, for disease recurrence. Disease free survival (DFS) shall be measured from the date of randomisation until date of disease recurrence or death (from any cause) in the absence of recurrence by investigational site assessment.

Patients will be followed for disease recurrence at 12 weeks, 24 weeks, and then every 24 weeks until 5 years (taken to be 264 weeks) and yearly thereafter. Following disease recurrence, patients will be followed for overall survival (OS) every 24 weeks until 5 years (taken to be 264 weeks), then yearly thereafter.

Following discontinuation of study drug, while patients are followed up for disease recurrence, SAEs considered related to the study treatment and procedures will be collected. Thereafter, at any time, if an investigator learns of any SAEs possibly related to AZD9291 including death, AstraZeneca should be notified.

At disease recurrence, patients will be restaged and all sites of NSCLC relapse will be recorded. Treatments received by the patient after relapse will be determined by the physician. Post recurrence cancer treatments and procedures will be recorded.

Tumour and blood sampling for biomarker analysis will also be performed. PK sampling will be performed.

An Independent Data Monitoring Committee (IDMC) will be convened and will meet approximately every 6 months for the first 2 years from the first patient randomised and approximately yearly thereafter. Further meetings for review of safety data may be convened at the discretion of IDMC. The IDMC will review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. Serious adverse events, adverse events, and other safety data will be reviewed, and individual and aggregated safety data will be evaluated by the IDMC. The IDMC will also perform a futility analysis.

Patients will be initially followed as per the study protocol until data cut-off for the primary analysis, estimated as 68-70 months following first subject randomised, based on a 28 month recruitment period. Results from the primary analysis will be reported in the Clinical Study Report. If there are meaningfully less than 70 DFS events in the IB population at the time of the primary analysis, further follow up of all patients according to the same study plan will be performed until completion of the final exploratory DFS analysis (hereafter referred to as the 'final DFS analysis').

Following the primary analysis (or 'until completion of final DFS analysis' if required), patients will be followed-up for survival according to a reduced study plan (OS period) until the data cut-off for the final OS analysis.

Following the final OS analysis, the ADAURA study was planned to be closed, and the collection of survival, cancer therapy, and safety data for globally recruited patients no longer on study treatment was to stop entirely. All patients and Investigators remain blinded to individual study treatment allocation. Following the final OS analysis, CSP edition 6 has introduced a further optional long-term OS follow-up. All patients in survival follow-up will be offered the opportunity to participate in the long-term OS follow-up. Patients who consent to participate will be followed yearly for survival until approximately 10 years after the last patient is randomised to capture long-term OS data in the study extension. Safety data (all serious or non-serious events of ILD/pneumonitis and cardiac failure, and all SAEs) for patients who are treated with open-label osimertinib will be collected as described in Section 6.3. Any patients still on open-label osimertinib and deriving clinical benefit can continue to receive treatment until they meet a discontinuation criteria, as outlined in Section 3.10. Following the completion of the study extension, any patients still on open-label osimertinib will be managed outside of the study per Section 7.3.3. At this point, any SAEs will be reported outside of the database, only reported as per Section 6.4 and Section 6.5.

Objectives

Primary Objective	**Outcome Measure**
To assess the efficacy of AZD9291 compared to placebo as measured by disease free survival (DFS)	• DFS by investigator assessment
Secondary Objective:	**Outcome Measure:**
To further assess the efficacy of AZD9291 compared with placebo	At time of primary analysis: • DFS rate at 2, 3, 4 and 5 years • Overall Survival (OS) • OS rate at 2, 3, 4 and 5 years
To assess the effect of AZD9291 compared with placebo on health-related quality of life (HRQoL)	Changes in generic HRQoL as measured by the SF-36 (vers2, standard)
To characterise the pharmacokinetics (PK) of AZD9291 and its metabolites (AZ5104 and AZ7550)	PK plasma concentrations of AZD9291, and metabolites AZ5104 and AZ7550; and ratio of metabolite to AZD9291 for each PK sample (included in CSR) PK data from this study will be analysed using a population PK approach and reported separately to the Clinical Study Report (CSR). Data from this study may form part of a pooled analysis with data from other studies

Safety Objective:	**Outcome Measure**
To assess the safety and tolerability profile of AZD9291 compared with placebo	• Adverse events (graded by CTCAE v4) • Clinical chemistry, haematology and urinalysis • Vital signs, Physical Examination, Weight • Digital ECG • LVEF • WHO Performance Status • Ophthalmologic assessment

Exploratory Objective:	**Outcome Measure:**
To compare health resource use associated with AZD9291 treatment versus placebo	Health Resource Use Module

To compare the effects of AZD9291 or placebo on post recurrence outcomes	• Time to next treatment (s) • Type of recurrence (local/regional or distant) • Site (s) of recurrence • Type of next treatment (s) (including procedures, radiotherapy and anticancer agents) • PFS as determined by investigator assessment
To further assess the efficacy of AZD9291 compared with placebo	• OS • OS rate at 2, 3, 4, and 5 years
To assess the efficacy of AZD9291 in patients with confirmed baseline T790M status (positive / negative) using a high sensitivity method yet to be determined (retrospective)	• DFS by investigator assessment • OS
To collect and store biopsy material (multiple cores where possible) from all screened patients for exploratory analysis of molecular mechanisms associated with development of NSCLC and response to treatment.	Key genetic and proteomic markers to include, but not limited to, EGFR mutations, human epidermal growth factor receptor 2 (HER2), and proto-oncogene encoding Hepatocyte Growth Factor Receptor (cMET) expression and/or amplification. Data generated may be reported separately and may also form part of a pooled analysis with other AZD9291 studies.
To collect and store tumour and plasma samples for potential exploratory research into factors that may influence susceptibility to development of NSCLC and/or response to AZD9291 (where response is broadly defined to include efficacy, tolerability or safety) and to assess the relationship between blood-borne biomarkers and selected efficacy endpoints. Tissue and plasma samples may be used to support diagnostic development.	Evaluate the feasibility of using circulating DNA, RNA, and/or protein (including but not limited to ctDNA) profiling approaches for detection of minimal residual disease (MRD) in early-stage NSCLC patients after completion of surgery (and chemotherapy in eligible patients). Investigate whether detection of MRD is impacted by tumour staging or adjuvant chemotherapy. Assess dynamics of circulating DNA, RNA, and/or protein as a proof of principle for early prediction of disease recurrence in the adjuvant setting. Investigate how circulating DNA, RNA, and/or protein relates with other efficacy endpoints, including DFS based on detection of tumour recurrence using imaging approaches. Investigate the prognostic value of DNA, RNA, and/or protein features in predicting response to AZD9291 in the adjuvant setting using baseline tumour tissue samples

To compare the baseline tumour EGFR mutation status in all randomised patients with evaluable results from baseline plasma.	Comparison of EGFR mutation status between tumour deoxyribonucleic acid (DNA) and plasma derived ctDNA.
To compare plasma-derived ctDNA EGFR mutation status at baseline and at disease recurrence.	Comparison of EGFR mutation status in plasma samples at baseline and at disease recurrence.
To assess any changes in EGFR mutation status (including T790M) using the mandated serial plasma samples coupled with a high sensitivity method yet to be determined (retrospective)	Assessment of EGFR mutation status in serial plasma samples
To explore the relationship between PK and selected endpoints (which may include efficacy, safety, and/or PRO), where deemed appropriate.	Correlation of PK with other primary/secondary/ exploratory endpoints in patients treated with AZD9291.

Target patient population

Male and female patients aged 18 years and over (patients from Japan/Taiwan aged at least 20 years) with histologically confirmed diagnosis of primary non-squamous non-small cell carcinoma of the lung, with complete surgical resection of the primary tumour, and who were classified post-operatively as Stage IB, II or IIIA on the basis of pathologic criteria are eligible for this study. Recruitment of patients with stage IB disease will be closed when approximately 210 (30%) have been randomised and recruitment of patients with stage II-IIIA disease will be closed when approximately 490 (70%) have been randomised. Patients must be confirmed to have a tumour that harbours one of the most common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19Del; L858R) either alone or in combination with other EGFR mutations as confirmed by a central test.

Patients may have received prior adjuvant platinum doublet chemotherapy for a maximum of 4 cycles in accordance with standard of care but must not have received prior radiotherapy. Pre-operative (neo-adjuvant) platinum based or other chemotherapy is not allowed.

Duration of treatment

Treatment with AZD9291 (80 mg once daily) or placebo will commence following randomisation. Patients will continue on randomised treatment until recurrence of disease, treatment discontinuation criterion is met or treatment is completed. The maximum treatment duration period is 3 years (156 weeks). Should there be any patients on study drug at the time of data cut –off for primary analysis, they may continue treatment until 3 years (156 weeks) treatment is completed or a discontinuation criterion is met.

For patients eligible for open-label osimertinib upon recurrence:

Eligible patients can be offered open-label osimertinib upon recurrence, if the recurrence pattern is in line with the regional label, as described in Section 3.3. In line with the approved indication, these patients can continue to receive open-label osimertinib until disease

progression, or until a time when the Investigator considers that they are no longer deriving clinical benefit, or they stop taking treatment for any other reason including having met any of the criteria for treatment discontinuation. At the time of final OS analysis, a number of patients can still be on open-label osimertinib. These patients can continue treatment as long as, in the investigator's opinion, it is considered to be beneficial.

This is also applicable for patients participating in the study extension for an optional long-term OS follow-up. Following the completion of the study extension, any patients still on open-label osimertinib will be managed outside of the study per Section 7.3.3.

Investigational product, dosage and mode of administration

AZD9291 is an oral, potent, selective, central nervous system (CNS) active, irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) effective against both EGFR-TKI sensitising and resistance mutations in NSCLC with a significant selectivity margin over wild-type EGFR. AZD9291 (80 mg orally, once daily) or matching placebo, in accordance with the randomisation schedule, will be administered.

Statistical methods

Approximately 700 patients will be randomised in a 1:1 ratio (AZD9291: placebo) to this study. The primary endpoint is DFS and a hierarchical approach to the primary analysis will be employed. The primary analysis of DFS was planned to be conducted when approximately 247 disease recurrence events have been observed in approximately 490 patients (50% maturity) who are in Stage IIA-IIIA (i.e., non-Stage IB). Assuming 28 months non-linear recruitment, 247 DFS events are expected to occur approximately 68-70 months after the first patient is randomised in the study. If the DFS result in the stage II-IIIA population is statistically significant at the 5% (2-sided) alpha level, DFS in the overall population will then be tested.

If the true hazard ratio for the comparison of AZD9291 versus placebo in the non-IB population is 0.70, 247 disease recurrence events will provide 80% power to demonstrate a statistically significant difference in DFS at a 5% 2-sided significance level (this could translate to an improvement on median DFS from 40 months to 57 months, if DFS is exponentially distributed). The minimum DFS HR that would be statistically significant ($p<0.05$ 2-sided) is 0.78.

DFS in the non-Stage IB population will be analysed using a log rank test stratified by stage (II, IIIA), mutation type (Ex19del, L858R either alone or in combination with other EGFR mutations as confirmed by a central test) and race (Asian, Non-Asian). DFS in the overall population will be analysed using a log rank test stratified by stage (IB, II, IIIA), mutation type (Ex19del, L858R either alone or in combination with other EGFR mutations as confirmed by a central test) and race (Asian, Non-Asian).

Estimates of secondary endpoints of DFS rate at 2, 3, 4, and 5 years will be obtained for each arm of the study, from the Kaplan Meier plot of the primary endpoint of DFS.

OS analyses will also be conducted at the time of the DFS analyses and then again when approximately 94 OS events have been observed in the stage II-IIIA population. Further details on the multiple testing strategy is included in the SAP.

A futility analysis will be conducted. Details of this analysis will be included in the statistical analysis plan and IDMC charter. An IDMC will review the futility outcomes and provide a recommendation for whether the study should continue. The IDMC will also review safety on an ongoing basis.

A long-term OS analysis from the time of randomisation until date of death due to any cause will be conducted to obtain long-term follow-up OS data.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AZD9291	Osimertinib
BCRP	Breast Cancer Resistance Protein
BP	Blood pressure
CI	Confidence interval
CK	Creatine kinase
cMET	Proto-oncogene encoding Hepatocyte Growth Factor Receptor
CR	Complete response
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Event
*ct*DNA	Circulating tumour deoxyribonucleic acid
CTIS	Clinical Trial Information System
CYP	Cytochrome P450
DCO	Data cut-off
DES	Data Entry Site
DFS	Disease free survival
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic case report form
EBUS-TBNA	Endobronchial ultrasound transbronchial needle aspiration
EDoR	Expected Duration of Response
EGFR	Epidermal Growth Factor Receptor
EGFRm+	Epidermal Growth Factor Receptor mutation positive

Abbreviation or special term	Explanation
EGFR-TKI	Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor
EM	Erythema Multiforme
EMA	European Medicines Agency
EU	European Union
EU CTR	European Union Clinical Trials Registration
Ex19del	Deletions in exon 19
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin Fixed and Paraffin Embedded
FPI	First patient in
FSE	Feelings of Side effects
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GMP	Good Manufacturing Practice
HDPE	High-Density-Polyethylene
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard ratio
HRCT	High-resolution computed tomography
HIV	Human immunodeficiency virus
HRQoL	Health Related Quality of Life
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
IMP	Investigational medicinal product
INR	International Normalised Ratio
IP	Investigational Product
IRB	Independent Review Board
IUS	Intra uterine System
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier

Abbreviation or special term	Explanation
L858R	Exon 21
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LH	Luteinizing hormone
LIMS	Laboratory Information Management System
LPLV	Last patient last visit
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor and Welfare
MRI	Magnetic resonance imaging
MUGA	Multi Gated Acquisition Scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NIMP	Non-investigational medicinal product
NSCLC	Non-small Cell Lung Cancer
OAE	Other significant adverse events
ORR	Objective Response Rate
OS	Overall Survival
PD	Progression of disease
PFS	Progression free survival
PGx	Pharmacogenetic research
PK	Pharmacokinetics
PRO	Patient Reported Outcome
PSSR	Project Specific Safety Requirements
PTAP	Post Trial Access Program
QCP	Quantitative Clinical Pharmacology
QT	Interval on the electrocardiogram representing the duration of depolarization and repolarization of the heart
QTc	The QT interval corrected for heart rate
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SJS	Stevens-Johnson syndrome
SoC	Standard of Care

Abbreviation or special term	Explanation
SPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reactions
T790M	An amino acid substitution at position 790 in EGFR, from a threonine to a methionine
T790M+	T790M mutation positive
TCS DES	Tata Consulting Services Data Entry Site (also known as AZ DES)
TEN	Toxic epidermal necrolysis
TFST	Time to first subsequent therapy
TKI	Tyrosine kinase inhibitor
TSST	Time to second subsequent therapy or death
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
VATS	Video Associated Thoracic Surgery
WHO	World Health Organization

1. INTRODUCTION

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 (Ferlay et al 2013). 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 (Travis et al 2000). Unfortunately, at the time of diagnosis approximately 70% of NSCLC patients already have locally advanced or metastatic disease not amenable to surgical resection.

The primary treatment of early stage (I-IIIA) NSCLC is curative surgery. Only ~30% of patients present with stages I-IIIA lung cancer (Datta et al 2003), however, with the advent of lung cancer screening percentage is expected to increase (The National Lung Screening Trial Research Team 2011). Although patients treated with curative surgery have a better prognosis, the 5-year survival for patients treated with surgery alone remains low, ranging from 57% (stage IB) to 23% (stage IIIA) (Mountain 1997, ESMO 2013).

The poor survival rates following surgical resection for patients with stage II and III disease have led several groups to investigate the utility of adjuvant chemotherapy in improving lung survival outcomes. Five large randomised trials have been undertaken to determine if adjuvant platinum-based chemotherapy after curative surgery for NSCLC confers a survival advantage: ALPI (Scagliotti et al 2003); IALT (Arriagada et al 2004); JBR10 (Winton et al 2005); CALGB 9633(Strauss et al 2008); and ANITA (Douillard et al 2006). Three of these five

trials showed statistically significant improvements in overall survival, ranging from 4% *[IALT]* to 15% [JBR10] at 5 years, and absolute improvements in relapse-free rates at 5 years from 5,1%[IALT] to 12% [JBR10] were reported in three trials. Of the two trials that did not demonstrate improved survival, one [ALPI] suffered from poor compliance to the treatment regimen (69%), and the second was a smaller trial (n=344) limited to patients with stage IB disease [CALGB 9633], which was likely underpowered to detect a statistically significant improvement in overall survival. Interestingly, despite being limited to patients with stage IB disease, and utilizing a carboplatin rather than cisplatin based regimen, CALGB 9633 did demonstrate an overall survival hazard ratio comparable to the other adjuvant trials (HR=0.8) that included patients with more advanced disease, despite not achieving statistical significance. Of note post hoc analysis showed positive outcome in subgroup of patients with tumours ≥4 cm (Strauss et al 2008).

Since the publication of original adjuvant chemotherapy trials, a number of meta-analyses have indicated the benefit of adjuvant platinum-based chemotherapy after surgical resection for NSCLC (Pignon et al 2008; NSCLC Meta-analysis Collaborative Group 2010). In these meta-analyses, all-stage (IB-IIIa) hazard ratios were in the range of HR=0.86, corresponding to an absolute benefit of chemotherapy on overall survival of 4-5% at 5 years (Pignon et al 2008, NSCLC Meta-analysis Collaborative Group 2010)The benefit of adjuvant chemotherapy, however, was demonstrated to be stage dependent (albeit using older staging criteria versions), with the benefit only reaching statistical significance for stages II and III (Pignon et al 2008). The role of adjuvant chemotherapy in stage I disease is controversial (Wakelee at al 2007). A subgroup analysis in a trial of high-risk patients with stage IB disease (tumours > 4cm) suggested that there may be an overall survival advantage with adjuvant chemotherapy in this subgroup of patients, comparable to those observed in stage II and III disease, but these results were not conclusive (Strauss et al 2008).

Based on these findings, adjuvant post-operative platinum-based chemotherapy has become a standard of care in patients with resected stage II and III NSCLC. The benefit of post-operative chemotherapy in patients with stage IB NSCLC remains uncertain. However, there continues to be a significant need for new therapies to further improve clinical outcomes in patients with stage I-III NSCLC regardless of the use of postoperative chemotherapy.

Several trials, including the International Pan-Asia Study (IPASS) (Mok et al 2009) and the European Tarceva vs Chemotherapy trial (EURTAC) (Rosell et al 2012) have helped support epidermal growth factor receptor (EGFR*)* mutation status as a powerful predictive marker for response to EGFR tyrosine kinase inhibitors (TKIs) in metastatic NSCLC. The most common sensitising EGFR mutations are deletions in exon 19 (Ex19Del, 44% of all mutations) and the point mutation L858R in exon 21 (41% of all mutations)

The National Comprehensive Cancer Network (NCCN) has recommended testing all advanced NSCLC adenocarcinomas for EGFR mutations. In patients with EGFR mutant (EGFRm+) tumours, EGFR-TKI therapy is recommended in the first-line setting. This recommendation is based on superior response rates (approximately 70%), progression free survival (PFS, median of around 9 months), and a more favourable toxicity profile, compared

with that of chemotherapy. Mutations of EGFR occur in 10 to 15% of NSCLC patients in the Western world and 30 to 40% in Asia.

The efficacy of EGFR-TKIs in advanced EGFRm+ NSCLC has generated the hypothesis that these drugs could be effective as a component of the curative treatment of early stage EGFRm+ NSCLC. The impact of molecularly targeted therapies in other cancers serves as an example of what may be achievable. The improvements seen with imatinib (a tyrosine kinase inhibitor) in advanced gastrointestinal stromal tumour (GIST) and trastuzumab in metastatic breast cancer led to investigation of these drugs in early stage disease to improve cure rates. Significant improvement was seen in disease free survival (primary endpoint) with adjuvant imatinib following resection of high risk GIST (Dematteo et al 2009 Joensuu et al 2012); post-operative trastuzumab led to improved overall survival by nearly 50% in patients with resected Her-2 positive breast cancer (Romond et al 2005,Piccart-Gebhart et al 2005).

