Clinical Study Protocol

Drug Substance	Osimertinib (AZD9291)
Study Code	D5160C00036
Version	1.0

An Open-label, Non-randomised, Phase I Study to Assess the Effect of Single and Multiple Oral Doses of Osimertinib (TAGRISSO™)[1] on the Pharmacokinetics of a P-glycoprotein Probe Drug (Fexofenadine) in Patients with Advanced EGFRm NSCLC that have Progressed on a Prior EGFR-TKI Regimen

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

[1] TAGRISSO is a trade name of the AstraZeneca group of companies.

VERSION HISTORY

Version 1.0,
Initial creation

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

AstraZeneca

PROTOCOL SYNOPSIS

An Open-label, Non-randomised, Phase I Study to Assess the Effect of Single and Multiple Oral Doses of Osimertinib (TAGRISSO™) on the Pharmacokinetics of a P-glycoprotein Probe Drug (Fexofenadine) in Patients with Advanced EGFRm NSCLC that have Progressed on a Prior EGFR-TKI Regimen

International Co-ordinating Investigator

Study site(s) and number of patients planned

The study will be conducted at approximately 10 sites across Asia and Western Europe, with approximately 24 patients enrolled in order to achieve at least 18 evaluable patients.

Study period	Phase of development
Estimated date of first patient enrolled	I
Estimated date of last patient completed (pharmacokinetic [PK] phase)	

Study design

This is a Phase I, open-label, non-randomised, two-part study (PK phase and continued access) in patients with epidermal growth factor receptor (EGFR) mutation positive (EGFRm+) non-small cell lung cancer (NSCLC) who have progressed on an EGFR tyrosine kinase inhibitor (TKI). The PK phase will assess the effect of osimertinib on the PK parameters of fexofenadine following both single and multiple oral dosing of osimertinib.

Approximately 24 patients are planned to be enrolled in order to achieve at least 18 evaluable patients.

Continued access will allow patients to continue to take osimertinib tablets (80 mg once daily) as a single agent, after the PK phase (PK phase), if they and the Investigator agree that this is

appropriate. This will continue until the Investigator believes they are no longer deriving clinical benefit, or they stop taking osimertinib for any other reason. No clinical data will be collected during this phase other than sudden death of unknown reason, serious adverse events (SAEs) that may be related to osimertinib, outcomes of pregnancy and drug dispensing/accountability.

Patients not participating in continued access will return to the clinic for follow-up assessments 30 days (±7 days) after their last dose of osimertinib in the PK phase. If the patient's last dose of osimertinib is in continued access, the patient should be contacted 30 days after their last dose of osimertinib to follow-up any existing SAEs and monitor for new SAEs that may be related to the investigational product (IP).

Objectives

Primary Objective:	**Outcome Measure:**
To investigate the effect of osimertinib on the AUC and C_{max} of fexofenadine (a sensitive P-gp substrate) after both single and multiple osimertinib dosing	Fexofenadine AUC and C_{max} (alone and in combination with osimertinib)

AUC area under the plasma concentration time curve from zero to infinity; C_{max} maximum plasma concentration; P-gp P-glycoprotein.

Secondary Objective:	**Outcome Measure :**
To assess fexofenadine $AUC_{(0-t)}$, $t_{1/2\lambda z}$, t_{max}, CL/F and V_z/F in patients for fexofenadine administered alone and in combination with osimertinib	Fexofenadine t_{max}, AUC_{0-t}, CL/F,V_z/F, λ_z, $t_{1/2\lambda z}$ (alone and in combination with osimertinib)
To assess the PK of osimertinib and metabolites in combination with fexofenadine	Osimertinib and metabolites (AZ5104 and AZ7550): Single dose: AUC_{0-72}, C_{max}, t_{max}, and the metabolite ratio (AZ5104:osimertinib, AZ7550:osimertinib) MRC_{max}. Multiple dose: AUC_{tau}, $C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$ and CL_{ss}/F (osimertinib only). In addition, the metabolite ratios (AZ5104:osimertinib, AZ7550:osimertinib) $MRAUC_{tau}$ and $MRC_{ss,max}$. Trough concentrations on D11, D18, D25, and D32 for osimertinib and metabolites