Currently, the role of EGFR-TKIs as adjuvant therapy following complete surgical resection of the tumour remains under investigation. Two large randomised trials have evaluated EGFR-TKIs as adjuvant therapy in early stage resected NSCLC. Both trials were initiated prior to *EGFR* mutation status being confirmed as a predictive marker for response to EGFR-TKIs. The first was a phase III randomised controlled adjuvant study of 2 years of gefitinib versus placebo following surgical resection (stage IB-IIIA) [BR 19 study, Goss et al 2013). This study was terminated prematurely based on an unplanned analysis precipitated by the negative results of the ISEL trial, which evaluated gefitinib vs. placebo as a second/third line treatment in the advanced disease setting in an unselected NSCLC patient population (Thatcher et al 2005). Based on results of 503/1242 of the planned accrual, overall survival in this trial was not found to differ between treatment arms (Goss et al 2013). Although limited by the premature closure of the trial, the results of this study suggest that in the adjuvant setting, gefitinib is unlikely to provide any meaningful benefit in an unselected NSCLC population. In this study, only 15 patients had EGFR mutations, therefore meaningful conclusions could not be drawn for the use of adjuvant gefitinib in the EGFRm+ NSCLC patient population.

A second phase III randomised trial comparing two years of adjuvant erlotinib to placebo failed to demonstrate benefit of adjuvant EGFR-TKI therapy on prolonging disease-free survival, despite restricting enrolment to patients with high EGFR protein expression or increased EGFR gene copy number (Kelly et al 2015). However, after the RADIANT study had been initiated, increasing evidence suggested that EGFR mutation status was a more significant determinant of response to EGFR-TKI than either EGFR protein expression or EGFR gene amplification. A prospectively specified subgroup analysis in RADIANT examined the efficacy of adjuvant erlotinib in the EGFRm+ subgroup (N=161) (Kelly et al 2015). This data suggested that erlotinib may prolong DFS, compared to placebo (46.4 months vs 28.5 months respectively, HR=0.061, 95% CI: 0.384-0.981, p= 0.00391). However, due to hierarchical testing these results were not statistically significant. Furthermore, there were baseline imbalances between the treatment groups which could have influenced the magnitude of the differential. This study nevertheless is suggestive of a clinical benefit of an EGFR-TKI in the early EGFR m+ NSCLC setting.

Recently, two phase III studies in Chinese patients have demonstrated the efficacy of 2 years treatment with EGFR-TKIs in completely resected EGFR mutation positive early stage NSCLC as a therapeutic option rather than chemotherapy.

The ADJUVANT CTONG (Zhong et al 2018) and EVAN (Yue et al 2018) studies compared the use of gefitinib and erlotinib, respectively vs. post-operative vinorelbine plus cisplatin chemotherapy. A significant improvement in mDFS of 28.7 months for gefitinib vs 18.0 months for chemotherapy (HR: 0.60, 95% CI 0.42-0.87; p = 0.005); and 42.41 months for erlotinib vs 20.96 months for chemotherapy (HR: 0.271, 95% CI 0.137-0.535; p<0.001) was reported in CTONG and EVAN, respectively. The ADJUVANT CTONG and EVAN studies restricted enrolment to patients with stage II–IIIA (N1-N2) and IIIA (R0) respectively, whereas the RADIANT study population was similar to ADAURA (stages IB, II and IIIA). Moreover, in the RADIANT study, effects of erlotinib were compared with placebo in the adjuvant setting following no treatment or prior treatment with chemotherapy, whereas the ADJUVANT CTONG and EVAN studies provided a direct comparison between an EGFR-TKI and chemotherapy.

Overall, there are several reasons to hypothesise that effects of AZD9291 in the ADAURA study would outperform erlotinib and gefitinib data from RADIANT, EVAN and ADJUVANT CTONG studies. Firstly, AZD9291 has proven superior efficacy over first-generation EGFR-TKIs as first-line treatment in EGFR mutation-positive advanced NSCLC (Soria 2018). Secondly, in previous studies, treatment was limited to 2 years and recurrence occurred most frequently within 12 months of treatment discontinuation, or DFS benefit diminished. ADAURA study treatment duration is 3 years, as the safety profile of AZD9291 makes longer treatment feasible.

Lastly, in the RADIANT and ADJUVANT-CTONG studies, a high rate of brain metastases was reported with erlotinib (37.1%) and gefitinib (50%), respectively among patients who experienced disease recurrence (Kelly et al 2015; Xu et al 2018).

Preclinical data support the ability of AZD9291 to cross the blood–brain barrier and to penetrate the central nervous system (Ballard et al 2016). Additional clinical data show activity against CNS metastases from EGFR mutation-positive NSCLC patients treated with AZD9291 as first-line therapy. In patients with known or treated CNS metastases at trial entry, the objective response rate and the median duration of response (based on investigator assessment) were in line with the values in the overall population. The lower frequency of CNS progression with osimertinib compared with first-generation EGFR-TKIs (7 [3%] of 226 vs. 15 [7%] of 214) in the subgroup of patients without known or treated CNS metastases at study entry indicates a protective effect of osimertinib against the development of CNS metastases (Soria et al 2018, Reungwetwattana et al 2018); a similar or even lower rate of CNS metastases is expected in ADAURA.

1.1 Background and rationale for conducting this study

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. As a result, AZD9291 can effectively block EGFR signalling both in EGFR single mutant cells with activating EGFR mutations and in double mutant cells bearing both the primary EGFR activating and secondary resistance T790M mutation.

It is anticipated that achieving separation in activity between EGFR wild type and activating/T790M (resistance) mutations will provide distinct advantages over less selective first generation EGFR-TKIs with respect to toxicities from EGFR wild type inhibition (skin rash and diarrhoea. Indeed, preliminary data from an ongoing phase I study (D5160C00001) in EGFRm+/T790M+ previously treated NSCLC patients, and EGFRm+ treatment naïve NSCLC patients (i.e., first-line), has demonstrated good evidence of efficacy while treatment with AZD9291 has been well tolerated across a range of doses (Yang et al 2014, Ramalingam 2014). No dose-limiting toxicities were reported in any of the dose escalation cohorts 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. At this dose, CTCAE Grade ≥3 diarrhoea occurred in 1% (all grades 33%) and Grade ≥3 rash in 0% (all grades 32%) of patients which compares favourably with historical data for approved EGFR-TKI.

Pre-clinical data provides good evidence to support AZD9291 as a potentially better treatment option for first-line advanced and early stage EGFRm+ NSCLC compared to currently approved EGFR-TKIs. Unlike gefitinib, erlotinib, and afatinib, emergence of T790M does not appear to be a mechanism of preclinical resistance to AZD9291(Cross et al 2014) and in vitro data supports a slower time to resistance in response to AZD9291 treatment than that of first and second generation EGFR-TKIs. In a pre-clinical mouse model of EGFRm+ NSCLC, AZD9291 achieved superior durable complete responses compared to those achieved with gefitinib (Cross et al 2014).

Furthermore, emerging preclinical data indicate that AZD9291may have the potential to target brain metastases (a common site of relapse in NSCLC) more effectively than current EGFR-TKIs (Kim et al 2014). Brain metastases are detected in 20 to 30% of patients with advanced NSCLC upon initial diagnosis, and are associated with a poor prognosis (Porta et al 2011). Up to 50% of lung cancer patients will develop brain metastases at some point during the course of their disease. The first generation EGFR-TKI agents have demonstrated only limited efficacy in treating brain metastases (Bai and Han 2013, Shimato et al 2006). Data from RADIANT study showed that up 40% of patients treated with erlotinib developed disease relapse in the brain, suggesting suboptimal activity of erlotinib in the brain (Kelly et al 2015). Preclinical data suggest that AZD9291 is capable of crossing the blood brain barrier (See IB) and offers better exposure in this anatomically protected location. The central nervous system (CNS) is a common site of first progression for patients receiving treatment with a standard TKI, despite concomitant systemic disease control. Use of a drug which may more effectively penetrate the CNS has the potential to control prevent or delay the growth of subclinical brain metastases that were below the limits of detection at the time of diagnosis.

In the advanced EGFRm+ NSCLC setting, subjects who have previously progressed on an EFGR TKI and have a T790M+ tumour have achieved promising efficacy with AZD9291;

66% of subjects achieved a response, 90% achieved disease control, medium duration of response of 12.4 months and median PFS based on 38 % maturity of data was 13.5 months assessed by blinded independent central review (Janne at al 2015). Initial data showed that de novo T790M mutation occurs in less than 3% of the EGFRm+ patients before starting EGFR-TKI therapy (Pao et al 2005). More recently however, using high sensitivity methods, the de novo EGFR T790M mutation was detected in up to 40% of previously untreated NSCLC, suggesting that presence of de novo resistant clones may be more common than previously appreciated (Arcila et al 2011). Hence, AZD9291 could prevent or delay tumour growth arising from baseline presence of T790M resistance clones, and this may confer clinical advantage in the adjuvant setting.

In conclusion, the preclinical and clinical profile of AZD9291 suggest that AZD9291 could offer prolonged DFS in the adjuvant EGFRm+ NSCLC setting, and the data are encouraging for the investigation of AZD9291 as an adjuvant treatment for patients with early stage NSCLC who have undergone complete tumour resection.

1.2 Rationale for study design, doses and control groups

This is phase 3, double-blind, randomised, placebo-controlled study, to assess efficacy and safety of AZD9291 versus placebo in patients with completely resected stage IB-IIIA NSCLC, which has been centrally confirmed to have one of the two most common (Ex19del and L858R) EGFR-sensitising mutations, either alone or in combination with other EGFR mutations.

It is appropriate to select placebo as a comparator as no EGFR-TKI is currently approved for the adjuvant treatment of completely resected EGFR m+ NSCLC. Stage IIA to IIIA patients and stage IB patients have been selected as an appropriate patient population as they have been shown to benefit from adjuvant chemotherapy following tumour resection, and may further benefit from treatment with AZD9291.

Patients are eligible for the study irrespective of whether they are treated with adjuvant chemotherapy or not (pre-operative platinum based or other chemotherapy and pre-operative or post-operative radiation therapy is not allowed). Patients will be randomised to treatment (1:1) following recovery from surgery and completion of any adjuvant chemotherapy. To reduce risk of disease recurrence prior to randomisation, time limits have been set between the date of surgery and time to randomisation: ≤10 weeks between surgery and randomisation for patients who have not received adjuvant chemotherapy; ≤ 26 weeks may have elapsed between surgery and randomisation for patients who received adjuvant chemotherapy. Since stage of disease is prognostic factor for clinical outcome, patients will be stratified at randomisation based on stage of disease (Stage IB vs II vs IIIA).

The proportion of patients with stage IB cancer in this patient population is estimated to be 30-50%, however the proportion of patients randomised with stage 1B cancer will be capped at 30%. This is to ensure there are a sufficient number of patients to characterise the treatment effect within this better prognosis subgroup, whilst not significantly extending the time required to complete the study and delay a potentially useful therapy reaching future patients.

The sensitizing EGFR mutation status of patients will be tested and confirmed by a central tissue based diagnostic test prior to randomisation. Central testing will be performed to facilitate EGFR diagnostic development in this setting. Since results from a recent trial suggest that patients with exon 19 deletion might be associated with longer PFS compared to patients with L858 mutation at exon 21 (Zhang et al 2014), patients will be stratified at randomisation by EGFR mutation type (Ex19Del/L858R either alone or in combination with other EGFR mutations as confirmed by a central test).

The study is planned to be conducted globally. Asian ethnicity is thought to be a favourable prognostic factor for survival and response in NSCLC (Soo et al 2012) and so, patients will be stratified at randomisation by race (Asian/non-Asian).

The dose of AZD9291 in this study is 80 mg once daily. This dose was selected from a review of all available safety, tolerability, pharmacokinetics and efficacy data from study D5160C00001, in patients with advanced EGFRm+ NSCLC. As of August 2014, AZD9291 had been administered as a capsule formulation across the 20 to 240 mg once daily dose range in more than 253 patients with advanced NSCLC who have progressed following prior therapy with an EGFR-TKI: 20 mg (n=21), 40 mg (n=58), 80 mg (n=90), 160 mg (n=63), and 240 mg (n=21). No dose-limiting toxicities (DLTs) have been reported at any dose level in the escalation cohorts during the 21-day DLT evaluation period. Emerging efficacy data have demonstrated durable objective responses from the starting dose level of 20 mg once daily (Ranson et al 2013, Yang et al 2014). The Objective Response Rate (ORR) in relapsed/refractory T790M+ patients was 61% (Yang et al 2014). The Phase II dose for the T790M+ clinical programme has been selected as 80 mg once daily based on both the activity in patients with T790M+ NSCLC and the low incidence of toxicity (Janne et al 2014, Yang et al 2014). The selected 80 mg dose is 4 fold higher than the minimum efficacious dose tested in study D5160C00001, whilst still being one third of the maximum dose level investigated (240 mg), also dose reduction to 40mg may be applied to manage drug toxicity. The dose assessment for the adjuvant EGFRm programme has incorporated all data from the T790M+ setting, together with an assessment of emerging preliminary data from more than 50 EGFRm+ patients who are receiving AZD9291 as first-line treatment for advanced/metastatic NSCLC (30 patients at 80 mg and 30 patients at 160 mg). An in-depth review of the first-line data included evaluation of safety, efficacy, and PK/exposure data and revealed a very consistent picture with the later-line T790M+ data. Therefore, based on this comprehensive review of all available safety, tolerability, efficacy, and PK data from study D5160C00001, supported by a very robust package of data in approximately 300 first- and later-line patients (with duration of treatment exceeding 10 months for many patients), 80 mg once daily was selected as the recommended dose for the adjuvant EGFRm clinical programme. This dose is considered to provide the optimum risk/benefit ratio in this patient population and will therefore be used in this Phase III study.

As of 12 November 2019, a total of 3862 subjects (3744 NSCLC patients and 118 healthy volunteers) have been included in the osimertinib clinical development programme. Of these 3862 subjects, 2607 subjects received osimertinib monotherapy (2489 patients and 118 healthy volunteers), 381 patients received osimertinib in combination with another treatment, and 874 patients were exposed to comparator treatment (including placebo). Of the

874 patients exposed to comparator treatment, 190 patients subsequently crossed over to osimertinib monotherapy from the comparator treatment during the study, and 684 patients were exposed to comparator treatment only (including placebo).

In addition to the clinical development programme, 4055 NSCLC patients have participated in the osimertinib Early Access Programmes (EAP) and Named Patient Supply (NPS), and 3014 patients participated in the ASTRIS real world evidence (RWE).

Investigation of another molecularly targeted tyrosine kinase inhibitor (imatinib) as an adjuvant treatment following complete gross resection of Kit (CD117) positive Gastrointestinal Stromal Tumors (GIST) led to a recommendation for three years of imatinib treatment over one year of imatinib treatment. In the single arm prospective SELECT study which evaluated erlotinib as a 2 years adjuvant treatment in completely resected EGFRm+ NSCLC patients, whilst recurrences were rare on erlotinib, most occurred in the 12 months after discontinuation, suggesting that longer duration of adjuvant treatment may be beneficial. The improved outcomes with longer duration of targeted agent in the adjuvant setting of the molecularly defined malignant tumours for highly dependent or addictive pathways such as ER+ or Her2+ Breast Cancer provides an added rationale for testing activated EGFR suppression in the adjuvant setting of EGFRm NSCLC. Given that the highest rate of recurrence is seen within the first 2-3 years after complete tumour resection, it seems reasonable to aim at least 2-3 years of treatment duration in this setting. The RADIANT study used 2 years of erlotinib treatment and showed strong positive signal for an improved treatment outcome in an exploratory subgroup of patients with EGFRm NSCLC. In this exploratory analysis, the EGFRm subgroup showed diminishing DFS benefit after 2 years, potentially due to duration of erlotinib treatment being limited to 2 years (Kelly et al 2015).

In comparison with erlotinib AZD9291 has higher selectivity against the mutant EGFR and offers a wider therapeutic margin between wild type and mutant EGFR that is likely to result in a better tolerability profile suitable for long-term use in these patients. The examples of endocrine agents use in adjuvant HR+ breast cancer as well as imatinib in adjuvant GIST suggest that longer use is usually associated with extra efficacy benefit with these molecularly targeted agents.

The primary endpoint of this study is disease free survival (DFS). DFS represents a direct measure of the study drug's efficacy as it is not confounded by the efficacy of subsequent therapies used after disease relapse. Moreover, historical data showed that the DFS benefit seen with the use of chemotherapy in this disease setting was consistent with an improvement in the OS outcome, which suggests an association between these 2 endpoints in this setting (ILAT; JBR.10; ANITA; CALBG 9633; Mauguen et al 2014; Big Lung Trial). DFS has been the primary basis of approval for adjuvant breast cancer hormonal therapy, adjuvant colon cancer, and adjuvant cytotoxic breast cancer therapy. DFS may be associated with an improvement in symptom control, and Health Related Quality of Life (HRQoL) (Janne et al 2014), which will be measured within the study.

Overall, the totality of primary, secondary, and exploratory endpoints in this study will allow a robust characterisation of the overall benefit/risk ratio of adjuvant AZD9291 in the EGFRm+ NSCLC patient population following complete surgical resection.

In summary, the emerging encouraging data for EGFR-TKIs in the adjuvant setting of patients diagnosed with early stages of EGFRm NSCLC warrant further clinical investigation to provide definitive evidence of their clinical utility in this setting.

AZD9291 has several potential advantages over the 1st and 2nd generation EGFR-TKIs, such as wider therapeutic margin due to its higher selectivity for the EGFRm target which is likely to result in an improved tolerability profile; better penetration through blood brain barrier which has the potential to improve prevention of disease recurrence with brain involvement; and also ability to block the most common escape mechanism these tumours develop in response to treatment with 1st and 2nd EGFR-TKIs. Taken together with the encouraging clinical data in the advanced EGFRm NSCLC AZD9291 represents a very promising agent to be investigated in the adjuvant setting.

1.3 Rationale for osimertinib upon recurrence

The FLAURA trial was a double-blind, phase 3 trial involving patients with previously untreated advanced NSCLC with EGFR mutations that compared the efficacy and safety of osimertinib with that of first-generation EGFR-TKIs, gefitinib or erlotinib (with both drugs included in the comparator group).

Osimertinib has demonstrated clinically meaningful and statistically significant superior PFS compared with an investigator choice of gefitinib or erlotinib in first-line setting patients with first-line locally advanced or metastatic EGFRm positive NSCLC (median 18.9 months vs. 10.2 months; HR 0.46; 95% confidence interval [CI], 0.37 to 0.57; P<0.001) (Soria et al 2018). Benefit was observed both in patients with and without brain metastases at baseline. At a later data cut-off, overall survival was statistically significantly longer for patients in the osimertinib arm compared with the SoC arm (median OS 38.6 months vs. 31.8 months; HR 0.7999; 95% CI 0.6409, 0.9963; p=0.0462) (Ramalingam et al 2020).

The safety profile of osimertinib was similar to that of the comparator EGFR-TKIs. Osimertinib was associated with a somewhat lower rate of adverse events leading to permanent discontinuation than were standard EGFR-TKIs. The frequency of dose interruption and dose reduction due to adverse events was similar in the two groups. No new safety signals were observed, and adverse events of grade 3 or higher and rates of treatment discontinuation because of adverse events were similar in the two groups, despite the longer duration of exposure to AZD9291. On the basis of these efficacy and safety data, the indication for AZD9291 was extended to include first-line treatment in patients with advanced NSCLC.

Based on this approval, osimertinib is the preferred first-line treatment option for patients with advanced/metastatic EGFRm NSCLC in standard of care (Refer to NCCN guidelines current version and ESMO guidelines). In light of all of the above, open label osimertinib will be

made available to patients who at the time of disease recurrence are living with advanced/metastatic EGFRm NSCLC.

1.4 Unplanned Interim Analysis of ADAURA (IDMC7)

Following the recommendation of the IDMC after their 7th meeting, an interim analysis was conducted with a DCO of 17 January 2020 (Wu et al 2020).

A total of 682 patients were randomised to receive treatment with osimertinib 80 mg once daily (N=339) or placebo (N=343). Demographic and disease characteristics of randomised patients were well-balanced between the treatment arms.

The HR for DFS in patients with stage II-IIIA disease was 0.17 (99.06% CI: 0.11, 0.26), demonstrating a statistically significant and clinically meaningful 83% reduction in the risk of disease recurrence or death for patients treated with osimertinib compared with patients treated with placebo.

The HR for the overall population was 0.20 (99.12% CI: 0.14, 0.30), demonstrating a statistically significant and clinically meaningful 80% reduction in the risk of disease recurrence or death for patients treated with osimertinib compared with patients treated with placebo.

At the time of the DCO, OS data were immature with 29 events overall (4.3% of patients): 9 in the osimertinib arm and 20 in the placebo arm.

IDMC considered this data to be indicative of overwhelming efficacy in the osimertinib arm in terms of primary endpoint. The safety profile of patients treated with osimertinib in ADAURA was considered consistent with previous trials with osimertinib. Based on the totality of the data from ADAURA, FLAURA and the approved label for osimertinib, access to open-label osimertinib for eligible patients in the ADAURA study was introduced (see Section 3.3). Patients and investigators remain blinded to individual treatment allocations. Following disease recurrence, at the request of the Investigator patients may be unblinded to aid future treatment decisions (see Section 3.8).

1.5 Benefit/risk and ethical assessment for conducting the ADAURA study

Although there can be no certainty of clinical benefit to patients, success of other targeted agents in the adjuvant setting with or without chemotherapy, non-clinical characteristics of AZD9291, the preliminary data of EGFR-TKIs in this setting, the preliminary clinical efficacy and safety data with AZD9291 in the ongoing phase I trial (D5160C00001) all support the notion that EGFR mutation inhibition may be a valid strategy for the adjuvant treatment of completely resected NSCLC tumours which are driven via this pathway. Specifically, the safety profile of AZD9291 in the ongoing phase I trial extended to phase II and ongoing clinical program was already favourable at the time of study start-up with the majority of toxicities being low grade EGFR related adverse events (Common Terminology Criteria for Adverse Event [CTCAE] Grade 1 or 2), i.e., diarrhoea and skin rash.

Based on the information available at the time of IDMC7, AZD9291 remains generally well tolerated in the metastatic setting. The majority of adverse reactions are of Grade 1 or 2 severity, and the most frequent reactions are typical EGFR-TKI side effects including rash and diarrhoea. Interstitial lung disease (ILD) or ILD-like adverse drug reactions (e.g., pneumonitis) are commonly reported (3.9% of patients in Phase I-III studies), and occasionally fatal (0.4%) for patients receiving AZD9291. Details of important identified and potential risk for AZD9291 can be found in the Investigators' brochure.

All trials of AZD9291 exclude patients with clinically significant toxicities related to prior treatments in addition to specifically excluding patients with a history of ILD or clinically active ILD as this is an uncommon but well documented EGFR-related toxicity. Patients requiring radiotherapy will be excluded from participation due to the potential risk of radiation induced pneumonitis. In the pre-clinical studies, the principal target organ findings were consistent with inhibition of wild type EGFR (atrophic, inflammatory and degenerative changes in the skin, cornea, gastrointestinal tract and female reproductive tract). Other target organ findings of potential clinical relevance were seen in the male reproductive tract and male mammary gland. All patients will be assessed for possible known EGFR-related toxicities and detailed information on the management of EGFR-related gastrointestinal, dermatological, and ophthalmologic toxicities is being provided for all AZD9291 studies.

It is therefore, reasonable to evaluate the oral administration of AZD9291 in comparison to placebo as adjuvant therapy in preventing or delaying the recurrence of disease in EGFRm+ NSCLC patients who have undergone complete surgical resection and standard of care chemotherapy where applicable.

1.6 Study design

This is a phase 3, double-blind, randomised, placebo-controlled, study, to assess the efficacy and safety of AZD9291 versus placebo in patients with stage IB-IIIA non squamous, non small cell lung cancer (NSCLC) with a centrally confirmed, common sensitising EGFR mutations (Ex19del and L858R either alone or in combination with other EGFR mutations) as confirmed by a central test, who have had complete tumour resection, with or without postoperative adjuvant chemotherapy.

Patients will be randomised 1:1 to receive either AZD9291 or placebo. Patients must have sufficiently recovered from surgery and completed any standard of care adjuvant chemotherapy if applicable prior to randomisation. Patients must be randomised within 10 weeks of complete surgical resection if adjuvant chemotherapy was not administered and within 26 weeks if adjuvant chemotherapy was administered.

Accounting for patients who are found to have wild type EGFR, sample attrition and 10% screen fail rate for other reasons, it is estimated that 3200 patients will be screened to randomise approximately 700 patients. It is assumed that approximately 60% of patients will be recruited from Asia and 40% from non-Asian countries. The proportion of patients randomised with stage IB cancer will be 30% and the proportion of patients randomised with Stage II-IIIA cancer will be 70%.Patients will be stratified by stage (IB vs II vs III), mutation

type status as confirmed by a central laboratory using a tissue based test (Ex19Del/L858R either alone or in combination with other EGFR mutations as confirmed by a central test), and race (Asian/ non-Asian).

Following complete resection and prior to treatment initiation, all patients will be required to have a baseline CT scan (chest and abdomen including liver and adrenal glands) within 28 days of treatment initiation to confirm that disease is not present. Patients will continue on randomised treatment until recurrence of disease, treatment discontinuation criterion is met or treatment is completed. The treatment duration period is 3 years (156 weeks). Patients being on study drug at the time of DFS analysis may continue treatment until discontinuation criterion is met or 3 years (156 weeks) treatment is completed.

Patients will undergo safety assessments at baseline, 2 weeks, 4 weeks, 12 weeks and every 12 weeks until treatment is completed or discontinued. All study patients must have a 28 day follow up visit after treatment is stopped.

Patients will undergo regular radiological assessments for disease recurrence at 12 weeks, 24 weeks and then every 24 weeks until 5 years (264 weeks), then yearly thereafter. DFS shall be measured from the day of randomisation until date of recurrence or death (by any cause) in the absence of recurrence by investigational site assessment.

Patients who discontinue treatment prior to disease recurrence will continue to be followed for DFS according to study plan. Following disease recurrence, patients will undergo radiological imaging for subsequent progression in accordance with local clinical practice, and will be followed for survival every 6 months until 5 years (264 weeks), post-randomisation, then yearly thereafter. Follow up will continue until the study is closed.

At disease recurrence, patients will be restaged and all sites of NSCLC relapse will be recorded. Treatments received by the patient after relapse will be determined by the physician. Post recurrence cancer treatments and procedures will be recorded. Tumour and blood sampling for biomarker, translational science and pharmacokinetics will also be performed.

Patients will be initially followed as per the study protocol until data cut-off for the primary analysis, estimated as 68-70 months following first subject randomised, based on a 28 month recruitment period. Results from the primary analysis will be reported in the Clinical Study Report. If there are meaningfully less than 70 DFS events in the IB population at the time of the primary analysis, further follow up of patients according to the same study plan may be performed until completion of the final exploratory DFS analysis (hereafter referred to as the ‘final DFS analysis’).

Following the primary analysis (or ‘final DFS analysis’ if required) patients will be followed-up for survival according to a reduced study plan (OS period) until the data cut-off for the final OS analysis. The final OS analysis will be conducted when approximately 94 OS events in the stage II-IIIA population have been observed.

Following the final OS analysis, the ADAURA study database was planned to be closed, and the collection of survival, cancer therapy, and safety data for globally recruited patients no

longer on study treatment was to stop entirely. All patients and Investigators remain blinded to individual study treatment allocation. Following the final OS analysis, CSP edition 6 has introduced a further optional long-term OS follow-up. All patients in survival follow-up will be offered the opportunity to participate in the long-term OS follow-up. Patients who consent to participate will be followed yearly for survival until approximately 10 years after the last patient is randomised to capture long-term OS data in the study extension. Safety data (all serious or non-serious events of ILD/pneumonitis and cardiac failure, and all SAEs) for patients who are treated with open-label osimertinib will be collected as described in Section 6.3. Any patients still on open-label osimertinib and deriving clinical benefit can continue to receive treatment until they meet a discontinuation criteria, as outlined in Section 3.10. Following the completion of the study extension, any patients still on open-label osimertinib will be managed outside of the study per Section 7.3.3. At this point, any SAEs will be reported outside of the database, only reported as per Section 6.4 and Section 6.5.

If the EDC system is not available, AstraZeneca will collect information on SAEs, overdose and pregnancy (as per Section 6.4, Section 6.5, and Section 6.6) via paper and emailed to Tata Consulting Services Data Entry Site (TCS DES) (also known as AZ DES).

Based on the study analysis following IDMC7 (2020), eligible patients can be offered open-label osimertinib upon recurrence, if the recurrence pattern is in line with the regional label, as described in Section 3.3. In line with the approved indication, these patients can continue to receive open-label osimertinib until disease progression, or until a time when the Investigator considers that they are no longer deriving clinical benefit, or they stop taking treatment for any other reason including having met any of the criteria for treatment discontinuation (Section 3.10).

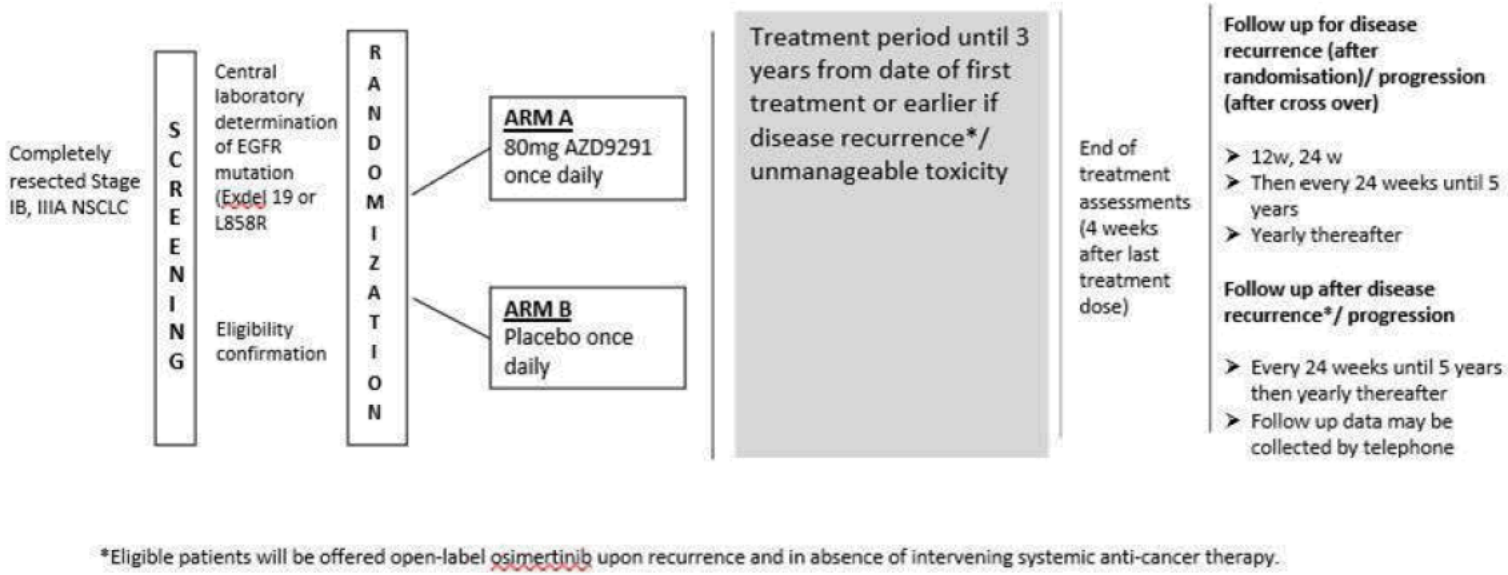
1.7 Study extension for long-term OS follow-up

After the final OS analysis, a study extension has been added to allow the optional longer-term survival follow-up of patients in the ADAURA trial until approximately 10 years after the last patient is randomised, which will further characterise long-term patient outcomes in the adjuvant setting. All patients in survival follow-up will be offered the opportunity to participate in the long-term OS follow-up.

Each patient will provide written informed consent to participate in the optional long-term OS follow-up.

Patients and Investigators remain blinded to individual treatment allocations during the long-term OS follow-up. Following disease recurrence, at the request of the Investigator patients may be unblinded to aid future treatment decisions (see Section 3.8).

Figure 1 Study design



*Eligible patients will be offered open-label osimertinib upon recurrence and in absence of intervening systemic anti-cancer therapy.

Following the final OS analysis, CSP edition 6 has introduced long-term OS follow-up. A study extension has been added to allow the optional longer-term survival follow-up of patients. All patients in survival follow-up will be offered the opportunity to participate in the long-term OS follow-up. Patients who consent to participate will be followed yearly for survival until approximately 10 years after the last patient is randomised to capture long-term OS data in the study extension. Survival data may be collected by telephone or in-person.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
To assess the efficacy of AZD9291 compared to placebo as measured by disease free survival (DFS)	DFS by investigator assessment

2.2 Secondary objectives

Secondary Objective:	**Outcome Measure:**
To further assess the efficacy of AZD9291 compared with placebo	At time of primary analysis: DFS rate at 2, 3, 4, and 5 years Overall Survival (OS) OS rate at 2, 3, 4 and 5 years
To assess the effect of AZD9291 compared with placebo on health-related quality of life (HRQoL)	Changes in generic HRQoL as measured by the SF-36 (vers2, standard)
To characterise the pharmacokinetics (PK) of AZD9291 and its metabolites (AZ5104 and AZ7550)	PK plasma concentrations of AZD9291, and metabolites AZ5104 and AZ7550; and ratio of metabolite to AZD9291 for each PK sample (included in CSR) PK data from this study will be analysed using a population PK approach and reported separately to the Clinical Study Report (CSR). Data from this study may form part of a pooled analysis with data from other studies

2.3 Safety objectives

Secondary Objective:	**Outcome Measure:**
To assess the safety and tolerability profile of AZD9291 compared with placebo	Adverse events (graded by CTCAE v4) Clinical chemistry, haematology and urinalysis Vital signs, Physical Examination, Weight Digital ECG LVEF WHO Performance Status Ophthalmologic assessment

2.4 Exploratory objectives

Exploratory Objective:	**Outcome Measure:**
To compare health resource use associated with AZD9291 treatment versus Placebo	Health Resource Use Module
To compare the effects of AZD9291 with placebo on post recurrence outcomes.	Time to next treatment (s) Type of recurrence (local/regional or distant) Site (s) of relapse Type of next treatment (s) (including procedures, radiotherapy and anticancer agents) PFS as determined by investigator assessment
To further assess the efficacy of AZD9291 compared with placebo	OS OS rate at 2, 3, 4, and 5 years
To assess the efficacy of AZD9291 in patients with confirmed baseline T790M status (positive / negative) using a high sensitivity method yet to be determined (retrospective)	DFS by investigator assessment OS
To collect and store biopsy material (multiple cores where possible) from all screened patients for exploratory analysis of molecular mechanisms associated with development of NSCLC and response to treatment.	Key genetic and proteomic markers to include, but not limited to, EGFR mutations, human epidermal growth factor receptor 2 (HER2), and proto-oncogene encoding Hepatocyte Growth Factor Receptor (cMET) expression and/or amplification. Data generated may be reported separately and may also form part of a pooled analysis with other AZD9291 studies.

Exploratory Objective:	**Outcome Measure:**
To collect and store tumour and plasma samples for potential exploratory research into factors that may influence susceptibility to development of NSCLC and/or response to AZD9291 (where response is broadly defined to include efficacy, tolerability or safety) and to assess the relationship between blood-borne biomarkers and selected efficacy endpoints. Tissue and plasma samples may be used to support diagnostic development.	Evaluate the feasibility of using circulating DNA, RNA, and/or protein (including but not limited to ctDNA) profiling approaches for detection of minimal residual disease (MRD) in early-stage NSCLC patients after completion of surgery (and chemotherapy in eligible patients). Investigate whether detection of MRD is impacted by tumour staging or adjuvant chemotherapy. Assess dynamics of circulating DNA, RNA, and/or protein as a proof of principle for early prediction of disease recurrence in the adjuvant setting. Investigate how circulating DNA, RNA, and/or protein relates with other efficacy endpoints, including DFS based on detection of tumour recurrence using imaging approaches. Investigate the prognostic value of DNA, RNA, and/or protein features in predicting response to AZD9291 in the adjuvant setting using baseline tumour tissue samples
To compare the baseline tumour EGFR mutation status in all randomised patients with evaluable results from baseline plasma.	Comparison of EGFR mutation status between tumour deoxyribonucleic acid (DNA) and plasma derived ctDNA.
To compare plasma-derived ctDNA EGFR mutation status at baseline and at disease recurrence.	Comparison of EGFR mutation status in plasma samples at baseline and at disease recurrence.
To assess any changes in EGFR mutation status (including T790M) using the mandated serial plasma samples coupled with a high sensitivity method yet to be determined (retrospective).	Assessment of EGFR mutation status in serial plasma samples.
To explore the relationship between PK and selected endpoints (which may include efficacy, safety, and/or PRO), where deemed appropriate.	Correlation of PK with other primary/secondary/exploratory endpoints in patients treated with AZD9291.

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

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

3.1 Inclusion criteria

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

1. Provision of informed consent prior to any study specific procedures, sampling, and analyses
2. Male or female, aged at least 18 years. Patients from Japan/Taiwan aged at least 20 years
3. Histologically confirmed diagnosis of primary non-small cell lung cancer (NSCLC) on predominantly non-squamous histology
4. MRI or CT scan of the brain must be done prior to surgery as it is considered standard of care. Patients in whom this was not done prior to surgery may still be enrolled if appropriate imaging is performed prior to randomisation, i.e., MRI or CT of brain.
5. Patients must be classified post-operatively as Stage IB, II or IIIA on the basis of pathologic criteria. Staging will be according to the TNM staging system for lung cancer (7th edition)
6. Confirmation by the central laboratory that the tumour harbours one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), either alone or in combination with other EGFR mutations including T790M.
7. Complete surgical resection of the primary NSCLC is mandatory. All gross disease must have been removed at the end of surgery. All surgical margins of resection must be negative for tumour. Resection may be accomplished by open or Video Associated Thoracic Surgery (VATS) techniques
   - Refer to Section 4.1.2 for additional guidance
8. Complete recovery from surgery and standard post-operative therapy (if applicable) at the time of randomisation. Treatment cannot commence within 4 weeks following surgery. No more than 10 weeks may have elapsed between surgery and randomisation for patients who have not received adjuvant chemotherapy; no more than 26 weeks may have elapsed between surgery and randomisation for patients who received adjuvant chemotherapy.
   - Complete post-operative wound healing must have occurred following any surgery
   - For patients who received post-operative adjuvant platinum-based chemotherapy, a minimum of 2 weeks must have elapsed (but no more than 10 weeks) from the last administered dose of chemotherapy to the date of randomisation (refer to Section 7.8.1 for additional guidance).
   - Patients must have recovered from all toxicities of prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2 prior platinum therapy related neuropathy.