AZ5104 and AZ7550 are metabolites of osimertinib

AUC area under the plasma concentration-time curve from zero extrapolated to infinity; AUC_{0-72} area under plasma concentration-time from time zero to 72 hours post-dose; AUC_{0-t} area under plasma concentration-time from time zero to the last quantifiable concentration; AUC_{tau} area under plasma concentration-time from time zero to the end of the dosing interval; CL/F apparent plasma clearance following oral administration; CL_{ss}/F apparent plasma clearance at steady state; C_{max} maximum plasma concentration; $C_{ss,max}$ maximum plasma concentration at steady state; $C_{ss,min}$ minimum plasma concentration over the dosing interval; $MRAUC_{tau}$ metabolite-parent ratio of AUC_{tau}; MRC_{max} metabolite-parent ratio of C_{max}; $MRC_{ss,max}$ metabolite-parent ratio of $C_{ss,max}$; λ_z terminal rate constant; $t_{1/2\lambda z}$ terminal half-life; t_{max} time to C_{max}; $t_{ss,max}$ time to $C_{ss,max}$; V_z/F apparent volume of distribution.

Safety Objective:	**Outcome Measure :**
To investigate the safety and tolerability of osimertinib when administered in combination with fexofenadine in NSCLC patients	AEs/SAEs graded by Common Terminology Criteria for Adverse Events (CTCAE) (Version 4) Vital signs (blood pressure /pulse/temperature/height/weight) Laboratory parameters (clinical chemistry/haematology/urinalysis) Physical examination Ophthalmology Standard 12-lead electrocardiograms (ECGs) Echocardiogram/multiple gated acquisition scan (MUGA)

Exploratory Objective:	**Outcome Measure :**
To provide data to allow analysis using population PK approaches	Population PK analyses for C_{max}, AUC and other PK parameters as appropriate. Population PK analyses, if conducted, will be reported separately from the CSR.
To collect optional plasma samples for deoxyribonucleic acid (DNA) extraction and storage to enable an investigation into the impact of host polymorphisms of (ADME)-related genes on the absorption, distribution, metabolism and excretion of osimertinib	

Target patient population

Male and female patients aged 18 years or over with advanced EGFRm+ NSCLC who have progressed on prior therapy with an approved EGFR-TKI agent. Patients must have confirmation of histological or cytological NSCLC and Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1.

Duration of treatment

The PK phase consists of a 4-week screening period followed by an approximately 7-week treatment period. The PK phase is further divided into 2 treatment periods which are separated by a 3 to 7 day washout period between fexofenadine doses. During Treatment Period 1, patients will receive a single oral dose of fexofenadine on Day 1. Following a washout period at the end of Treatment Period 1, patients will enter Treatment Period 2. On Day 1 of Treatment Period 2 (Visit 6), each patient will receive a single oral dose of osimertinib 80 mg in combination with a single oral dose of fexofenadine (note that Treatment Period 2 re-starts with "Day 1"). Patients will then receive osimertinib 80 mg once daily from Day 4 to Day 41 inclusive. In addition, patients will receive a single oral dose of fexofenadine on Day 39 (Treatment Period 2).

On completion of the PK phase, patients may continue to take osimertinib tablets as a single agent (continued access phase) if they and the Investigator agree that this is appropriate. Patients should enter the continued access phase immediately on Day 42 after collections of the 72-hour fexofenadine sample (ie, approximately 24 hours after the last dose of osimertinib received in the PK phase) and will receive osimertinib 80 mg once daily for the duration of their participation.

Investigational product, dosage and mode of administration

Osimertinib 80 mg administered orally as a tablet formulation and fexofenadine hydrochloride 120 mg administered orally as a tablet formulation as follows:

In Treatment Period 1: on Day 1 a single dose of fexofenadine hydrochloride 120 mg will be administered fasted from at least 1 hour before dosing to at least 1 hour after dosing.

There will be a 3- to 7-day washout period between the first dose of fexofenadine administered in Treatment Period 1 and the first dose administered in Treatment Period 2.

In Treatment Period 2: on Day 1 a single dose each of osimertinib 80 mg and fexofenadine hydrochloride 120 mg, will be administered (at the same time) fasted from at least 1 hour before dosing to at least 1 hour after dosing.

On Day 4 after the 72 hour sample collection, patients will commence daily dosing with osimertinib 80 mg. Patients will receive once daily treatment with osimertinib 80 mg through Day 38; osimertinib can be administered with or without food, and should be taken at the same time every day.

On Day 39 (±3 days), osimertinib 80 mg and fexofenadine hydrochloride 120 mg will be administered (at the same time) fasted from at least 1 hour before dosing to at least 1 hour after dosing. Once daily osimertinib administration will continue for 2 additional days through Day 41 (±3 days), which can be administered with or without food, and should be taken at the same time every day.

In continued access: osimertinib 80 mg once daily can be administered with or without food.