9. World Health Organization Performance Status of 0 to 1
10. Female patients should be using highly reliable contraceptive measures, should not be breast feeding, and must have a negative pregnancy test prior to first dose of study drug; or female patients must have an evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:
    - Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.
    - Women less than 50 years old would be consider postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone (LH) and follicle-stimulating hormone (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.

    Male patients should be willing to use barrier contraception, i.e., condoms (see Section 3.9).
11. For inclusion in the optional genetics research study, patients must provide informed consent for genetic research.

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

3.2 Exclusion criteria

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

1. Previous randomisation and treatment in the present study
2. Treatment with any of the following:
    - Pre-operative or post-operative or planned radiation therapy for the current lung cancer
    - Pre-operative (neo-adjuvant) platinum based or other chemotherapy
    - Any prior anticancer therapy, including investigational therapy, for treatment of NSCLC other than standard platinum based doublet post-operative adjuvant chemotherapy
    - Prior treatment with neoadjuvant or adjuvant EGFR-TKI
    - Major surgery (including primary tumour surgery, excluding placement of vascular access) within 4 weeks of the first dose of study drug
    - 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 inducers of CYP3A4 (at least 3 weeks prior).
    - Treatment with an investigational drug within five half-lives of the compound or any of its related material, if known.

3. Patients who have had only segmentectomies or wedge resections
4. History of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer, or other solid tumours curatively treated with no evidence of disease for > 5 years following the end of treatment and which, in the opinion of the treating physician, do not have a substantial risk of recurrence of the prior malignancy.
5. Any unresolved toxicities from prior therapy greater than 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). Active infection will include any patients receiving intravenous treatment for infection; active hepatitis B infection will, at a minimum, include all patients who are hepatitis B surface antigen positive (HbsAg positive) based on serology assessment. Screening for chronic conditions is not required.
7. 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.
8. Any of the following cardiac criteria:
    - Mean resting corrected QT interval (QTc) >470 msec, obtained from 3 ECGs, using the screening clinic ECG machine-derived QTcF value.
    - 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, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval.
9. Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.
10. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:
    - Absolute neutrophil count <1.5 x 10^9/L.
    - Platelet count <100 x 10^9/L.
    - Haemoglobin <90 g/L.
    - Alanine aminotransferase (ALT) >2.5x the upper limit of normal (ULN).
    - Aspartate aminotransferase (AST) >2.5xULN.

- Total bilirubin >1.5xULN or >3xULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia).
- Creatinine >1.5xULN 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 >1.5xULN.

11. Women who are breast feeding.
12. History of hypersensitivity to active or inactive excipients of AZD9291 or drugs with a similar chemical structure or class to AZD9291.
13. 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.
14. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca representative and/or staff at the study site).

In addition, the following are considered criteria for exclusion from the exploratory genetic research only:

1. Prior allogeneic bone marrow transplant.
2. Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

Procedures for withdrawal of incorrectly enrolled subjects see Section 3.5.

3.3 Eligibility for post-recurrence open-label osimertinib

In addition to meeting inclusion/ exclusion criteria listed in Sections 3.1 and 3.2, patients who receive open-label osimertinib will also have to fulfil the following criteria.

1. Patients must have locally advanced recurrence not amenable to definitive treatment and/or curative approach; or distant metastatic recurrence (recurrence stage IV per AJCC 7th edition). Such recurrence must be confirmed with unequivocal imaging findings or biopsy confirmation.
2. Most recent haematology panel, chemistry panel, ECG and LVEF assessments will have been completed within 4 weeks prior to the start of open-label osimertinib treatment and do not show any clinically significant findings.
3. Patient deemed likely to benefit from and tolerate open-label osimertinib per accepted clinical guidelines and regional package insert.
4. Patient will have received appropriate guidance from the treating Investigator regarding post-recurrence treatment options, and will have signed the most recent Informed Consent Form.
5. Patients must not receive any other systemic anti-cancer therapies (other than osimertinib) between the discontinuation of study treatment and the start of treatment with open-label osimertinib.

6. Past medical history of ILD/pneumonitis, drug-induced ILD/pneumonitis, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD/pneumonitis.
7. Patients with recurrence eligible for open-label osimertinib should have completed imaging modalities for chest, abdomen (including liver and adrenal glands) and brain with contrast at the time of recurrence.
8. Patients with any unresolved toxicity CTCAE Grade 3 or higher from the prior study treatment should be excluded.

3.4 Subject enrolment and randomisation

Investigators should keep a record in the screening log of patients who entered the screening.

The Investigators will:

1. Obtain signed informed consent for Screening Part I from the potential patient before mandatory tumour sample is sent to central laboratory for *EGFR* testing.
2. Obtain a unique enrolment number (PPD code) through the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS).
3. Obtain main informed consent before any study specific procedures other than EGFR testing are performed.
4. Determine patient eligibility. See Section 3.

   At randomisation Visit, once the patient is confirmed to be eligible, the Principal Investigator or suitably trained delegate will:

5. Obtain a unique randomisation number via IVRS/IWRS.

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

Note: Section 4.1 describes the procedures to be carried out during Screening period.

3.5 Procedures for handling incorrectly enrolled or randomised 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.

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

3.6 Methods for assigning treatment groups

Eligible patients will be centrally randomised to receive either 80 mg AZD9291 orally once daily or matching placebo in a 1:1 ratio using the IVRS/IWRS system.

Patients will be stratified at randomisation based on:

- Stage (IB vs II vs IIIA)
- EGFR mutation (Ex19Del or L858R) In the rare event that a patient has both of these sensitizing mutations, they should be stratified to Ex19Del
- Race (Asian/Non-Asian)

3.7 Methods for ensuring blinding

Investigational product (IP, also referred to as 'study drug' in this protocol) will be labelled using a unique material pack code, which is linked to the randomisation code. The IVRS/IWRS will assign the bottles of study material to be dispensed to each patient. This is a double-blind study wherein each patient will receive either the active drug or matching placebo. The active drug and placebo tablets will be identical and presented in the same packaging to ensure blinding of the medication.

3.8 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigators from the IVRS/IWRS. Routine procedures for this will be described in the IVRS/IWRS user manual that will be provided to each site.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. Additionally, at the request of the Investigator, following disease recurrence the patient can be unblinded to their treatment allocation to guide future anti-cancer therapy. In both cases, the Investigator documents and reports the action to AstraZeneca representative, without revealing the treatment given to patient to the AstraZeneca representative. For patients being considered for open-label osimertinib upon recurrence, please see Section 3.3.

AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

3.9 Restrictions

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

1. Female patients of child-bearing potential should use highly reliable methods of contraception from the time of screening until 6 weeks after discontinuing study drug. Acceptable methods of contraception are provided in Appendix H (Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods).
2. Male patients should be asked to use barrier contraceptives (i.e., by use of condoms) during sex with all partners during the trial and for a washout period of 4 months. Patients should avoid procreation for 4 months after completion of study drug. Patients should refrain from donating sperm from the start of dosing until 4 months after discontinuing study drug
3. Once enrolled, all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods that are known to be potent inducers of CYP3A4 whenever feasible; but patients may receive any medication that is clinically indicated for treatment of AEs. 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 electronic case report form (eCRF). Guidance on medicines to avoid, medications that require close monitoring, and on washout periods is provided (See Appendix F).
4. If medically feasible, patients taking regular medication, with the exception of strong inducers of CYP3A4, should be maintained on their regular medication throughout the study period. Patients taking concomitant medications whose disposition is dependent upon the Breast Cancer Resistance Protein (BCRP) and/or P-glycoprotein (P-gp) with a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving AZD9291. Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (See Appendix F).

   Patients taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP-mediated increase in exposure. If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.
5. Other anti-cancer therapies including investigational agents, and radiotherapy should not be given while the patient is still on study drug and/or has no disease recurrence

3.10 Discontinuation of investigational product or open-label osimertinib

Patients may be discontinued from IP or open-label osimertinib in the following situations:

- Patient decision. The patient is at any time free to discontinue his/her participation in the study, without prejudice
- Adverse event
- Pregnancy
- Severe non-compliance with the study protocol as judged by the Investigator and/or AstraZeneca representative
- Patients who are incorrectly initiated on IP
- Disease recurrence (for select patients who might have the option of open-label osimertinib upon recurrence, please also see Section 3.3)
- Subsequent progression (for patients who started open-label osimertinib upon recurrence) or until a time when the investigator considers that they are no longer deriving clinical benefit.
- Patients experiencing ILD/pneumonitis, or QTc prolongation with signs/symptoms of serious arrhythmia will not be permitted to restart study treatment.
- Patient completes the treatment period of 3 years (156 weeks) as planned (not applicable to patients receiving open-label osimertinib upon recurrence)

3.10.1 Procedures for discontinuation of a subject from investigational product or open-label osimertinib

At any time, patients are free to discontinue IP without prejudice to further treatment. A patient that decides to discontinue IP will always be asked about the reason(s) for discontinuation of IP and the presence of any AEs. The patient or representative will return all unused study drugs. This will also apply to patients on open-label osimertinib.

As long as the patient does not withdraw consent for the study, visits will be continued according to study plan. Treatment discontinuation visit will be conducted as soon as possible after the patient received the last dose of investigational product and safety follow up will be performed 28 days (+7 days) after drug discontinuation.

“Follow up until disease recurrence” visits should continue according to study plan if the patient discontinues study treatment prior to disease recurrence. Radiological assessments will be performed at 12 weeks, 24 weeks and then every 24 weeks up to 5 years and yearly thereafter (+/- 7 days) (relative to randomisation) until disease recurrence. Serious adverse events considered related to the study procedures must be collected while patients are followed up for disease recurrence.

On discontinuation of randomised study drug, patients will be treated in accordance with the local SoC.

Patients who go onto open-label osimertinib as subsequent therapy will also continue visits according to study plan.

If a patient is withdrawn from study, see Section 3.11.

3.11 Criteria for withdrawal from study

At any time, patients are free to withdraw from the study without prejudice to further treatment. A patient who decides to discontinue IP treatment and follow –up assessments will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. Adverse events will be followed up (See Section 6.3.2); all IPs should be returned by the patient or caretaker.

If patients wish to withdraw their consent to both study drug and study assessments, they should be asked if they are willing to continue with survival follow-up (which can be conducted by telephone). If patients wish to withdraw their consent to further participation in the study entirely, including survival follow-up, this should be clearly documented in the patient notes, "Informed Consent Form addendum – options for withdrawal of consent" and in the clinical study database.

For the OS endpoints, the status of ongoing, withdrawn (from the study), and "lost to follow-up" patients at the time of the primary analysis and final OS analysis, and also at the time of the long-term OS analysis for patients who consent to long-term OS follow-up, should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's current physician, and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

Withdrawn patients will not be replaced.

3.11.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Eligibility Criteria not Fulfilled' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).

3.11.2 Withdrawal of the informed consent

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

A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. The subject or representative will return unused AZD9291 tablets.

If patients wish to withdraw their consent different option of withdrawal should be discussed and clearly documented in "Informed Consent Form addendum – options for withdrawal consent" and patient notes.

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

3.12 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, study patients 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 patient at the time of discontinuation of follow-up must be recorded in the eCRF. 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 patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study plan up to completion of final DFS analysis

	Screening		Treatment Period					Post-Treatment			
Visit	**Part I**	**Part II [a]**	**Randomisation**	**Week 2**	**Week 4**	**On treatment**	**Treatment discontinuation [b]**	**28 day Follow up [c]**	**Follow-up until disease recurrence [d]**	**Follow up for survival**	**Protocol Section**
Timing (timing of each visit to be calculated based on date of randomisation visit)		**Day -28 to Day -1**	**Day 1**	**Week 2**	**Week 4**	**Week 12 then every 12 weeks until 3 years (156 weeks)**			**Week 12, Week 24 and then every 24 weeks until 5 years (264 weeks) / yearly thereafter**	**Every 24 weeks until 5 years (264 weeks) / yearly thereafter**	
Visit window	**N/A**	**N/A**	**N/A**	**+/- 1 day**	**+/- 3 days**	**+/-7 days**		**+ 7 days**	**+/-7 days**	**+/-7 days**	
Written informed consent for pre - screening	X										4.1.1 10.4
Written main informed consent [e]		X									4.1.1 10.4
Tumour sample [f]	X										4.1.3
Tumour sample at disease recurrence (optional)						X[g]			X[g]		5.7.2
Demographics	X										
Medical/surgical history		X	X								

	Screening		**Treatment Period**					**Post-Treatment**			
Visit	**Part I**	**Part II [a]**	**Randomisation**	**Week 2**	**Week 4**	**On treatment**	**Treatment discontinuation [b]**	**28 day Follow up [c]**	**Follow-up until disease recurrence [d]**	**Follow up for survival**	**Protocol Section**
Timing (timing of each visit to be calculated based on date of randomisation visit)		**Day -28 to Day -1**	**Day 1**	**Week 2**	**Week 4**	**Week 12 then every 12 weeks until 3 years (156 weeks)**			**Week 12, Week 24 and then every 24 weeks until 5 years (264 weeks) / yearly thereafter**	**Every 24 weeks until 5 years (264 weeks) / yearly thereafter**	
Visit window	**N/A**	**N/A**	**N/A**	**+/- 1 day**	**+/- 3 days**	**+/-7 days**		**+ 7 days**	**+/-7 days**	**+/-7 days**	
Inclusion/exclusion criteria		X	X								3.1 3.2
Physical examination, height (at screening only), and weight		X	X	X	X	X	X		X		5.2.2
Smoking history		X									
WHO performance status		X	X	X	X	X	X		X		5.3.1
Pregnancy test (WOCBP only)		X	At Investigator's discretion								5.2.1
Ophthalmologic assessment		X	As clinically indicated								5.2.6.1
Vital signs		X	X[h]	X	X	X	X				5.2.5
Clinical Chemistry/Haematology/Urinalysis		X	X[h]	X	X	X	X				5.2.1

	Screening		**Treatment Period**					**Post-Treatment**			
Visit	**Part I**	**Part II [a]**	**Randomisation**	**Week 2**	**Week 4**	**On treatment**	**Treatment discontinuation [b]**	**28 day Follow up [c]**	**Follow-up until disease recurrence [d]**	**Follow up for survival**	**Protocol Section**
Timing (timing of each visit to be calculated based on date of randomisation visit)		**Day -28 to Day -1**	**Day 1**	**Week 2**	**Week 4**	**Week 12 then every 12 weeks until 3 years (156 weeks)**			**Week 12, Week 24 and then every 24 weeks until 5 years (264 weeks) / yearly thereafter**	**Every 24 weeks until 5 years (264 weeks) / yearly thereafter**	
Visit window	**N/A**	**N/A**	**N/A**	**+/- 1 day**	**+/- 3 days**	**+/-7 days**		**+ 7 days**	**+/-7 days**	**+/-7 days**	
ECG [i]		X	X[h]		X	X	X				5.2.3
Echocardiogram/MUGA (for LVEF)		X				X	X				5.2.4
MRI/contrast CT of brain		X[j]									
CT of Chest and abdomen (including liver and adrenal glands) with contrast for disease control [k]		X [l]				At Week 12, Week 24 and then every 24 weeks relative to randomisation (±7 days) until 5 years, then yearly until disease recurrence/primary analysis/'final DFS analysis' ↔					5.1
Other imaging [m]		X	As clinically indicated								5.1
Genetic consent and blood sample (optional) [n]		X									5.6

	Screening		**Treatment Period**					**Post-Treatment**			
Visit	**Part I**	**Part II [a]**	**Randomisation**	**Week 2**	**Week 4**	**On treatment**	**Treatment discontinuation [b]**	**28 day Follow up [c]**	**Follow-up until disease recurrence [d]**	**Follow up for survival**	**Protocol Section**
Timing (timing of each visit to be calculated based on date of randomisation visit)		**Day -28 to Day -1**	**Day 1**	**Week 2**	**Week 4**	**Week 12 then every 12 weeks until 3 years (156 weeks)**			**Week 12, Week 24 and then every 24 weeks until 5 years (264 weeks) / yearly thereafter**	**Every 24 weeks until 5 years (264 weeks) / yearly thereafter**	
Visit window	**N/A**	**N/A**	**N/A**	**+/- 1 day**	**+/- 3 days**	**+/-7 days**		**+ 7 days**	**+/-7 days**	**+/-7 days**	
Plasma sample for ctDNA and blood borne biomarkers **[o]**			X (pre dose)			X	X		X		5.7.3
PK blood sample (AZD9291 and metabolites)					X [p]	X [p]					5.4
SF – 36			X (pre dose)			X [q]	X				5.3.4.1
Health Resource Module [r]			X (pre dose)	X	X	X	X				5.3.4.4
Adverse event review		X							X[s]		6
Treatment dispensed/returned			X		X	X					7.7
Concomitant medication		X									7.8

	Screening		**Treatment Period**					**Post-Treatment**			
Visit	**Part I**	**Part II [a]**	**Randomisation**	**Week 2**	**Week 4**	**On treatment**	**Treatment discontinuation [b]**	**28 day Follow up [c]**	**Follow-up until disease recurrence [d]**	**Follow up for survival**	**Protocol Section**
Timing (timing of each visit to be calculated based on date of randomisation visit)		**Day -28 to Day -1**	**Day 1**	**Week 2**	**Week 4**	**Week 12 then every 12 weeks until 3 years (156 weeks)**			**Week 12, Week 24 and then every 24 weeks until 5 years (264 weeks) / yearly thereafter**	**Every 24 weeks until 5 years (264 weeks) / yearly thereafter**	
Visit window	**N/A**	**N/A**	**N/A**	**+/- 1 day**	**+/- 3 days**	**+/-7 days**		**+ 7 days**	**+/-7 days**	**+/-7 days**	
Post study treatment discontinuation anti-cancer procedures and treatment								X	X	X	5.3.3
Subsequent response/progression data [t]										X (freq as per SoC)	
Survival Status										X[u]	5.1.3

a) If screening assessments completed within 14 days they do not need to be repeated on Day 1 if patient's condition has not changed
b) Treatment discontinuation visit to be performed only for the patients who prematurely discontinued treatment. For the patient who completed 3 years treatment (156 weeks), the last visit (Week 156) in treatment period will be considered as treatment discontinuation.
c) As a minimum, telephone contact should be made with the patient 28 days (+7 days) following discontinuation of study drug
d) Follow –up until disease recurrence visits to performed for the patients who discontinue/completed treatment before disease recurrence
e) Consent may be taken any time prior to 28 days window; Screening Part II period will start with first study-related assessment
f) Mandatory: sufficient quantity for central confirmation of EGFR mutation status, retrospective T790M testing and for exploratory analyses
g) Optional: tumour sample at disease recurrence
h) Assessments to be completed pre-dose on the visit day

i) All ECG data (with the exception of screening ECGs) will be collected digitally for the first year, standard ECGs will be performed thereafter; ECG is also to be performed in event of a cardiac AE

j) MRI or contrast CT of brain must be done before randomisation if not performed prior to surgery. MRI/contrast CT scans of the brain must also be conducted at recurrence.

k) In the rare case where a patient is intolerant of the contrast medium, the preferred imaging would be CT chest without contrast and MRI abdomen with contrast however non contrast abdominal CT will also be accepted. All recurrences on study need to be confirmed with imaging of the chest and abdomen (including liver and adrenal glands). The imaging method used at baseline (CT or MRI) must be used at each subsequent follow-up assessment. MRI/contrast CT scans of the brain must be conducted at recurrence.

l) Baseline scans within 28 days of first dose

m) Required only if suspicious signs/symptoms are not covered by CT of chest and abdomen (including liver and adrenal glands) at baseline and follow -up

n) If for any reason a sample is not drawn prior to dosing, it may be taken at any visit until the last study visit

o) Plasma samples 10ml prior to first randomised dose on Day 1; 20-30 ml at every 12 weeks visits. If patient discontinues study treatment prior to disease recurrence, samples should continue to be collected in accordance with the scan schedule until disease recurrence is noted.

p) Blood sampling at 4 weeks, 24 weeks, 48 weeks, 96 weeks after randomisation. Blood draw to occur 3 times at each visit at following time points: pre-dose, between 0,5 -1,5h post dose, between 2-4 h post dose. 96 week PK sample post IDMC7 analysis will not be collected.

q) SF 36 at 12 weeks, 24 weeks and then every 24 weeks relative to randomisation (± 7 days) until disease recurrence

r) Patients will be asked about any health resource use between visits (i.e., excluding routine follow-up clinic visits associated with the clinical trial but including both planned and unplanned admissions) at every scheduled visit during the study.

s) AEs ongoing at treatment discontinuation to be followed through to resolution; thereafter, only SAEs /concomitant medications for SAEs considered related to IP and study procedures to be recorded in eCRF

t) Investigator assessment of response/progression to be collected

u) To establish survival status patient will be contacted in the week following date of DCO for IDMC and in the two weeks following date of DCO for primary analysis and subsequent analyses.

Table 2 Study Plan for OS period - post final DFS analysis and up to final OS analysis

	Treatment Period		Post-Treatment		
Visit	**On treatment**	**Treatment discontinuation[a]**	**28 day Follow up[b]**	**Follow up for survival**	**Protocol Section**
Timing (timing of each visit to be calculated based on date of randomisation visit)	**Week 12 then every 12 weeks until 3 years (156 weeks)**			**Every 24 weeks until 5 years (264 weeks) / yearly thereafter**	
Visit window	**+/-7 days**		**+ 7 days**	**+/-7 days**	
Tumour sample at disease recurrence (optional)	X[c]				5.7.2
Physical examination and weight	X	X			5.2.2
WHO performance status	X	X			5.3.1
Pregnancy test (WOCBP only)	At investigator's discretion				5.2.1
Ophthalmologic assessment	As clinically indicated				5.2.6.1
Vital signs	X	X			5.2.5
Clinical Chemistry/Haematology/Urinalysis	X	X			5.2.1
ECG[d]	X	X			5.2.3
Echocardiogram/MUGA (for LVEF)	X	X			5.2.4
Imaging	As per local clinical practice				
Plasma sample for ct DNA and blood borne biomarkers[e]	X	X			5.7.3
Adverse event review[f]	X				6
Treatment dispensed/returned	X				7.7

	Treatment Period		**Post-Treatment**		
Visit	**On treatment**	**Treatment discontinuation[a]**	**28 day Follow up[b]**	**Follow up for survival**	**Protocol Section**
Timing (timing of each visit to be calculated based on date of randomisation visit)	**Week 12 then every 12 weeks until 3 years (156 weeks)**			**Every 24 weeks until 5 years (264 weeks) / yearly thereafter**	
Visit window	**+/-7 days**		**+ 7 days**	**+/-7 days**	
Concomitant medication	X				7.8
Post study treatment discontinuation anti-cancer procedures and treatment			X	X	5.3.3
Survival Status				X[g]	5.1.3

a) Treatment discontinuation visit to be performed only for the patients who prematurely discontinued treatment. For the patient who completed 3 years treatment (156 weeks), the last visit (Week 156) in treatment period will be considered as treatment discontinuation.

b) As a minimum, telephone contact should be made with the patient 28 days (+7 days) following discontinuation of study drug

c) Optional: tumour sample at disease recurrence

d) All ECG data (with the exception of screening ECGs) will be collected digitally for the first year, standard ECGs will be performed thereafter; ECG is also to be performed in event of a cardiac AE

e) Plasma samples 20-30 ml at every visits

f) AEs ongoing at treatment discontinuation to be followed through to resolution

g) To establish survival status patient will be contacted in the week following date of DCO for IDMC and in the two weeks following date of DCO for primary analysis and subsequent analyses.

Table 3 Study plan for the study extension post final OS analysis and up to long-term OS analysis

Visit[a]	Follow-up- for survival[b]	Protocol Section
Timing (timing of each visit to be calculated based on date of randomisation visit)	**Yearly**	1.7, 4.5
Visit window	**±30 days**	
Survival Status[c]	X	4.3.5

a) Visits can be conducted by telephone or in person.
b) Each patient will provide written informed consent to participate in the study extension.
c) To establish survival status, patient will be contacted on a yearly basis. At the time of analysis, the patient will be contacted for survival status in the 2 weeks following the date of DCO for the long-term OS analysis.

Safety data (all serious or non-serious events of ILD/pneumonitis and cardiac failure, and all SAEs) for patients who are treated with open-label osimertinib will be collected as described in Section 6.3 and Section 6.4.

4.1 Enrolment/screening period

It is recommended that the screening assessments are performed in a stepwise process beginning with the confirmation of EGFR mutation status determined by the designated central laboratory. However, screening assessments may be done in parallel to the EGFR mutation assessment, as appropriate. Procedures will be performed according to the Study Plan (Table 1). Radiological assessments and other clinical data obtained as SoC prior to consent may be used for the study, provided the assessments fall within the protocol specified period prior to the first dose of the study drug.

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

4.1.1 Written informed consent

- Each potential patient will provide written informed consent for Screening Part I before tumour sample is sent to central laboratory for EGFR testing.
- The main informed consent will be provided by the patient prior to starting any study specific procedures other than tumour sample testing at central laboratory. Patient will also be required to provide consent for collection of blood samples during the randomisation, study treatment and post treatment period. Patients will be required to provide consent for these samples to be used for mandatory analysis to explore the relationship between emergence and changes of EGFR mutation in ctDNA and time to disease recurrence, retrospective analysis for a range of oncology biomarkers or to enable diagnostic

development. This consent is included in the main patient informed consent form (ICF) (see Section 10.4).

- Additionally, patients will be given the option to consent to the tumour sample collection after disease recurrence, use of tumour and plasma samples for exploratory analysis and the host pharmacogenetics research component of the study, each in a separate ICF.

4.1.1.1 Written informed consent for the long-term OS follow-up in the study extension

- All patients in survival follow-up will be given the option to participate in the long-term OS follow-up. Each patient will provide written informed consent to the optional long-term OS follow-up in the study extension, in a separate ICF. Patients will be followed yearly for survival until approximately 10 years after the randomisation of the last patient.

4.1.2 Complete resection

Complete surgical resection of the primary NSCLC is mandatory with all surgical margins being negative for tumour.

Surgery may consist of lobectomy, sleeve resection, bilobectomy or pneumonectomy as determined by the attending surgeon based on the intraoperative findings. Patients who have had only segmentectomies or wedge resections are not eligible for this study.

All patients must be staged according to the 7th edition of AJCC Cancer Staging Manual, 2010. Although the study will be analysed according to the AJCC 7th edition, all randomised patients will also be staged at baseline according to the AJCC 8th edition classification.

4.1.3 Mandatory screening tumour biopsy sample for mutation analysis

Tumour sample must be formalin fixed and paraffin embedded (FFPE). Cytology samples are unsuitable for testing and should not be provided. Sites should ship the FFPE tumour sample to the testing laboratory as soon as it is available. Blocks (multiple cores) must be provided wherever possible. Unstained, archived tumour tissue sample in a sufficient quantity to allow for central analysis of EGFR mutation status, retrospective testing of T790M and exploratory analysis should be provided.

The Investigator will be asked to provide:

- Formalin-fixed, paraffin-embedded tumour tissue blocks (multiple cores if possible), or
- 10 to 20 (a minimum of 10) re-cut unstained sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides. Each section is to be 5 µm thick.

This biopsy sample will be submitted for central testing in pre-screening period (Screening Part I).

If the first biopsy submitted for central testing is not confirmed as EGFR mutation positive due to test failure, a further biopsy sample may be submitted for central testing. Central re-tests on a new sample can only be performed if the original testing failed. Re-tests are not permitted if the central EGFR testing result is EGFR mutation negative, or does not report an EGFR eligible mutation (Exon 19 Deletion or L858R).

4.1.4 Assignment of patient screening/randomisation number

As per standard, enrolment number (PPD code) is assigned to the patient once consent for Screening Part I is signed and Principal Investigator or delegate should perform enrolment/screening call (See Section 3.4). During the randomisation visit patient will receive randomisation number via IVRS/IWRS.

Screening procedures will be performed according to the Study Plan Table 1.

4.2 Treatment period

Patients will be randomised at Visit Day1 and receive either AZD9291 or matching placebo. Patients will take the first dose of study drug within 2 days of randomisation and will continue treatment until recurrence of disease, treatment discontinuation criterion is met or treatment is completed. The treatment duration period is 3 years (156 weeks), except for patients who receive open-label osimertinib after recurrence and continue until subsequent progression or another one of the situations described in Section 3.10.

The assessments required during the treatment period are detailed in the Study Plan (Table 1).

4.3 Follow-up period

4.3.1 Discontinuation visit

A Discontinuation visit will be performed only for the patients who prematurely discontinued treatment. For the patient who completed 3 years treatment, the last visit (Month 36) in treatment period will be considered as treatment discontinuation. Refer to Table 1 for details.

4.3.2 Twenty-eight day follow–up

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

4.3.3 Disease recurrence follow–up (up to completion of final DFS analysis)

Patients who complete study treatment prior to disease recurrence or discontinue study drug for reasons other than disease recurrence will be followed up at 12 weeks, 24 weeks and then every 24 weeks up to 5 years (264 weeks) relative to randomisation and yearly thereafter.

In addition to radiological assessments, the following assessments are also required during Disease recurrence Follow up as detailed in the Study Plan (Table 1).

- Physical examination
- WHO Performance Status
- Plasma samples for ctDNA and blood borne biomarkers
- Serious Adverse event collection (causally related)
- Tumour sample collection at disease recurrence (optional)

4.3.4 Survival follow–up (up to final OS analysis)

Assessments for survival should be made every 24 weeks up to 5 years (264 weeks) after randomisation and yearly thereafter following disease recurrence. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician.

In addition to the survival status, the following assessments are required post recurrence as detailed in the study plan (Table 2).

- Anti-cancer therapy, radiotherapy and surgery
- Serious Adverse event collection (causally related)
- Subsequent response and progression data (PFS) in accordance with local practice until the first confirmed disease progression on a subsequent treatment (not collected post primary analysis or post 'Final DFS analysis' if required)

Survival data will be collected up to the time of the final OS analysis. Patients should be contacted in the week following date of DCO for IDMC and in the two weeks following date of DCO for primary analysis and subsequent analyses. The status of ongoing, withdrawn (from the study), and "lost to follow-up" patients at the time of each of the efficacy analyses should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patient's general practitioner, and checking publicly available death registries. In the event that the patient has withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

4.3.5 Survival follow-up in the study extension for long-term OS analysis

For patients who consent to long-term OS follow-up, assessments for survival should be made yearly until approximately 10 years after the last patient is randomised.

Survival information may be obtained in-person or via telephone contact with the patient, patient's family, or by contact with the patient's current physician. Please refer to Table 3 for further details.

At the time of analysis, the patient will be contacted for survival status in the 2 weeks following the date of DCO for the long-term OS analysis.

The status of ongoing, withdrawn (from the study), and "lost to follow-up" patients should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner, and checking publicly available death registries.

4.4 Study plan for patients eligible for open-label osimertinib

Prior to starting open-label osimertinib treatment, all eligible patients need mandatory reconsenting with an updated version of the ICF. Data relating to physical examination, vital signs (pulse and BP), restaging imaging assessments such as CT of chest and abdomen (including liver and adrenal glands), and MRI CT of brain with contrast for disease control must be available prior to starting osimertinib treatment, in line with the criteria detailed in Section 3.3. If these assessments were completed for treatment discontinuation visit and no longer than 28 days prior to open label osimertinib, then they do not need to be repeated. In addition to meeting inclusion/exclusion criteria listed in Sections 3.1 and 3.2, patients who receive open-label osimertinib will also have to fulfil the eligibility criteria in Section 3.3.

Patients on open-label osimertinib also continue the study plan described for the follow up period, as in Section 4.3.4 [Survival follow-up (up to final OS analysis)] and Section 4.3.5 (Survival follow-up in the study extension for long-term OS analysis).

Patients must have started open-label osimertinib prior to the DCO for the long-term OS analysis.

Safety data collection for patients on open-label osimertinib will follow the schedule for patients who discontinue the study drug for any reason but are still participating in the trial, as detailed in Section 6.3.1.

4.5 Study plan for the study extension for long-term OS analysis

Following the final OS analysis, CSP edition 6 has introduced a further optional long-term OS follow-up. All patients in survival follow-up will be offered the opportunity to participate in the long-term OS follow-up. Patients who consent to participate will be followed yearly for survival until approximately 10 years after the last patient is randomised to capture long-term OS data in the study extension. Each patient will provide written informed consent to participate in the optional long-term OS follow-up in the study extension, in a separate ICF.

Eligible patients can be offered open-label osimertinib upon recurrence (as first-line treatment), if the recurrence pattern is in line with the regional label, as described in Section 3.3. In line with the approved indication, these patients can continue to receive open-label osimertinib until disease progression, or until a time when the Investigator considers that they are no longer deriving clinical benefit, or they stop taking treatment for any other reason including having met any of the criteria for treatment discontinuation. At the time of the long-term OS analysis, a number of patients can still be on open-label osimertinib. Any patients still on open-label osimertinib at the completion of the study extension will be

managed outside of the study per Section 7.3.3. At this point, any SAEs will be reported outside of the database, only reported as per Section 6.4 and Section 6.5.

Safety data (all serious or non-serious events of ILD/pneumonitis and cardiac failure, and all SAEs) for patients who are treated with open-label osimertinib will be collected as described in Section 6.3. Survival information may be obtained in-person or via telephone contact with the patient, patient's family, or by contact with the patient's current physician (see Table 3).

The status of ongoing, withdrawn (from the study), and "lost to follow-up" patients should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries.

A long-term OS analysis from the time of randomisation until date of death due to any cause will be conducted to obtain long-term follow-up OS data. At the time of analysis, the patient will be contacted for survival status in the 2 weeks following the date of DCO for the long-term OS analysis.

5. STUDY ASSESSMENTS

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

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

For details of data and study management see Section 9.4 of Clinical Study Protocol.

5.1 Efficacy assessments

5.1.1 Disease-free survival

Disease-free survival is the primary endpoint in this study and is defined as the time from the date of randomisation until the date of disease recurrence or death from any cause in the absence of disease recurrence. Disease recurrence is defined as evidence of disease recurrence on CT or MRI scan and/or pathological disease on biopsy by investigational site assessment.

The imaging modalities used for radiological assessments will be CT scans of the chest and abdomen (including liver and adrenal glands) with contrast. In the rare case where a patient is intolerant of the contrast medium the preferred imaging would be CT chest without contrast and MRI abdomen with contrast; however a non-contrast abdominal CT will also be accepted. The methods used at baseline (CT or MRI) must be used at each subsequent follow-up assessments. A pre-surgical MRI or contrast CT scan of the brain is considered standard of

care and must be done prior to surgery. Patients in whom this was not done prior to surgery may still be enrolled providing that appropriate imaging is performed prior to randomisation. Any other sites where disease is suspected at baseline must also be imaged to confirm absence of disease prior to randomisation into the study. The baseline assessments should be performed within 28 days prior to study drug initiation. Subsequent assessments are to be performed at 12 week, 24 week and then every 24 weeks until 5 years (264 weeks), and then yearly thereafter relative randomisation, until disease recurrence is recorded. If a patient discontinues treatment prior to disease recurrence or receives other anti-cancer treatment, patient should continue to be imaged in accordance with this schedule until disease recurrence is noted. It is important to follow the assessment schedule as closely as possible. If scans are performed outside of the scheduled visit (± 7 days window interval) and the patient has not recurred, every attempt should be made to perform the subsequent scans at their scheduled time points. Any other sites at which a new disease is suspected should also be appropriately imaged during the study.

5.1.2 Evidence of disease recurrence

Recurrence will be categorised as local/regional or distant. When recurrence is first documented at any site, all sites of recurrence should be identified. All recurrences on study need to be confirmed with imaging of the chest and abdomen (including liver and adrenal glands). The imaging method used at baseline (CT or MRI) must be used at each subsequent follow-up assessment. MRI/contrast CT scans of the brain must be conducted at recurrence. Local or regional recurrence.

Local or regional recurrence is defined as recurrence in the area of the tumour bed, hilum or mediastinal lymph nodes. Loco-regional recurrence of the disease should be cytologically/histologically confirmed.

5.1.2.1 Distant recurrence

Distant recurrence is defined as spread of disease beyond the area of the tumour bed, hilum or mediastinal lymph nodes. Distant recurrence should be diagnosed by radiological examination and/or histopathological confirmation when the metastatic lesion is easily accessible for biopsy.

5.1.2.2 Dating of recurrence

Dating of recurrence should always be based on the first onset of a sign but never on the onset of a symptom. The date of first detection of a palpable lesion is acceptable only when the diagnosis of tumour involvement is subsequently established. The diagnosis of recurrent disease by radiographs or scans should be dated from the date of the first positive record, even if this is determined in retrospect or tissue confirmation occurs subsequent to the initial appearance of a suspicious area/lesion on a scan.

If there is equivocal progression medical monitor/study physician should be contacted.

5.1.2.3 Post-recurrence

Following recurrence patient management is at the discretion of the investigator, and tumour assessments will be in accordance with local policy. Date of the first subsequent progression as determined by the investigator will be recorded.

5.1.3 Overall Survival

Overall survival is defined as the time from randomisation to the date of death (from any cause) or to the date the patient was last known to be alive.

Following randomisation and up to final OS analysis, patients will be followed up for survival every 24 weeks for 5 years (264 weeks) and then yearly thereafter, until the study is closed.

5.1.3.1 Overall survival – long-term OS survival

Following the final OS analysis, patients who consent to participate in long-term OS follow-up will be followed yearly for survival until approximately 10 years after the last patient is randomised.

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 Table 1. Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date and results (values, units, and reference ranges) will be recorded on the appropriate eCRF. The clinical chemistry, haematology, and urinalysis will be performed at a local laboratory at or near to the Investigator site. If clinical chemistry, haematology, and urinalysis assessments have been performed within 14 days pre-randomisation, they do not have to be repeated prior to commencing treatment on randomisation visit Day 1 if the patient's condition has not changed (i.e., no new treatment during this period of time, no new complication, or aggravation). Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. The number of samples/blood volumes is therefore subject to site-specific change.

The following laboratory variables will be measured (3).

Table 4 Laboratory safety variables

Clinical chemistry	Haematology
S/P-Albumin	B-Haemoglobin
S/P-ALT	B-Leukocyte
S/P-AST	B-Haematocrit
S/P-Alkaline phosphatase	B-RBC count
S/P-Bilirubin, total	B-Absolute leukocyte differential count:

Clinical chemistry	**Haematology**
S/P-Calcium, total	Neutrophils
S/P-Creatinine	Lymphocytes
S/P-Glucose (fasting, on PK days only)[a]	Monocytes
S/P-LDH[b]	Basophils
S/P-HbA1C	Eosinophils
S/P-Magnesium	B-Platelet count
S/P-Potassium	B-Reticulocytes
S/P-Sodium	**Urinalysis**
S/P-Urea nitrogen/BUN	U-Glucose
	U-Protein
	U-Blood

ALT=alanine aminotransferase; AST=aspartate aminotransferase; B=blood; BUN=blood urea nitrogen; HbA1C=haemoglobin A1C; LDH=lactate dehydrogenase; P=plasma; RBC=red blood cells; U=urine; S=serum.

[a] Patients will be required to fast (water only) for at least 8 hours prior to the collection of a fasting glucose sample required on PK days. Random glucose sample will be collected on non-PK days.