Statistical methods

Plasma concentrations of osimertinib, AZ5104, AZ7550, fexofenadine and the derived PK parameters will be summarised by treatment using descriptive statistics and displayed graphically as appropriate.

To assess the effect of osimertinib on the PK of fexofenadine, natural log-transformed C_{max} and AUC (or AUC_{0-t}, if AUC is not adequately estimable) will be analysed separately and compared between treatments using a linear mixed effects model, with treatment as a fixed effect and patient as a random effect. The following comparisons will be performed:

- Fexofenadine and osimertinib single doses (Treatment Period 2 Day 1) versus fexofenadine single dose (Treatment Period 1).

- Fexofenadine single dose and osimertinib at steady state (Treatment Period 2 Day 39) versus fexofenadine single dose (Treatment Period 1).

Estimates of the mean difference between treatments and corresponding confidence intervals (CIs) will be calculated. The mean differences and the CIs will be back-transformed to the original scale in order to give estimates of the ratios and the associated 90% CIs. Additionally, back-transformed geometric means together with 95% CIs for AUC and C_{max} will be estimated and presented for treatment.

Furthermore, for fexofenadine, analyses of t_{max} will be performed using the Wilcoxon Signed Rank Test. The Hodges-Lehmann median estimator of the difference in treatments (fexofenadine plus osimertinib –fexofenadine alone) and 90% CIs will be presented.

Steady state of osimertinib and its metabolites will be assessed graphically.

Safety data will be listed and summarised using descriptive statistics.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
λ_z	Terminal rate constant
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AUC	Area under plasma concentration-time curve from zero to infinity
AUC_{0-t}	Area under plasma concentration-time curve from time zero to the last quantifiable time point
AUC_{tau}	Area under plasma concentration time curve during the dosing interval
AUC_{0-72}	Area under plasma concentration-time curve from time zero to 72 hours post-dose
BCRP	Breast cancer resistance protein
BP	Blood pressure
CI	Confidence interval
CL/F	Apparent plasma clearance following oral administration
CL_{ss}/F	Apparent plasma clearance following oral administration at steady state
C_{max}	Maximum plasma drug concentration
$C_{ss,max}$	Maximum plasma concentration at steady state
$C_{ss,min}$	Minimum plasma concentration at steady state
CRF	Case Report Form (electronic/paper)
CRO	Contract Research Organisation
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event

Abbreviation or special term	Explanation
%CV	Coefficient of variation
DAE	AE leading to discontinuation of IP
DDI	Drug-drug interaction
DILI	Drug-Induced Liver Injury
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EGFRm+	activating mutations in EGFR
EGFR-TKI	EGFR-tyrosine kinase inhibitor(s)
FSH	Follicle-stimulating hormone
%GCV	Percent geometric coefficient of variation
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
IATA	International Airline Transportation Association
IB	Investigator Brochure
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
INR	International normalised ratio
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational product
IUD	Intrauterine device
LH	Luteinizing hormone
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
MR	Metabolite to parent ratio
MUGA	Multiple gated acquisition scan
NSCLC	Non-small cell lung cancer
OAE	Other significant AE(s)
PK	Pharmacokinetic(s)
P-gp	P-glycoprotein
PHL	Potential Hy's law
PI	Principal Investigator
PXR	Pregnane X receptor
QTcF	QT interval corrected for heart rate using Fridericia's correction factor
SD	Standard deviation
$t_{½\lambda z}$	Terminal half-life
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
t_{max}	Time to reach maximum plasma concentration
$t_{ss,max}$	Time to reach maximum plasma concentration at steady state
ULN	Upper limit of normal
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
V_z/F	Apparent volume of distribution
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Investigators should be familiar with the current osimertinib (TAGRISSO™ [2]; AZD9291) Investigator Brochure (IB).

Lung cancer has been the most common type of cancer in the world for several decades, and by 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths (18.2% of the total) (Ferlay et al 2010). Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis approximately 70% of NSCLC patients already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of early stage NSCLC patients who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer (Pisters and Le Chevalier 2005). Patients presenting with unselected advanced NSCLC have a median overall survival of 10 to 12 months (Bonomi 2010).

Treatment of advanced NSCLC can be guided by the presence of certain molecular drivers such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase and KRAS mutations. EGFR tyrosine kinase inhibitors (TKIs) are now the established first line therapy in patients with NSCLC known to have activating mutations in EGFR (EGFRm+)(NCCN 2012). Patients with EGFRm+ NSCLC who receive EGFR-TKIs have a median overall survival of more than 2 years (Heuckmann et al 2012). The incidence of EGFRm+ NSCLC is approximately 10% to 15% and 30% to 40% of patients in the West and Asia, respectively. Second line therapy for EGFRm+ NSCLC is usually a platinum based chemotherapy.