[b] LDH is an additional variable collected at Screening visit only.

Additionally, at the Screening Visit, a pregnancy test (blood or urine tests are acceptable based on the site's standard clinical practice) will be collected from all women of child-bearing potential only.

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

Note: In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥2xULN, please refer to Appendix E, 'Actions required in cases of combined increase of aminotransferase and total bilirubin (Hy's Law)', for further instructions (Section 6.3.7 and Appendix E).

5.2.1.1 Volume of blood

Total mandatory blood volume in the 5 years study period (including 3 years (156 weeks) treatment) is 674-844 mL (4).

Table 5 Blood sample volumes

Visit	Safety (mL)[a]	PK analysis (mL)	Plasma (mL)	PGx (mL)
Screening	15			10 (optional)[c]
Day 1	15		10	
Day 14	15			
Month 1	15	6 (3 x 2 mL x 1)		
On treatment visits (13 visits)	15 (13x15 mL)	6 (3 x 2 mL x 3)	20 - 30 (13 x 20 ml – 30 ml)	
Treatment discontinuation	15		20 - 30	
Disease recurrence FU [b]			20 - 30 (4 x 20 ml - 30 ml)	
SUBTOTAL (mandatory)	**270**	**24**	**370-540**	**10**

PGx=pharmacogenetics; PK=pharmacokinetics.

[a] For safety, assumes 6 mL clinical chemistry and 9 mL haematology per visit. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. The number of samples/blood volumes is therefore subject to site-specific change.

[b] Up to 4 visit taken into account

[c] If for any reason the sample is not drawn prior to dosing, it may be taken at any visit until the last study visit.

5.2.2 Physical examination

All patients will have a physical examination performed and weight assessed at the time points indicated in the Study Table 1,which includes an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems. Height will only be measured during the Screening period, and it will be documented in the eCRF.

5.2.3 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, indicated in the Study Plan Table 1, 3 ECG recordings should be taken at about 5 minute intervals. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study if possible.

After ECGs have been performed, 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

medical history condition. For all ECGs details of rhythm, ECG intervals, and an overall evaluation will be recorded.

For the first year (Week 48) of subject participation in the study, all ECG data will be collected digitally; thereafter standard /ECGs will be performed.

Digital ECG will be transferred electronically for central analysis as described in the study specific ECG manual. The investigator may choose to perform a non-digital ECG at the time of the screening visit in order to identify patients eligible for study entry. If a non-digital ECG is performed at the screening visit it cannot subsequently be used as a baseline recording, in this situation an ECG will need to be collected on the baseline visit in digital form.

Heart rate, PR, R-R, QRS, and QT (QTcF) intervals will be determined and reviewed by an external cardiologist.

If there is a clinically significant abnormal ECG finding during the treatment period, this should be recorded on the AE eCRF, according to standard adverse events collection and reporting processes. A 28-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.

Patients experiencing a QTc greater than 500 msec on at least 2 separate ECGs must have AZD9291 treatment interrupted until the QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec (see Section 6.9.5).

Patients experiencing QTc prolongation with signs/symptoms of serious arrhythmia will not be permitted to restart study treatment.

5.2.4 Echocardiogram/MUGA scan

An Echocardiogram or MUGA scan to assess LVEF will be performed at the visits as shown in the Study Plan (Table 1). The modality of the cardiac function assessments must be consistent throughout i.e., if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans. The subjects should also be examined using the same machine and operator whenever possible.

5.2.5 Vital signs

5.2.5.1 Pulse and blood pressure

Supine blood pressure and pulse rate will be measured after 10 minutes rest. Assessments will be performed at the visits as shown in the Study Plan (Table 1) and additionally at the discretion of the Investigator if clinically indicated.

Clinically significant changes in vital signs (pulse and BP) should be recorded as an AE if applicable.

5.2.6 Other safety assessments

5.2.6.1 Ophthalmologic exam

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

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

Ophthalmology examination results should be collected in the eCRF.

5.3 Other assessments

5.3.1 WHO performance status

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

- 0 = Fully active, able to carry out all pre-disease activities without restrictions.
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
- 2 = Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
- 4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair.

5.3.2 Record concomitant medication use

Information on any treatment within the 4 weeks prior to initiation of study drug and all concomitant treatments given up to 28 days after completion or discontinuation of study treatment with reasons for the treatment, will be recorded in the eCRF. Please refer to Section 7.8.

5.3.3 Post study treatment discontinuation anti-cancer procedures and treatment

Any subsequent anti-cancer procedures and therapies given to the patient will be captured via eCRF.

Data captured will include:

- Date of anti-cancer treatment (s) (including procedures and radiotherapy)
- Types of next treatment (s) (including procedures and radiotherapy)

5.3.4 Patient Reported Outcomes

The PRO questionnaire used in this study is SF-36.

5.3.4.1 SF-36

Patients will be asked to complete a paper based version of the SF-36 v 2 standard (Appendix G) at the clinic according to the Study Plan (Table 1). The SF-36 v2 is a validated instrument measuring general health status. The standard version of SF-36 (Appendix G) has a recall period of four weeks.

The SF-36 v2 consists of 36 items combined into domains, and two aggregated summary scores: MCS (Mental Component Summary) and PCS (Physical Summary Component) (Ware et al 1993).

The eight domains are Physical Functioning (PF, items 3a-3j), Role-Physical (RP, role limitations caused by physical health problems, items 4a-4d), Bodily Pain (BP, items 7 and 8), General Health (GH, items 1, and 11a-11d), Vitality ((VT, items 9a, 9e, 9g, and 9i), Role-Emotional (RE, role limitations caused by emotional problems, items 5a-5c), Social Functioning (SF, items 6 and 10), and Mental Health (MH, items 9b, 9c, 9d, 9f, and 9h). All of the 36 items (self-reported health transition) are used to score the eight SF-36 domains.

5.3.4.2 Derivation or calculation of variables

The eight domains of the SF-36v2 standard includes items as described previously. The items use Likert scales with 3-6 points. Raw scores for the scales are computed across items in the same domain and are then transformed via a weighting system to a 0-100 domain with higher scores indicating better health.

5.3.4.3 Administration of PRO questionnaire

Appropriate procedures for minimising bias and enhancing compliance will be followed throughout the study. To ensure this, all study personnel will be trained to instruct the patient in a standardised way and further be responsible for providing all relevant instructions and training to the patients. A standardised procedure for the administration of the PRO questionnaire should be applied.

Each centre must allocate responsibility for completion of the PRO questionnaire to a specific individual (i.e., a Research Nurse). It is also important that the significance and relevance of the data are explained carefully to participating patients so that they are motivated to comply with data collection. The following applies to completing the PRO questionnaire:

- The patient must complete it in private, taking his or her own time.
- The patient must complete it before any investigations or discussions about their disease with the clinic staff.
- It must be completed prior to any other study-related procedures.

- The patient should be given sufficient time to complete at their own speed, and the patient should be reassured that there are no right or wrong answers and that the answers are strictly confidential.
- Help should not be given from relatives or clinical, with the exception that the patient can receive help from a study nurse in understanding the instructions. However under no circumstances should help in interpreting the questions or in selecting responses be provided.
- A form will be completed by the clinic staff to indicate if a questionnaire has been completed at each visit, and if not, the reason will be recorded.
- On completion of the questionnaire it should be handed back to the person responsible for questionnaires who should check for completeness.
- Only one answer should be recorded for each question.

The questionnaire will be administered in all countries for which a validated questionnaire is available

5.3.4.4 Health Resource Use Module

Healthcare Resource Use Module will be completed by the investigational site for any healthcare resource use between visits. The site will ask patients for any health resource use between visits (i.e., excluding routine follow-up clinic visits associated with the clinical trial but including both planned and unplanned admissions) during treatment period.

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

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

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

Health resources use module will not be collected for patients who receive open-label osimertinib treatment.

5.4 Pharmacokinetics

5.4.1 Collection of samples

Pharmacokinetics blood sampling (2 mL each) will be performed for all patients at pre-dose, 0.5 to 1.5 hours, and 2 to 4 hours post dose on Week 4, Week 24, Week 48 and Week 96. Week 96 PK sample post IDMC7 analysis will not be collected. Dose time information must be collected on both the day of PK sampling (to determine the exact times of the post-dose PK

samples), and the day immediately prior to PK sampling (to allow the pre-dose PK sample to be used). The date and time of collection of each sample and the date and time of dose will be recorded. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Placebo samples will not be analysed unless specified. No further PK samples will be collected from patients who receive for open-label osimertinib.

5.4.2 Determination of drug concentration

Samples for determination of AZD9291 (and metabolite) concentrations in plasma will be collected and analysed by Covance on behalf of AstraZeneca. Full details of the analytical method used will be described in a separate bioanalytical report. All samples still within the known stability of the analytes of interest (i.e., AZD9291 and AZ5104) at the time of receipt by the bioanalytical laboratory will be analysed.

For each placebo subject, samples will only be analysed on a 'for cause' basis, e.g., if no quantifiable concentrations were observed in a subject's samples when the drug was expected to be present.

In addition, the PK samples may be subjected to further analyses by AstraZeneca in order to further investigate the presence and/or identity of additional drug metabolites and correlate PK with other primary, secondary, and exploratory endpoints in patients treated with AZD9291. Any results from such analyses will be reported separately from the Clinical Study Report (CSR). Details on sample processing, handling, shipment, and storage are provided in the Laboratory Manual.

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

5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of or destroyed and anonymised by pooling after the bioanalytical report finalization or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless requested for future analyses.

Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a bioanalytical report.

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

5.5 Pharmacodynamics (not applicable)

5.6 Pharmacogenetics

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

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

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

- Analysis of genes that may affect efficacy, safety, and tolerability (for example, but not limited to, drug metabolising enzymes and drug transporters).
- Genetic research into genes that may contribute to the development of, or susceptibility to NSCLC.

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

5.6.1 Collection of pharmacogenetic samples

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

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

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

5.6.2 Storage, re-use and destruction of pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years from the date of the last patient last visit (LPLV), after which they will be destroyed. Deoxyribonucleic acid is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

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

5.7 Exploratory research

Tumour and blood samples will be collected (as described in the Study Plan (Table 1) and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, and clinical outcomes.

The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

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

5.7.1 Provision of tumour material for exploratory research

Provision of tumour material at Screening Part I for central testing of EGFR mutation status and T790M is mandatory, additionally patients will be asked to consent to the optional exploratory research on already provided tumour sample. Unused tumour tissue samples will be stored for a period of 15 years unless it is requested to be repatriated. For further details, see the Laboratory Manual.

5.7.2 Collection of tumour biopsy samples at disease recurrence

Paraffin embedded tumour tissue will be collected at disease recurrence from patients who agreed with this optional assessment and if consent has been obtained for this research. These samples will be sent to a central laboratory on collection prior to being sent to the AstraZeneca or its designee for storage. These samples will be used for exploratory biomarker analyses. Samples collected from primary tumour or metastases will be accepted. The investigator will be asked to provide:

- Formalin-fixed, paraffin-embedded tumour tissue blocks, or
- 10 to 20 (a minimum of 10) re-cut unstained sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides. Each section is to be 5 µm thick.

Unused tumour tissue samples will be stored for a period of 15 years unless it is requested to be repatriated. For further details, see the Laboratory Manual.

5.7.3 Collection of plasma samples for analysis: blood-borne biomarkers and circulating deoxyribonucleic acid

All patients will be requested to provide a series of blood samples to generate plasma samples. These samples will be used for the extraction and analysis of ctDNA. The ctDNA will be used to explore the relationship between emergence and dynamic changes of EGFR mutation including T790M (as well as other known markers of TKI resistance) in ctDNA and time to disease recurrence. The samples will be analysed for a range of oncology biomarkers, which may correlate with drug response and/or disease recurrence or to enable diagnostic development.

The sample can be used for additional research and the patient will be asked to sign optional consent for these testing.

Plasma samples will be taken as described in the Study Plan (Table 1). Details on sample processing, handling, shipment, and storage are provided in the Laboratory Manual

5.7.4 Storage, re-use and destruction of biological samples

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

5.7.5 Labelling and shipment of biological samples

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

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

All tumour samples should be shipped at ambient temperature as per the Laboratory Manual directly to the testing laboratory. Tumour material for T790M testing may be sent to the AstraZeneca or its designee for storage prior to retrospective analysis.

5.7.6 Chain of custody of biological samples

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

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

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

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

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

5.7.7 Withdrawal of Informed Consent for donated biological samples

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

Where collection of the biological samples is an optional part of the study, then the patient may withdraw consent for the use of these samples and continue in the study.

The Principal Investigator:

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

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

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

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., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

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

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events in the eCRF

Adverse events will be collected from the time of signature of main informed consent throughout the Treatment Period and including the safety follow-up period. The safety follow-up period is defined as 28 days after study drug is discontinued. Serious AEs occurring in the safety follow-up period should be reported to AstraZeneca in the usual manner (see Section 6.4).

For each patient who discontinues study drug for any reason, but is still participating in the trial:

- Follow-up information on all ongoing AEs should continue to be collected during post-treatment follow-up.
- Serious AEs considered related to IP and study procedures must continue to be collected and reported to AstraZeneca using standard SAE timelines and process. All deaths must continue to be collected on the death eCRF page after disease recurrence and during the post – treatment follow up.

All serious or non-serious events of ILD/pneumonitis and cardiac failure, and all SAEs occurring in patients who are treated with open-label osimertinib must be collected and reported to AstraZeneca using standard timelines and process. Otherwise, non-serious AEs do not need to be reported for these patients who are being treated per label. Treating Investigators must follow instructions in package for this group of patients.

6.3.2 Follow-up of unresolved adverse events

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

6.3.3 Variables

The following variables will be collected for each AE:

- Adverse event (verbatim)
- The date when the AE started and stopped
- Changes in CTCAE grade (for skin reactions and diarrhoea only); maximum CTCAE grade for all other AEs
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Adverse event caused patient's withdrawal from study (yes or no)
- Outcome

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

- Date AE met criteria for serious SAE
- Date Investigator became aware of SAE
- Adverse event 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)
- Description of SAE

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

disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

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

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as 'yes.'

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

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: 'Have you/the child had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to the recording of a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

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

If deterioration in a laboratory value, vital sign, ECG, or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or other finding will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical, rather than the laboratory term (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).

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

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

6.3.7 Hy's Law

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

Details of identification of Hy's Law cases and actions to take are detailed in Appendix E.

6.3.8 Disease recurrence

Events, which are unequivocally due to disease recurrence, should not be reported as an AE during the study.

6.3.9 New cancers

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

6.3.10 Handling of deaths

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

- Death, which is unequivocally due to disease relapse and progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the eCRF module, but should not be reported as a SAE during the study.
- Where death is not clearly due to disease progression of the disease under study, the AE causing the death should be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.
- Deaths with an unknown cause should always be reported as a SAE, but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes.

6.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform 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 works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one 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 AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

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

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

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

If an investigator learns of any SAEs, including death, at any time and he/she considers there is a reasonable possibility that the event is related to AZD9291, the investigator should notify AstraZeneca representative. Such cases should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

6.5 Reporting of serious adverse events post final OS analysis

If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the IP, the investigator should notify AstraZeneca (see Section 6.4).

For patients who are treated with open-label osimertinib, SAEs will be collected as described in Section 6.3.

Following the completion of the study extension, any patients still on open-label osimertinib will be managed outside of the study per Section 7.3.3. At this point, any SAEs will be reported outside of the database, only reported as per Section 6.4 and Section 6.5.

6.6 Overdose

There is no definition of what constitutes an overdose. In the Phase I study, 355 subjects 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 overdoses should be recorded as follows:

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

If an overdose on an IMP or AstraZeneca NIMP occurs in the course of the study, the Investigator or other site personnel inform the appropriate AstraZeneca representatives 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 one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs, for overdoses associated with an SAE (Section 6.4) and within 30 days for all other overdoses.

6.7 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca during the study and within 6 weeks of the last dose of AZD9291.

6.7.1 Maternal exposure

If a patient becomes pregnant during the course of the study, IP 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 patient was discontinued from the study.

If any pregnancy occurs in the course of the study or within 6 weeks of the last dose of investigational product 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 (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.7.2 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.

To capture information about a pregnancy from the partner of a male patient, 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 IP dose and until 4 months after the last IP dose should be followed up and documented.

6.8 Medication error, drug abuse, and drug misuse

6.8.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, i.e., immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 6.4) and **within 30 days** for all other events.

6.8.2 Medication error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the subject received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g., medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, e.g., wrong route or wrong site of administration
- Drug not taken as indicated e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g., kept in the refrigerator when it should be at room temperature
- Wrong subject received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to subject (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed drug dose(s) e.g., forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication
- In open-label studies, even if an AZ product

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

6.8.3 Drug abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

6.8.4 Drug misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

6.9 Management of investigational product-related toxicities

Dose reduction levels for AZD9291 are provided in Table 6.

Table 6 Dose reduction levels

	AZD9291
Starting dose	80 mg AZD9291/matching placebo
Reduced dose	40 mg AZD9291/ matching placebo

6.9.1 General dose adjustments on adverse events

All patients to commence treatment at the starting dose level as shown in Table 6.

If a patient experiences a CTCAE grade 3 or higher or unacceptable toxicities lower grades not attributable to the disease or disease-related processes under investigation, where the Investigator considers the AE of concern to be specifically associated with the study drug 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 withholding AZD9291/matching placebo, study drug may be restarted at the same dose (starting dose) or reduced dose 40 mg AZD9291/matching placebo using the rules for dose modifications (Table 7) at the discretion of the investigator/ and with discussion and agreement with Study Physician if needed. If restarting at the same dose level, patients should be closely monitored for 3 days following the restart of treatment. If within 3 days there is recurrence of same toxicity, a dose reduction should be considered at the Investigator's discretion.

If the toxicity does not resolve to ≤CTCAE Grade 2 after 3 weeks of withholding AZD9291/matching placebo, then the patient can be withdrawn from the study treatment after discussion with the study medical monitor/physician and observed until resolution of the toxicity. There will be no individual modifications to treatment schedule in response to toxicity, only potential dose reduction or dose interruption.

Patients who receive open-label osimertinib will follow the approved local label for dose modification guidelines.

6.9.2 Skin reactions

It is recommended that all patients follow a program of sun protective measures while receiving study drug and for 3 to 4 weeks after discontinuing study drug.

The aim is to reduce the risk of development of skin reactions or minimise the severity of skin reactions and minimise the requirement for dose reduction of study drug. If a patient develops a skin reaction, a variety of agents can be used. These include mild to moderate strength steroid creams, either topical or systemic antibiotics, topical or systemic antihistamines, and retinoid creams, as deemed appropriate by the Investigator upon assessment of the skin reaction. Immediate symptomatic treatment should be provided.

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

- Changes in the characteristics of skin reactions will be collected in the "SKNREAC" eCRF.
- Changes in the CTCAE grade of skin reactions will be collected in the AE eCRF.
- Skin biopsies of skin reactions may be taken.

Erythema multiforme and Stevens-Johnson syndrome, and toxic epidermal necrolysis

Case reports of Erythema multiforme (EM) and toxic epidermal necrolysis (TEN) have been uncommonly reported, and Stevens-Johnson syndrome (SJS) have been rarely reported, in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of EM, TEN, and SJS. If signs and symptoms suggestive of EM develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. If signs and symptoms suggestive of SJS appear, osimertinib should be interrupted. Osimertinib should be discontinued immediately if SJS or TEN is diagnosed.

6.9.3 Aplastic anaemia

Rare reports of aplastic anaemia have been reported in association with osimertinib treatment. Some cases had a fatal outcome. Before initiating treatment, patients should be advised of signs and symptoms of aplastic anaemia including but not limited to persistent fever, bruising, bleeding, pallor. If signs and symptoms suggestive of aplastic anaemia develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. osimertinib should be discontinued in patients with confirmed aplastic anaemia.