Unfortunately, acquired TKI resistance ultimately develops in the vast majority of patients with advanced EGFR mutation-positive NSCLC and progression generally occurs within 1 year. Although multiple mechanisms are involved, in approximately 60% of patients, the acquired resistance involves the emergence of an EGFR second-site point mutation that results in substitution of threonine with methionine at amino acid position 790 in exon 20 of EGFR (EGFR T790M; Su et al. 2012, Travis et al. 2011). This mechanism is considered to be a major route of development of resistance to the EGFR-TKI class of therapy (Herbst et al. 2008, Pao et al. 2005, Su et al. 2012, Yu et al. 2013). Survival rates of patients with advanced EGFR mutation-positive NSCLC who progress following treatment with EGFR-TKI is low, with a median OS of approximately 12 months (Fukuoka et al. 2011, Wang et al. 2012, Wu et al. 2010).

Treatment with platinum-based doublet chemotherapy is associated with significant toxicity (eg, nausea; vomiting; bone marrow suppression resulting in high risk of infection and

[2] TAGRISSO is a trade name of the AstraZeneca group of companies.

bleeding; alopecia; fatigue; and peripheral neuropathy), supporting the importance of finding new treatment options that are efficacious and better tolerated in this patient population.

Current NCCN guidelines include osimertinib as one of the treatments for second-line and later-line EGFR T790M mutation-positive NSCLC (NCCN 2016).

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

In vitro studies have shown that osimertinib has the potential to act as an inhibitor and inducer of the CYP3A4 metabolic pathway. An initial study with simvastatin as the probe CYP3A4 substrate showed 9% and 23% decrease of the area under plasma concentration-time curve from zero to infinity (AUC) and maximum plasma concentration ($C_{max)}$ of simvastatin. The lower bound of the 90% confidence interval (CI) of the decrease in C_{max} was below the no effect limit. Since osimertinib is both an inhibitor and an inducer of CYP3A4, the effect on CYP3A4 may not be translated to other pregnane X receptor (PXR) substrates (such as P-gp). Based on the request of the EMA and in accordance of the EMA guidelines on drug-drug interaction (DDI) evaluation (EMA 2012), a study on a non-CYP3A4 mediated probe PXR substrate will therefore provide clear evidence of the potential for osimertinib to be a perpetrator of DDI mediated by PXR activation. Hence, the current study has been designed to investigate the effect of osimertinib on the pharmacokinetics (PK) of fexofenadine, a known P-gp substrate. The results will support classification of the potency of osimertinib as an inhibitor or inducer of PXR pathway and will support labelling statements around the use of non-CYP3A4 mediated PXR substrates.

In the US, osimertinib received accelerated approval from the Food & Drug Administration (FDA) on 13 November 2015 for use in the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as determined by an FDA-approved test, after disease has progressed on or after EGFR-TKI therapy. This indication was approved based on tumour response rate and duration of response. Continued approval for this indication is contingent upon verification and description of clinical benefit in confirmatory trials. On 02 February 2016, osimertinib was granted conditional approval in the European Union for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation positive NSCLC. In Japan, osimertinib obtained full approval on 28 March 2016 from the

Japanese Ministry of Health, Labour and Welfare (MHLW) for treatment of patients with EGFR T790M mutation-positive inoperable or recurrent NSCLC that is resistant to EGFR-TKI therapy. Osimertinib was approved in Israel on 5 May 2016 for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR-TKI therapy. Osimertinib was approved in South Korea on 19 May 2016 for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have been previously treated with EGFR-TKI therapy.

1.2 Rationale for study design, doses and control groups

This two-part study will allow the impact of orally-dosed osimertinib on the PK of fexofenadine to be characterised, and will provide information on the potential DDI between fexofenadine and osimertinib:

- The PK phase will assess the effect of osimertinib on the PK parameters of fexofenadine following both single and multiple oral dosing of osimertinib.

- Continued access will allow patients who have completed the PK phase to receive a therapeutic dose of osimertinib on a continuous basis and therefore possibly gain clinical benefit.

A sequential design has been chosen for the PK phase as a substantial washout between treatments would be required in a randomised cross-over design which is not medically appropriate for the patient population participating in this study.

The rationale for the doses of study treatments chosen are as follows:

- Osimertinib 80 mg once daily will deliver exposure that has been previously demonstrated to be acceptable and tolerated in patients with cancer, and is the dose approved for use in this patient population.

- Fexofenadine hydrochloride 120 mg once daily is a typical dose used clinically and has previously been utilised in DDI studies.

The initial comparison of single dose fexofenadine data obtained on Day 1 of Treatment Period 2, when given with a single dose of osimertinib, will exclusively assess the potential of osimertinib to inhibit P-gp. Osimertinib will be subsequently dosed to steady state in order to determine its overall impact on a change in P-gp activity, if any, as inducer or inhibitor of P-gp. Osimertinib and its metabolites reach steady-state in plasma by 21 days of dosing. An additional 10-11 days of dosing will ensure that the PXR activated P-gp enzymes reach steady state. Hence, a minimum of 32 days of osimertinib dosing is utilized in this study. Fexofenadine exhibits linear pharmacokinetics. A single dose of fexofenadine given under each of the 2 concomitant osimertinib conditions compared to a single dose of fexofenadine given alone should be sufficient to evaluate a potential inhibitory effect of osimertinib on P-gp (Day 1 of Treatment Period 2) and potential induction of P-gp by osimertinib (Day 39, Treatment Period 2), if any.

Patients with cancer are required for this study because pre-clinical toxicology data preclude the use of osimertinib in healthy volunteers with multiple dosing. This study requires osimertinib to be at steady state to maximise the likelihood of seeing an effect on fexofenadine PK.

Safety and tolerability data will be collected as per regulatory and ethical guidelines and will expand the safety/tolerability database for patients with EGFRm+ NSCLC treated with oral osimertinib tablets.

1.3 Benefit/risk and ethical assessment

This study is robustly designed to assess the primary objective while minimising the number of patients exposed to osimertinib. Osimertinib demonstrates acceptable benefit-risk profile in patients with NSCLC as evidenced by its approval from the regulatory agencies in US, EU, Japan, Israel and South Korea. Clinical tolerability data from patients indicate that osimertinib is generally well tolerated by patients with advanced cancer (please refer to Section 1.3 of the IB for details). Importantly, data from a Phase I study (D5160C00001) in this patient population has demonstrated osimertinib to be well tolerated, with good evidence of efficacy. All studies of osimertinib exclude patients with clinically significant toxicities related to prior treatments in addition to specifically excluding patients with a history of interstitial lung disease (ILD) or clinically active ILD as this is an uncommon but well documented EGFR related toxicity. All patients are assessed for known EGFR related toxicities and detailed information on the management of toxicities related to investigational product (IP) is provided for all osimertinib studies (Section 6.7). Possible side-effects of using fexofenadine include, but are not limited to: headache, drowsiness, dizziness, nausea, fatigue, hypersensitivity reactions (with manifestations such as angioedema, chest tightness, dyspnoea, flushing and systemic anaphylaxis), insomnia, nervousness, sleep disorders or nightmares/excessive dreaming (paroniria), tachycardia, palpitations, diarrhoea, rash, urticarial and pruritus.

All adverse events (AEs), vital signs, electrocardiograms (ECGs) and laboratory data will be collected and reviewed by the clinical study team on an ongoing basis.

Although patients may not benefit from fexofenadine, there may be some benefit gained from osimertinib. Further benefit may be gained during continued access. If the Investigator believes it is in the patient's interest, the patient may continue treatment with osimertinib until such time as the Investigator believes they are no longer deriving clinical benefit or they stop taking osimertinib for any other reason.

In addition to the potential effect on P-glycoprotein (P-gp), clinical studies indicate that osimertinib inhibits the breast cancer resistance protein (BCRP) transporter. Also, exposure of osimertinib is decreased when co-administered with strong CYP3A inducers. Measures have been taken in this protocol to provide appropriate restrictions and/or direction for use of concomitant medications which are substrates for these metabolising enzymes or transporters.

The data generated from this study will support labeling of osimertinib for appropriate use in patients with NSCLC. The overall risk for the patients who participate in this study to assess how co-administration of osimertinib affects the PK of fexofenadine is acceptable.

1.4 Study Design

This is a Phase I, open-label, non-randomised, two-part study in patients with EGFRm+ NSCLC who have progressed on an EGFR-TKI.

The PK phase will assess the effect of osimertinib on the PK parameters of fexofenadine following both single and multiple oral dosing of osimertinib.

Continued access will provide patients with further access to osimertinib after the PK phase.

The study will be conducted at approximately 10 sites across Asia and Western Europe, with approximately 24 patients enrolled in order to achieve at least 18 evaluable patients. Additional patients may be dosed to ensure the minimum number of evaluable patients. For full details of the study plan and timing of procedures, see Section 4.