6.9.4 Gastrointestinal toxicities

Nausea, vomiting, or both may be controlled with anti-emetic therapy.

Management of diarrhoea should be based on local clinical practice. Changes in CTCAE grade of diarrhoea will be captured in the AE eCRF.

6.9.5 QTc prolongation

In light of the potential for QT changes associated with AZD9291, electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) must be corrected to be within normal ranges prior to first dose and electrolyte levels monitored during study treatment.
Patients with QTcF prolongation to >500 msec should have study treatment interrupted and regular ECGs performed until resolution to <481 msec or recovery to baseline if baseline QTcF is ≥ 481 msec and then restarted at a reduced dose (40 mg) or at 80mg (at the discretion of the investigator). If the toxicity does not resolve to ≤ CTCAE grade 1 within 21 days the patient will be permanently withdrawn from study treatment.

If the toxicity does not resolve to Grade ≤1 within 21 days, the patient will be permanently withdrawn from study treatment.

Patients experiencing QTc interval prolongation with signs/symptoms of serious arrhythmia will not be permitted to restart study drug and it should be permanently discontinued.

6.9.6 Interstitial lung disease

If a new or worsening of pulmonary symptoms (e.g., dyspnoea) or occurrence of a radiological abnormality suggestive of ILD/pneumonitis is observed, an interruption in study drug dosing is recommended, and the Study Physician should be informed. It is strongly

recommended to perform a full diagnostic workup to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema, or pulmonary haemorrhage. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, haematological parameters) will be captured by eCRF. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered and study drug permanently discontinued. In the absence of a diagnosis of ILD, study drug may be restarted following consultation with the Study Physician.

Patients experiencing confirmed ILD/pneumonitis will not be permitted to restart study drug, which should be permanently discontinued.

6.9.7 Keratitis

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

6.9.8 Changes in cardiac contractility

Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and AZD9291has not been established. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

6.10 Study governance and oversight

6.10.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be convened and will meet approximately every 6 months for the first 2 years from the first patient randomised and approximately yearly thereafter. Further meetings for review of safety data may be convened at the discretion of IDMC. The IDMC will review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. Serious adverse events, adverse events, and other safety data will be reviewed, and individual and aggregated safety data will be evaluated by the IDMC. Furthermore, an IDMC will review the futility analysis outcomes and provide a recommendation for whether the study should continue. Full details of the IDMC procedures and processes can be found in the IDMC Charter.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product

AstraZeneca will supply AZD9291 as tablets for oral administration as a single daily dose of 80 mg.

Tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Bottles will be dispensed to patients in the AstraZeneca packing provided. The packaging includes bottles, caps, and a label. Bottle tampers should not be broken prior to dispensing the study drug to a patient.

Table 7 Identity of investigational products

Investigational product	Dosage form and strength
Test product	
AZD9291	40mg tablets 80mg tablets
Placebo	
AZD9291-matching placebo	NA

7.2 Dose and treatment regimens

Tablets can be taken whole with approximately 240 mL water, with or without regard to food.

Patients will be required to fast (water only) for at least 8 hours prior to the collection of a fasting glucose sample as per the Study Plan (See Table 1) and Section 5.2.1.

Study drug will be distributed as following:

- Randomisation – enough study drug for 1 month
- Week 4 visit – enough study drug for 2 months
- Week 12 visit onwards – enough study drug for 3 months

Individual bottles will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS.

Patients should swallow 1 tablet once daily, commencing on Day 1 but no later than within 2 days from randomisation day. Tablets should be taken whole with water.

The initial dose of AZD9291 80 mg once daily can be reduced to 40 mg once daily.

On site visit days on which PK samples are scheduled, the dosing should be delayed until arrival at the site. Patients should not take their dose until instructed to do so by site personnel.

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 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 study drug, they should not make up for this dose, but should take the next scheduled dose.

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

Additional information about AZD9291 may be found in the Investigator's Brochure.

7.3 Post study access to treatment

7.3.1 Patients receiving randomised study treatment

At the time of study analysis completion (final analysis per CSP v5.0), a number of patients may still be on study drug. These patients are to continue treatment until completion of the treatment duration, as long as, in the Investigator's opinion, they are gaining clinical benefit.

The treatment can be continued within the current study, and the following will apply:

- Assessment will revert to standard of care at particular site.
- There will be no further data collection except SAE reporting. Clinical Study Database would be closed.
- Paper form process will be used for SAE reporting. All SAEs, overdoses and pregnancies will be reported until 30 days after last dose.
- Study drug will be supplied to sites. Drug dispensation and reconciliation will be handled by site on each patient's visit.
- The study will be open until the last patient treated. Final Last Subject Last visit will be defined as the last patient's treatment discontinuation.

7.3.2 Patients receiving open-label osimertinib after recurrence

After the final OS analysis, AstraZeneca will continue to supply open-label osimertinib to patients receiving open-label osimertinib as long as, in the Investigator's opinion, the patient is gaining clinical benefit from active treatment. However, if osimertinib becomes available via commercial supply, where local regulations allow, patients should be switched from clinical study supplies to marketed product in those countries where it is approved for the disease under study.

7.3.3 Patients receiving open-label osimertinib post final OS analysis/during study extension for long-term OS analysis

After the final OS analysis, AstraZeneca will continue to supply open-label osimertinib to patients in both treatment arms as long as, in the Investigator's opinion, the patient is gaining clinical benefit from active treatment.

Patients are to be followed in accordance with the Medical SoC and as deemed appropriate by the investigators. It is recommended that investigators continue to observe ongoing patients at the frequency employed per protocol. Protocol dose modification and stopping criteria are to be followed while a patient is receiving osimertinib. A change in the dose/schedule of osimertinib should only occur for safety reasons, based on the Investigator's judgement, and should generally follow the approach for dose reduction and discontinuation as described in this protocol.

In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the Investigator. AstraZeneca will work with the Investigator to transition the patient(s) to alternative supply, where possible.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patient(s) currently receiving treatment with osimertinib may then be transitioned to such a study, and the current study would reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any patient who would be eligible to move to such a study would be given a new informed consent, as applicable.

7.4 Labelling

Labels 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, Study Code, For Clinical Trial use only, and/or any other market specific requirements.

7.5 Storage

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

7.6 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF. Reasons for dose interruption, reduction, or omission will also be recorded in the eCRF. This information plus drug accountability for all study drugs at every visit will be used to assess compliance with the treatment.

7.7 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 drug dispensed to and returned from the patient.

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

7.8 Concomitant and other treatments

Information on any treatment within the 4 weeks prior to initiation of study drug and all concomitant treatments given up to 28 days after discontinuation of study treatment, with reasons for the treatment, will be recorded in the eCRF. Thereafter, only subsequent regimens of anti-cancer therapy will be recorded in eCRF.

Please see Section 3.9 for restricted concomitant medications during the study.

Other anti-cancer therapies, investigational agents, and radiotherapy should not be given while the patient is on study drug.

Pre-medication will be allowed after, but not before, the first dose of study drug. This includes management of diarrhoea, nausea, and vomiting, which should be administered as directed by the Investigator.

Use of concomitant medications that may cause QTc prolongation (e.g., antiemetic) should be avoided (Appendix F).

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

7.8.1 Previous anti-cancer therapy

No prior anticancer therapy in preceding 5 years, including investigational therapy, with the exception of standard post-operative adjuvant chemotherapy for the treatment of NSCLC.

For patients who received post-operative adjuvant platinum-based chemotherapy, a minimum of 2 weeks must have elapsed but no more than 10 weeks from the last administered dose of chemotherapy to the date of randomisation.

If adjuvant platinum based chemotherapy is given, it is strongly recommended that this will be started within 8 weeks of surgery.

Patients who discontinue chemotherapy for toxicity prior to completion of all planned chemotherapy are eligible.

7.8.2 Other concomitant treatment

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

8. STATISTICAL ANALYSES

8.1 Statistical considerations

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalised around the time of first patient in (FPI). All analyses will be performed by AstraZeneca or its representatives.

A single, primary analysis was planned for this study, with a further analysis performed only if there are meaningfully less than 70 DFS events in the Stage IB population. The primary endpoint of DFS and secondary endpoint of OS will be tested in the subset of patients with stage IIA-IIIA cancer as well as in the overall population, therefore in order to strongly control the type I error at 5% (2-sided), a hierarchical testing procedure will be employed across these endpoints.

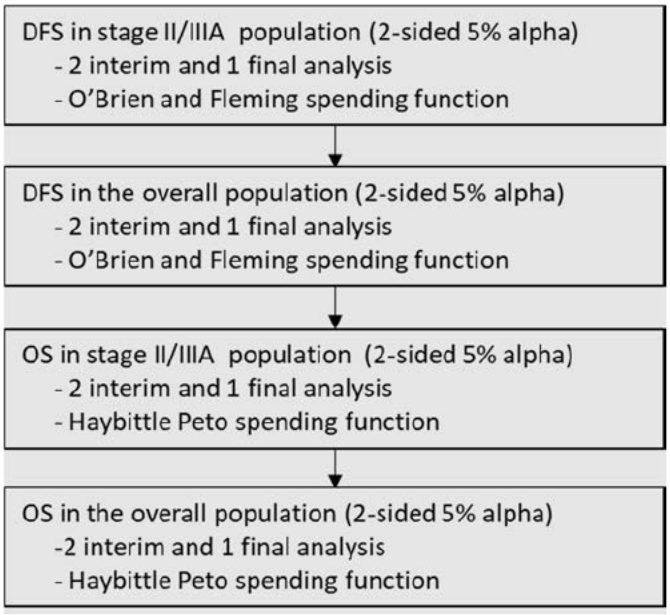
The primary analysis of DFS was planned to be conducted when approximately 247 disease recurrence events have been observed in approximately 490 patients who are in Stage IIA-IIIA (i.e., non-IB). If the DFS result is statistically significant at the 5% (2-sided) alpha level, DFS in the overall population will then be assessed.

For the overall population analysis, it is estimated that there will be approximately 317 DFS events in approximately 700 patients, i.e., approximately 70 events in the Stage IB subgroup. If, however, there are meaningfully less than 70 DFS events (defined as 63 DFS events or less) in the Stage IB subgroup at the time of the primary analysis, additional follow up of patients may be performed and a further analysis of DFS may be conducted when there are approximately 70 DFS events in the Stage IB subgroup. Results from any additional analyses will be reported as an addendum to the CSR.

If the DFS results in both the non-Stage-IB population and the overall population are statistically significant, OS will then be assessed in the stage II/IIIA population, and then in the overall population if statistical significance is reached in the stage II/IIIA population.

An unplanned interim analysis for superiority was conducted by the IDMC and therefore efficacy analysis has been conducted prior to approximately 247 DFS events occurring in the stage II-IIIA population. Given this, the interim analysis has been taken into account to control the type I error rate at 5% (2-sided) and the multiple testing procedure has been revised. Further details regarding the multiple testing strategy is provided in the SAP and presented in the Table 8 below.

Table 8 MTP diagram



An IDMC will review safety data on an ongoing basis and will conduct a futility analysis. Details of this analysis will be included in the statistical analysis plan and IDMC charter.

8.2 Sample size estimate

Approximately 700 patients will be randomised in a 1:1 ratio (AZD9291:Placebo) to this study. The primary endpoint of the study is DFS based on investigator assessment and will be assessed firstly in the stage II-IIIA population and then the overall population.

The primary analysis of DFS is planned to occur when approximately 247 disease recurrence events have been observed in approximately 490 patients who are in Stage IIA-IIIA (i.e., non-IB). If the true DFS hazard ratio (HR) for the comparison of AZD9291 versus placebo in this patient population is 0.70, 247 disease recurrence events will provide 80% power to demonstrate a statistically significant difference in DFS at a 5% 2-sided significance level (this could translate to an improvement in median DFS from 40 months to 57 months, assuming DFS is exponentially distributed). The minimum DFS HR that would be statistically significant ($p<0.05$, 2 sided) is 0.78.

If the true DFS HR for the comparison of AZD9291 versus placebo in the overall population is 0.70, 317 disease recurrence events will provide ~90% power to demonstrate a statistically significant difference (this could translate to an improvement in median DFS from 46 months to 66 months, assuming DFS is exponentially distributed).

At the time of the primary analysis (when approximately 247 DFS have been observed), it is anticipated that approximately 195 OS events (28% maturity) will have occurred (assuming a median OS of 96 months for the placebo arm). If the true OS HR for the comparison of AZD9291 versus placebo is 0.66, 195 death events provides approximately 80% power to

demonstrate a statistically significant difference. With 195 death events and assuming a true OS HR of 0.85 there is approximately 90% chance of observing a HR < 1.02.

Assuming 28 months non-linear recruitment, the data cut-off for the primary analysis is estimated to occur approximately 68-70 months after first patient randomised.

It is estimated that 3200 patients will be screened in order to randomise 700 patients.

8.3 Definitions of analysis sets

8.3.1 Efficacy analysis set

The full analysis set (FAS) will include all randomised patients. The full analysis set will be used for all efficacy analyses and treatment groups will be compared on the basis of randomised study treatment, regardless of the treatment actually received.

8.3.2 Safety analysis set

The safety analysis set (SAS) will consist of all patients who received at least one dose of study treatment. Safety data will not be formally analysed but summarised using the safety analysis set, according to the treatment received; i.e., erroneously treated patients (e.g., those randomised to treatment A but actually given treatment B) will be summarised according to the treatment they actually received.

8.3.3 PK analysis set

Pharmacokinetic Analysis Set is defined as patients in the FAS who have at least one measurable PK concentration, supported by the relevant date and time of this sample. For each time a PK sample was taken from a subject, the dosing data for that day and for multiple dosing, the dose date for the 2 days prior to the sample days must be available. For any individual sample from a subject to be included in the PK analysis set, the full sample data and dosing data need to be present for that sample/subject.

The pharmacokineticist will agree to the strategy for dealing with data affected by protocol deviations before any formal statistical analysis is performed. Important protocol deviations include changes to the procedures that may impact the quality of the data or any circumstances that can alter the evaluation of the PK. Examples include, but not limited to, vomiting following oral dosing occurring within the timeframe of 2 times the median t_{max}; sample processing errors that lead to inaccurate bioanalytical results; incomplete dose administered; incomplete PK profile collected; and/or use of disallowed concomitant medication. In the case of an important protocol deviation or event, affected PK data collected will be excluded from the summaries and statistical analyses, but will still be reported in the study result listings. Important deviations will be listed and summarised in the CSR.

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variables

8.4.1.1 DFS

DFS is defined as the time from the date of randomisation until the date of disease recurrence or death (by any cause in the absence of recurrence).

Patients who are disease-free and alive at the time of analysis will be censored at the date of their last follow-up assessment. The DFS time will always be based on scan/assessment dates and not visit dates. If assessments contributing towards a particular visit are performed on different dates, for example, a biopsy confirming disease recurrence following the scan where recurrence was suspected, the date of recurrence will be the earliest of the dates of the assessment that triggered the recurrence.

DFS rate at 2, 3, 4 and 5 years is defined as the proportion of patients alive and disease free at 2, 3, 4 and 5 years, respectively, estimated from Kaplan Meier plots of the primary endpoint of DFS at the time of the primary analysis.

8.4.1.2 OS

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

Note: Survival calls will be made in the week following date of DCO for IDMC and in the two weeks following date of DCO for primary analysis and subsequent analyses and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO. Death dates may be found by checking publicly available death registries.

OS rate at 2, 3, 4, and 5 years is defined as the proportion of patients alive at 2, 3, 4, and 5 years respectively, estimated from a Kaplan Meier plot of OS at the time of the primary analysis and any further timepoints. Long-term OS data captured in the long-term OS follow-up will be analysed as described in Section 8.8.

8.4.1.3 Progression-free survival (PFS) (exploratory)

PFS is defined as the time from the date of randomisation to the date of disease progression or death. Patients alive and for whom a disease progression has not been observed should be censored at the last time known to be alive and without a disease progression; i.e., censored at the last progression assessment date if the patient has not had a progression or death.

8.4.1.4 Time to first subsequent therapy or death (exploratory)

Time to first subsequent therapy (TFST) or death is defined as the time from the date of randomisation to the earlier of the date of anti-cancer therapy or procedure start date following

study drug discontinuation, or death. Any patient not known to have had a subsequent therapy/procedure or not known to have died at the time of the analysis will be censored at the last known time to have not received subsequent therapy; i.e., the last follow-up visit where this was confirmed.

8.4.1.5 Time to second subsequent, therapy or death (exploratory)

Time to second subsequent therapy (TSST) or death is defined as the time from the date of randomisation to the earlier of the date of second subsequent anti-cancer therapy or procedure start date following study drug discontinuation, or death. Any patient not known to have died at the time of the analysis and not known to have had a second subsequent therapy/procedure will be censored at the last known time to have not received second subsequent therapy, i.e., the last follow-up visit where this was confirmed.

8.4.1.6 Brain metastases

The number of patients developing brain metastasis during the study treatment will be summarised.

8.4.1.7 Health-related Quality of Life and symptoms

Subjects will complete a paper version of the SF-36 v2 questionnaire. The SF-36 v2 is a validated instrument for measuring a person's general health status (Ware et al, 1993) over the past 28 days. The SF-36 v2 includes 8 domains Physical Functioning (PF); Role Limitations-Physical (RP), Vitality (VT), General Health Perceptions (GH), Bodily Pain (BP), Social Function (SF), Role Limitations-Emotional (RE), and Mental Health (MH) and can be summarised into 2 summary scores, the Physical Component Summary (PCS) and Mental Component Summary (MCS). Final scores for each scale range from 0-100 with higher scores indicating better health. The general population has a mean score of 50 with a standard deviation of 10.

The absolute values and change from baseline will be calculated for each domain and summary scale at each post-baseline assessment.

8.4.1.8 Health Resource Use Module

The Health Resource Use Module will be assessed in terms of symptoms for admission and type of admission (planned/unplanned hospitalisation, outpatient visits, or emergency department visits).

8.4.2 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs (pulse and BP), ECG, LVEF, WHO performance status, and ophthalmologic assessment. These will be collected for all patients.

8.4.2.1 Adverse events

Adverse events (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by patient.

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

Any AE occurring within 28 days of discontinuation of study drug (i.e., the last dose of AZD9291/placebo) and prior to the start of a new anti-cancer treatment will be included in the AE summaries. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study drug) will be flagged in the data listings. Please refer to Section 6.3.1.

8.4.2.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs (pulse and BP)/ECG data will be performed for identification of OAEs.

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

8.4.3 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analysis of the plasma concentration data for AZD9291 and its metabolites will be performed by or on behalf of Quantitative Clinical Pharmacology (QCP), AstraZeneca.

Plasma concentrations will be listed and summarised by sampling interval in the CSR. The ratio of metabolite to AZD9291 will also be calculated and summarised.

Pharmacokinetic data from this study will be analysed using a population PK approach, which may include exploring the influence of covariates on PK, if the data allow. The data collected in this study may also be combined with similar data from other studies and explored using population PK and/or pharmacokinetic-pharmacodynamic methods. The results of any such analyses will be reported separately from the CSR.

8.5 Methods for statistical analyses

All efficacy analyses will be performed on the FAS population. Results of all statistical analyses will be presented using a 95% confidence interval (CI) and 2-sided p-value.