PK phase

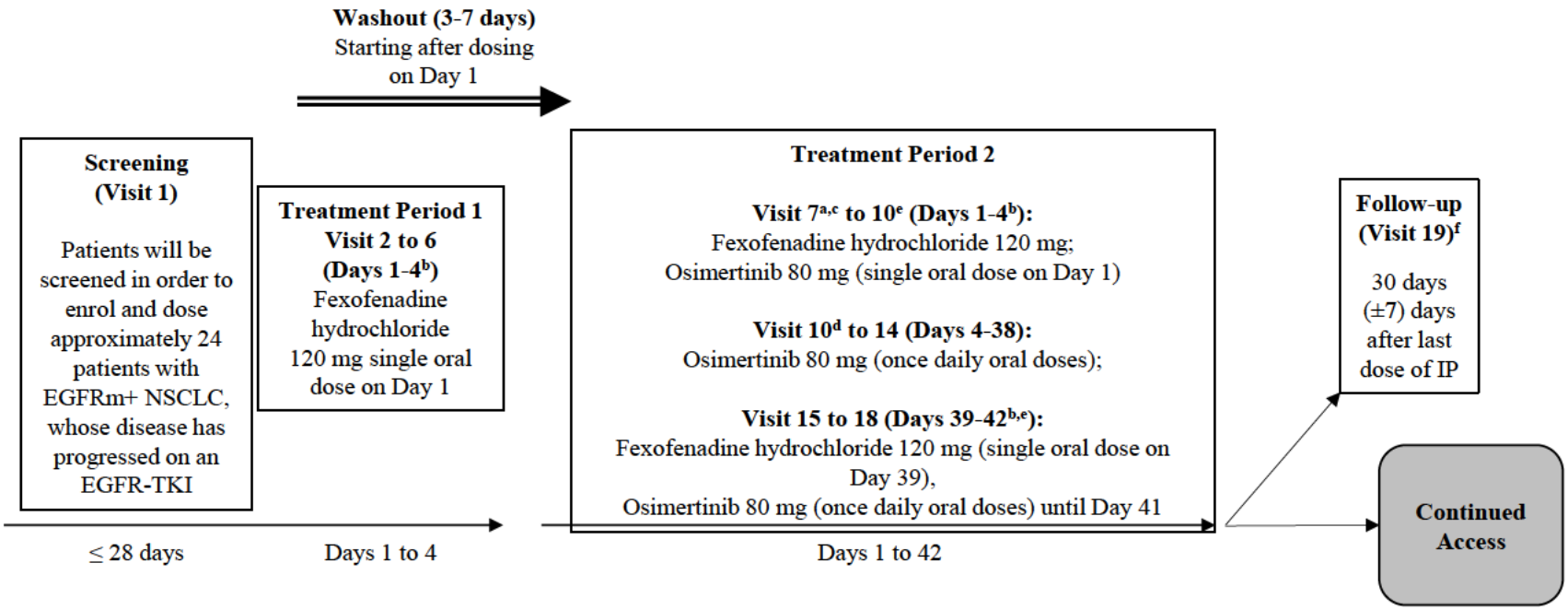
The PK phase is a non-randomised, open-label, 2-period design. Treatment Period 1 and Treatment Period 2 are separated by a 3 to 7 day washout period between doses. A study flow chart for the PK phase is presented in Figure 1. Patients will receive osimertinib 80 mg as a single dose on Day 1 of Treatment Period 2, then 80 mg once daily for 38 days (from Day 4 to Day 41 in Treatment Period 2). Patients will also receive a single oral dose of fexofenadine on Day 1 in Treatment Period 1, and on Days 1 and 39 in Treatment Period 2.

Continued access

On completion of the PK phase (ie, following collection of the 72-hour fexofenadine sample on Day 42), patients may continue to take osimertinib tablets (80 mg once daily) as a single agent in continued access if they and the Investigator agree that this is appropriate. This will continue until the Investigator believes they are no longer deriving clinical benefit, or they stop taking osimertinib for any other reason. No clinical data will be collected during this phase other than sudden death of unknown reason, serious adverse events (SAEs) that may be related to osimertinib, outcomes of pregnancy and drug dispensing/accountability.

If a patient discontinues treatment during the PK phase, they will return to the clinic for follow-up assessments 30 days (±7 days) after their last dose of treatment in the PK phase. If the patient's last dose of osimertinib is in continued access, the patient should be contacted 30 days after their last dose of osimertinib to follow-up any existing SAEs, monitor for new SAEs that may be related to the IP, and record any sudden deaths of unknown cause.

Figure 1 Study flow chart



[a] Visit 7 procedures may start on the day of Visit 6 or up to 4 days after Visit 6.
[b] Blood samples will be collected for 72 hours after fexofenadine administration.
[c] Treatment may commence immediately after the 72 hour blood collection on Day 4 of Treatment Period 1, or an interval of up to 3 additional days may be included; the washout may not exceed 7 days between fexofenadine doses. In Treatment Period 2, from Day 4 (after the 72 hour blood collection, if applicable) until Day 41, patients will receive a daily dose of osimertinib 80 mg.
[d] Osimertinib dosing starts on Day 4 after collection of the 72-hour blood samples.
[e] Osimertinib 80 mg plus fexofenadine hydrochloride 120 mg administered together on Day 39, followed by osimertinib for 2 additional days. Final fexofenadine blood sample will be collected at 72 hours (on Day 42).
[f] For patients who withdraw from the study prematurely and do not go onto continued access.

EGFR epidermal growth factor receptor; EGFRm+ Activating mutations in EGFR; EGFR-TKI EGFR-tyrosine kinase inhibitor(s)

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To investigate the effect of osimertinib on the AUC and C_{max} of fexofenadine (a sensitive P-gp substrate) after both single and multiple osimertinib dosing	Fexofenadine AUC and C_{max} (alone and in combination with osimertinib)

AUC area under the plasma concentration time curve from zero to infinity; C_{max} maximum plasma concentration; P-gp P-glycoprotein.

2.2 Secondary objectives

Secondary Objective:	Outcome Measure :
To assess fexofenadine $AUC_{(0-t)}$, $t_{1/2\lambda z}$, t_{max}, CL/F and V_z/F in patients for fexofenadine administered alone and in combination with osimertinib	Fexofenadine t_{max}, AUC_{0-t}, CL/F,V_z/F, λ_z, $t_{1/2\lambda z}$ (alone and in combination with osimertinib)
To assess the PK of osimertinib and metabolites in combination with fexofenadine	Osimertinib and metabolites (AZ5104 and AZ7550): Single dose: AUC_{0-72}, C_{max}, t_{max}, and the metabolite ratio (AZ5104:osimertinib, AZ7550:osimertinib) MRC_{max}. Multiple dose: AUC_{tau}, $C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$ and CL_{ss}/F (osimertinib only). In addition, the metabolite ratios (AZ5104:osimertinib, AZ7550:osimertinib) $MRAUC_{tau}$ and $MRC_{ss,max}$. Trough concentrations on D11, D18, D25, and D32 for osimertinib and metabolites

AZ5104 and AZ7550 are metabolites of osimertinib

AUC area under the plasma concentration-time curve from zero extrapolated to infinity; AUC_{0-72} area under plasma concentration-time from time zero to 72 hours post-dose; AUC_{0-t} area under plasma concentration-time from time zero to the last quantifiable concentration; AUC_{tau} area under plasma concentration-time from time zero to the end of the dosing interval; CL/F apparent plasma clearance following oral administration; CL_{ss}/F apparent plasma clearance at steady state; C_{max} maximum plasma concentration; $C_{ss,max}$ maximum plasma concentration at steady state; $C_{ss,min}$ minimum plasma concentration over the dosing interval; $MRAUC_{tau}$ metabolite-parent ratio of AUC_{tau}; MRC_{max} metabolite-parent ratio of C_{max}; $MRC_{ss,max}$ metabolite-parent ratio of $C_{ss,max}$; λ_z terminal rate constant; $t_{1/2\lambda z}$ terminal half-life; t_{max} time to C_{max}; $t_{ss,max}$ time to $C_{ss,max}$; V_z/F apparent volume of distribution.

2.3 Safety objectives

Safety Objective:	Outcome Measure :
To investigate the safety and tolerability of osimertinib when administered in combination with fexofenadine in NSCLC patients	AEs/SAEs graded by CTCAE (Version 4) Vital signs (blood pressure /pulse/temperature/height/weight) Laboratory parameters (clinical chemistry/haematology/urinalysis) Physical examination Standard 12-lead ECGs Ophthalmology Echocardiogram/multiple gated acquisition scan (MUGA)

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measure :
To provide data to allow analysis using population PK approaches	Population PK analyses for C_{max}, AUC and other PK parameters as appropriate. Population PK analyses, if conducted, will be reported separately from the CSR.
To collect optional plasma samples for deoxyribonucleic acid (DNA) extraction and storage to enable an investigation into the impact of host polymorphisms of (ADME)-related genes on the absorption, distribution, metabolism and excretion of osimertinib	

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

Each patient 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 patients should fulfil the following criteria:

1. Provision of signed and dated, written informed consent prior to any study specific procedures, sampling and analyses. Procedures performed for routine clinical practice up to 2 weeks before the provision of written consent are acceptable if not intentionally done for study purposes.