8.5.1 Analysis of the primary variable(s)

DFS in the subset of patients with stage II-IIIA cancer will be analysed using a log rank test stratified by stage (II, IIIA), mutation type (Ex19Del, L858R either alone or in combination with other EGFR mutations) and race (Asian, Non-Asian) for the generation of the p-value and using the Breslow approach for handling ties. DFS in the overall population will be analysed using a long rank test stratified by stage (IB, II, IIIA), mutation status (Ex19Del, L858R either alone or in combination with other EGFR mutations as confirmed by a central test) and race (Asian, Non-Asian) for the generation of the p-value. The hazard ratio and confidence interval will be obtained directly from the U and V statistics as follows (Berry et al 1991, Selke and Siegmund 1983):

$$HR = \exp(U/V)$$

$$95\%\ CI\ for\ HR = (\exp\{U/V - 1.96/\sqrt{V}\}, \exp\{U/V + 1.96\sqrt{V}\})$$

Where $U = \Sigma_i(d_{1i}-e_{1i})$ is the log-rank test statistic (with d_{1i} and e_{1i} the observed and expected events in group 1) and $\sqrt{V}$ the standard deviation of the log-rank test statistic obtained from the LIFETEST procedure with a STRATA term for the stratification variables.

A Kaplan-Meier (KM) plot of DFS will be presented by treatment group.

The assumption of proportionality will be assessed. In the event of non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up. Proportionality will be tested firstly by examining the plots of complementary log-log (event times) versus log(time) and, if necessary, a time-dependent covariate will be fitted to assess the extent to which this represents random variation.

Sensitivity analyses

(a) Quantitative interactions

The presence of quantitative interactions will be assessed by means of an overall global interaction test. This will be performed by comparing the fit of a Cox proportional hazards model including treatment, all covariates, and all covariate-by-treatment interaction terms, with one that excludes the interaction terms and will be assessed at the 2- sided 10% significance level. If the fit of the model is not significantly improved then it will be concluded that overall the treatment effect is consistent across the subgroups.

If the global interaction test is found to be statistically significant, an attempt to determine the cause and type of interaction will be made. Stepwise backwards selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This

approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

Any quantitative interactions identified using this procedure will then be tested to rule out any qualitative interaction using the approach of Gail and Simon 1985. (Gail and Simon 1985).

(b) Evaluation-time bias

In order to assess possible evaluation-time bias that could occur if scans are not performed at the protocol-scheduled time points, the midpoint between the time of recurrence and the previous evaluable assessment will be analysed using a log rank test stratified by stage, mutation status and race.

(c) Attrition bias

Possible attrition bias will be assessed by repeating the primary DFS analysis, except that the actual DFS times rather than the censored times of patients who recurred or died in the absence of recurrence immediately following 2 or more non-evaluable assessments, will be included. In addition, patients who take subsequent therapy prior to recurrence or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. A Kaplan-Meier plot of the time to censoring, where the censoring indicator of the primary DFS analysis is reversed, will be presented.

There is no prospective central radiology review planned for this study. A central review of equivocal cases by a review committee may be conducted. A retrospective radiology review of all cases may also be undertaken.

There is no prospective central pathology review planned for this study. A retrospective review may be undertaken.

Subgroup analyses

Subgroup analyses will be conducted by comparing DFS between treatments in the following groups:

- Stage (IB, II, IIIA)
- EGFR mutation type (Ex19Del, L858R either alone or in combination with other EGFR mutations)
- EGFR mutation status detectable in plasma-derived circulating tumour deoxyribonucleic acid (ctDNA) (Ex19Del, L858R)
- Pre-treatment T790M (amino acid substitution at position 790 in EGFR, from a threonine to a methionine) mutation status (Positive, Negative)
- Race (Asian, Non-Asian)
- Adjuvant chemotherapy (Yes, No)

- Gender (Male, Female)
- Age at randomisation (<65, ≥65)
- Smoking history (Never, Ever).

The Breslow approach for handling ties will be used for Cox regression model in subgroup analysis.

8.5.2 Analysis of the secondary variable(s)

8.5.2.1 DFS rate

Kaplan-Meier plots will be produced to assess if recurrence rates have reached an apparent plateau. Estimates of DFS rate at 2, 3, 4 and 5 years obtained from the plot will be presented for each arm. If the shape of the DFS curve suggests a plateau, a cure rate model may also be fitted. From this, estimates of cure can be made for each arm.

8.5.2.2 OS

OS data will be analysed using a log rank test stratified by stage (IB, II, IIIA), mutation type (Ex19Del, L858R either alone or in combination with other EGFR mutations) and race (Asian, Non-Asian) for the generation of the p-value and using the Breslow approach for handling ties. The hazard ratio and confidence interval will be obtained directly from the U and V statistics, as described in Section 8.5.1 (provided there are sufficient events available for a meaningful analysis (>20 deaths), if not descriptive summaries will be provided).

A Kaplan-Meier plot of OS will be presented by treatment group.

Additional exploratory analysis of overall survival adjusting for the impact of subjects randomised to placebo who subsequently receive an EGFR-TKI for sensitising mutations and T790M may be conducted if this treatment sequence occurs in a proportion of subjects. Methods such as Rank Preserving Structural Failure Time (RPSFT) (Robins and Tsiatis 1991), Inverse Probability of Censoring Weighting (IPCW) (Robins and Finkelstein 2000) and other methods in development may be explored. An OS analysis in centres where no access to a T790M directed EGFR-TKI may also be performed. The decision to adjust and final choice of methods will depend on the observed data and the plausibility of the underlying assumptions.

8.5.2.3 OS rate

OS rate at 2, 3, 4, and 5 years will be estimated for each arm from a Kaplan-Meier plot of OS.

8.5.3 Analysis of health-related quality of life

The scores for each of the 8 health domain scores and for each of the physical and mental component summary measures from the SF-36 v2 will be summarised in terms of mean changes from baseline at each post-baseline assessment.

8.5.4 Futility analysis

The IDMC will conduct a futility analysis. Further details will be documented in the IDMC Charter prior to the first DMC safety review meeting. An IDMC will review the futility outcomes and provide a recommendation for whether the study should continue, stop or be modified in some way. The IDMC will also review safety on an ongoing basis.

8.6 Impact of COVID-19

Depending on the extent of any impact, summaries of data relating to patients diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued IP, and other protocol deviations) may be generated. More detail will be provided in the SAP.

8.7 Further analysis post IDMC7

Following the recommendation of the IDMC after their 7th meeting, an interim analysis was conducted with a DCO of 17 January 2020 (Wu et al 2020). Please see Section 1.4 and text below for full details.

Given the study has been unblinded and reported earlier than planned, the following further analysis will be conducted.

DFS

An exploratory analysis of DFS in the stage II-IIIA population will be conducted when approximately 247 DFS events have been observed. At this time, an analysis of DFS in the overall population will also be conducted (exploratory in nature). If there are less than 63 DFS events in the stage IB population at this time, follow-up for DFS will continue and a further exploratory analysis in the overall population will be conducted when at least 63 DFS events have occurred in the stage IB patients. Safety data, TFST, TSST and PFS may also be reported at this time(s).

OS

The final OS analysis will be conducted when approximately 94 OS events have been observed in the stage II-IIIA population (approximately 20% maturity). At this time, the final OS analysis will also be conducted in the overall population. A further exploratory analysis of OS landmarks at 3, 4 and 5 years may be conducted after this final OS analysis. Safety data may also be reported at this time(s).

8.8 Long-term OS analysis - study extension

A long-term OS analysis from the time of randomisation until date of death due to any cause will be conducted to obtain long-term follow-up OS data. Overall survival data captured during the study extension (up to approximately 10 years after the last patient is randomised) will be analysed using the methods stated in Section 8.5.2.2 and Section 8.5.2.3 above, as

appropriate. The formal statistical analysis is complete and p-values will not be calculated for this follow-up analysis.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures and the EDC systems utilised.

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

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

9.2 Monitoring of the study

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

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, 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 eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts).
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The Principal Investigator at each/the site should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP 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 CSA shall prevail.

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

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

9.3 Study timetable and end of study definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

- European Union requirements define study completion as the last visit of the last subject for any protocol related activity.
- Food and Drug Administration requirements defines two completion dates:
  - Primary Completion Date – the date that the final patient is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.
  - Study Completion Date – the date the final patient is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

For patients who do not consent to the long-term OS follow-up, a patient is considered to have completed the study if they have completed all phases of the study including the last visit prior to the final OS analysis.

For patients who consent to the long-term OS follow-up, a patient is considered to have completed the study if they have completed all phases of the study including the last visit of the study extension (see Table 3).

The study extension for the long-term OS analysis is expected to end by Quarter 2, 2029.

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

9.4 Data management

Data management will be performed by PAREXEL (or alternate vendor) according to the Data Management Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by the Medical Coding Team at PAREXEL (or alternate vendor).

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

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

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

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

Serious adverse event reconciliation

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

Data management of genotype data

Any genotype data generated in this study will be stored in the AstraZeneca genotyping Laboratory Information Management System (LIMS) database, or other appropriate secure System within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research may be reported in the eCSR for the main study, or in a separate report as appropriate.

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

Data associated with human biological samples

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

10. ETHICAL AND REGULATORY REQUIREMENTS

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organisation but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

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/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

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

Details of patient data protection are detailed in Appendix D.

Personal data breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller[1] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The Investigator should have a process in place to ensure that:

- Allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- Have taken all necessary steps to avoid personal data breaches and
- Have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (e.g., applying encryption, maintaining and keeping systems and information technology security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- Where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- Where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

[1] The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission

Notification of personal Data Breach to participants:

- Notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.
- If a personal data breach involving an AstraZeneca's representative device (i.e., Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.

The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

10.3 Ethics and regulatory review

An Ethics Committee (EC)/IRB should 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. The Investigator will ensure the distribution of these documents to the applicable EC/IRB, and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca representative before enrolment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca representative should approve any modifications to the ICF that are needed to meet local requirements.

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

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

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

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

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

10.4 Informed consent

The Principal Investigator(s) at each study 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 provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed ICFs 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 EC/IRB.

10.5 Changes to the protocol and informed consent form

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

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

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

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

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

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

10.6 Regulatory reporting requirements for serious adverse events

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for SUSAR according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
    - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with other safety documents within the study site Trial Master File and will notify the IRB/IEC, if appropriate according to local requirements.

10.7 Regulatory reporting requirements for serious breaches

- Prompt notification by the investigator to the sponsor of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
    - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, the sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - The sponsor will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, the sponsor is required to enter details of serious breaches into the EMA CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
  - the site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach.
  - a (potential) serious breach is promptly reported to the sponsor or delegated party, through the contacts (e-mail address or telephone number) provided by the sponsor.

10.8 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC/IRB 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, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca representative immediately if contacted by a regulatory agency about an inspection at the study site.

10.9 Dissemination of clinical study data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on www.astrazenecaclinicaltrials.com, http://www.clinicaltrials.gov and https://euclinicaltrials.eu/ as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

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Clinical Study Protocol Appendix A	
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Appendix A
Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the 26 Aug 2015 and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

Clinical Study Protocol Appendix B	
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Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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 patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

Clinical Study Protocol Appendix C

Drug Substance	AZD9291
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Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

Clinical Study Protocol Appendix D	
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Appendix D
Pharmacogenetics Research

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AE	Adverse event
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
LIMS	Laboratory information management system
NSCLC	Non-small Cell Lung Cancer

1. BACKGROUND AND RATIONALE

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

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

2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence pharmacokinetics (PK [i.e, absorption, distribution, metabolism, excretion]) or response (i.e., safety and efficacy) to AZD9291 and/or susceptibility to development of cancers. This may also involve using the DNA genetic variation information to better identify tumor specific mutations.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

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

3.1.2 Inclusion criteria

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

3.1.3 Exclusion criteria

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

3.1.4 Discontinuation of patients from this genetic research

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

Withdrawal of consent for genetic research: Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 3.10 of the main Clinical Study Protocol.

3.2 Collection of samples for genetic research

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

For blood volume, see Section 5.2.1.1 of the Clinical Study Protocol.

3.3 Coding and storage of DNA samples

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

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

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

4. ETHICAL AND REGULATORY REQUIREMENTS

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

4.1 Informed consent

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

4.2 Patient data protection

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

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

5. DATA MANAGEMENT

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

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

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

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

7. LIST OF REFERENCES

Not applicable.

Clinical Study Protocol Appendix E	
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Appendix E
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

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1. INTRODUCTION

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

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

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

2. DEFINITIONS

Potential Hy's Law (PHL)

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

Hy's Law (HL)

An HL case is defined as a study patient with an increase in serum AST or ALT ≥ 3x ULN together with TBL ≥ 2xULN, where no other reason can be found to explain the combination of increases, e.g., 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 (.i.e., on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

- ALT ≥ 3xULN
- AST ≥ 3xULN

- TBL ≥ 2xULN

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

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

4. FOLLOW-UP

4.1 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.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

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

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

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

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

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

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

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

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

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

- If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF 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') by applying serious criteria and causality assessment as per above.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to

determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

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

This section is applicable to patients who meet PHL criteria on study treatment (including the 30 day follow-up period post discontinuation of study treatment) after 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 patient's 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 Section 4.2 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, and/or 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.

7. 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 Section 6?

If No: Follow the process described in Section 6 of this Appendix.

If Yes: Determine if there has been a significant change in the patient's condition compared with when PHL criteria were previously met.

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

A 'significant' change in the patient's condition refers to a 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, and/or 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.

8. REFERENCES

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

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

Clinical Study Protocol Appendix F	
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Appendix F
Guidance regarding Potential Interactions With Concomitant Medications

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LIST OF TABLES

GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

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

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

AZD9291 is metabolized 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 should not be used during this study for any patient receiving study treatment.

Table 1 Drugs inducing CYP3A4

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

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

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

AZD9291 may increase the concentration of sensitive BCRP and Pgp substrates (concentration of the sensitive BCRP substrate, rosuvastatin and sensitive Pgp substrate, fexofenadine, are increased).

Table 2 Exposure, pharmacological action and toxicity may be increased by AZD9291

Warning of possible interaction	Advice
Rosuvastatin Sulfasalazine Doxorubicin Daunorubicin Topotecan Dabigatran Aliskiren Digoxin	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.

3. DRUGS THAT PROLONG QT INTERVAL

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics on the CredibleMeds® website https://www.crediblemeds.org/. The website categorizes drugs based on the risk of inducing Torsade de Pointes (TdP). During screening, all drugs that patients are currently receiving (prescription and non-prescription) should be checked against the Arizona Center CredibleMeds® website. In addition, any drugs intended for use following study treatment initiation should be checked against the aforementioned website.

3.1 Drugs with a known risk of Torsades de Pointes

Drugs in this category are known to prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended.

3.1.1 Before commencing study treatment

Drugs in the category of known risk of TdP **must** have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in Table 3

3.1.2 During study treatment

It is recommended that drugs in the category of known risk of TdP are not co-administered with study treatment (AZD9291) and for a period of two weeks after discontinuing study treatment. However, if it is considered essential for patient clinical management to co-administer these drugs with study treatment (AZD9291) close monitoring with ECGs is recommended.

The list of drugs may not be exhaustive and is subject to changes as new information becomes available. As such, investigators are recommended to search the Arizona Center CredibleMeds® website (https://www.crediblemeds.org/**) to check the most up to date information**.

Table 3 Drugs with a known risk of TdP[a]

Drug name	Withdrawal period prior to AZD9291 start
Aclarubicin, Anagrelide, Ciprofloxacin, Clarithromycin, Cocaine, Droperidol, Erythromycin, Levofloxacin, Ondansetron, Papaverine hydrochloride, Procainamide, Sulpiride, Sultopride, Terfenadine Terlipressin	2 days
Cilostazol, Cisapride, Disopyramide, Dofetilide, Domperidone, Flecainide, Gatifloxacin, Grepafloxacin, Ibutilide, Moxifloxacin, Oxaliplatin, Propofol, Quinidine, Roxithromycin, Sevoflurane, Sotalol, Sparfloxacin, Thioridazine	7 days
Azithromycin, Bepridil, Citalopram, Chlorpromazine, Dronedarone, escitalopram, Fluconazole, Halofantrine, Haloperidol, Levomepromazine, Levosulpiride, Mesoridazine	14 days
Donepezil, Terodiline	3 weeks
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide[b], Ibogaine	6 weeks
Pentamidine	8 weeks
Astemizole, Probucol, Vandetanib	4 months
Amiodarone, chloroquine	1 year

a This list should be checked against the full and most current list presented in the CredibleMeds® website (https://www.crediblemeds.org/)

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

3.2 Other TdP risk Categories

Patients receiving drugs that prolong QT interval or may increase the risk of TdP from other TdP risk categories can be enrolled, notwithstanding other exclusions and restrictions, if these drugs are considered essential for patient management and the patient has been stable on therapy. Close monitoring with ECGs and electrolytes is recommended.
Patients with **congenital long QT syndrome (CLQTS) are excluded** from this study.

3.3 Guidance regardless of TdP risk category

During study treatment and for a period of two weeks after discontinuing study treatment if it is considered essential for patient management to co-administer drugs known to prolong QTc interval, **regardless of TdP risk category**, close monitoring with ECGs and electrolytes is recommended.

Clinical Study Protocol Appendix G	
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Appendix G
Patient Reported Outcomes

The content of pages 150-155 was rendered since it presents information under copyright protection - questionnaire SF-36.

Clinical Study Protocol Appendix H	
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Appendix H
DEFINITION OF WOMEN OF CHILDBEARING POTENTIAL AND ACCEPTABLE CONTRACEPTIVE METHODS.

Contents

1. DEFINITION OF WOMEN OF CHILDBEARING POTENTIAL

1.1 Women of Childbearing Potential (WoCBP):

Women between menarche and menopause who have not been permanently or surgically sterilised and are capable of procreation.

1.2 Women NOT of Childbearing Potential:

Women who are permanently or surgically sterilised or post-menopausal (definitions below):

Permanent sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. Tubal occlusion is considered a highly effective method of birth control but does not absolutely exclude possibility of pregnancy. (The term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).

- Women who have undergone tubal occlusion should be managed on trials as if they are of WoCBP (e.g. undergo pregnancy testing etc, as required by the study protocol).
- Women will be considered post-menopausal if they are amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
- Women under 50 years old will be considered post-menopausal 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.
- Women over 50 years of age will be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments.

2. ACCEPTABLE CONTRACEPTION METHODS

Highly effective method of birth control is defined in Note 3 in ICH Guidance M3 (Nonclinical Safety Studies for the conduct of Human Clinical trials for Pharmaceuticals) as one that results in a low failure rate (e.g. less than 1 percent per year) when used consistently and correctly.

Note that women should have been stable on their chosen method of birth control for a minimum of 2 weeks before entering the trial. Generic names and examples of trade names are given. As trade names may vary, investigators should check the generic name of any contraception to ensure suitability.

Acceptable contraception methods are:

- Total sexual abstinence (abstinence must be for the total duration of the trial and the follow-up period)
- Vasectomised sexual partner plus male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia)
- Tubal occlusion plus male condom
- Intra-uterine Device (IUD) - provided coils are copper-banded, plus male condom
- Intra-uterine system (IUS) Levonorgestrel Intra Uterine System (eg, Mirena), plus male condom
- Medroxyprogesterone injections (Depo-Provera) plus male condom
- Etonogestrel implants (eg, Implanon, Norplan) plus male condom
- Normal and low dose combined oral contraceptive pills, plus male condom
- Norelgestromin / ethinylestradiol transdermal system plus male condom
- Intravaginal device (eg ethinylestradiol and etonogestrel) plus male condom
- Cerazette (desogestrel) plus male condom. Cerazette is currently the only highly efficacious progesterone-based pill

3. UNACCEPTABLE CONTRACEPTION METHODS

The following methods are considered not to be highly effective and are therefore not acceptable contraceptive methods in AstraZeneca clinical trials:

- Triphasic combined oral contraceptives (COCs)
- All progesterone only pills except, Cerazette
- All barrier methods, if intended to be used alone
- Non-copper containing Intra-Uterine Devices (IUDs)
- Fertility awareness methods
- Coitus interruptus