2. Male or female, aged ≥18 years

3. Histological or cytological confirmation diagnosis of NSCLC

4. Radiological documentation of disease progression while receiving previous continuous treatment with an EGFR-TKI eg, afatinib, gefitinib or erlotinib. In addition, other lines of therapy may have been given. All patients must have documented radiological progression on the last treatment administered prior to enrolling in the study.

5. Confirmation that the tumour harbours an EGFR mutation known to be associated with EGFR-TKI sensitivity (eg, G719X, exon 19 deletion, L858R, L861Q).

6. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1, with no deterioration over the previous 2 weeks.

7. Patients must have a life expectancy of ≥12 weeks, as estimated at the time of screening.

8. Females should be using adequate contraceptive measures (see Appendix E) and must have a negative serum pregnancy test prior to start of dosing if of child-bearing potential or must have evidence of non-child bearing potential by fulfilling one of the following criteria at screening (see details in Appendix E):

   - Post-menopausal, defined as aged ≥50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments

   - Women <50 years old who are considered as post-menopausal (amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments) and who have 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.

9. Male patients should be willing to use barrier contraception ie, condoms until 6 months after the last study drug is taken.

10. Patients are willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.

11. **For inclusion in optional genetic research**, patients must provide separate informed consent. If a patient declines to consent to optional genetic research, this does not exclude the patient from participating in any aspect of the study.

3.2 Exclusion criteria

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

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

2. Participation in another clinical study with an investigational product during the last 14 days (or a longer period, depending on the defined characteristics of the agents used).

3. Treatment with any of the following:

   - A 1st or 2nd generation EGFR-TKI (eg, afatinib, erlotinib or gefitinib) within 8 days or approximately 5 half-lives, whichever is the longer, of the first dose of study treatment (if sufficient wash-out time has not occurred due to schedule or PK properties, an alternative appropriate wash-out time based on known duration and time to reversibility of drug related AEs could be agreed upon by AstraZeneca and the Investigator).

   - Osimertinib in the present study (ie, dosing with osimertinib previously initiated in this study) or has previously received a 3rd generation EGFR-TKI (eg, CO-1686). Patients who were enrolled, screened but not dosed (ie, withdrew from the study prior to dosing) may be re-enrolled and rescreened if in the opinion of the Investigator, the reason(s) for earlier withdrawal no longer applies.

   - Any cytotoxic chemotherapy, investigational agents or other anticancer drugs from a previous treatment regimen or clinical study within 14 days of the first dose of study treatment.

   - Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study treatment.

   - Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment, with the exception of patients receiving radiation to more than 30% of the bone marrow, or with a wide field of radiation which must be completed within 4 weeks of the first dose of study treatment.

- Patients currently receiving (or unable to stop use at least 3 weeks prior to receiving the first dose of osimertinib) medications or herbal supplements known to be potent inducers of CYP3A4 or inducers/inhibitors of P-gp, as described in Appendix G.

4. Any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 at the time of starting study treatment; with the exception of alopecia and Grade 2 prior platinum-therapy related neuropathy.

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

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 study or which would jeopardise compliance with the protocol, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required.

7. Any of the following cardiac criteria:

   - Mean resting corrected QT interval corrected for heart rate using Fridericia's correction factor (QTcF) >470 msec, obtained from 3 ECGs.

   - Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (eg, complete left bundle branch block, third degree heart block, second degree heart block, PR interval >250 msec)

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

8. Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.

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

   - Absolute neutrophil count (ANC) $<1.5 \times 10^9$/L

   - Platelet count $<100 \times 10^9$/L

- Haemoglobin <90 g/L
- Alanine aminotransferase >2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases
- Aspartate aminotransferase >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases
- Total bilirubin >1.5 times ULN if no liver metastases or >3 times ULN in the presence of liver metastases
- Creatinine >1.5 times institutional ULN concurrent with creatinine clearance <50 mL/min (measured or calculated by Cockcroft-Gault formula); confirmation of creatinine clearance is only required when creatinine is >1.5 times institutional ULN.

10. Patients unable to swallow orally administered medication or patients with gastrointestinal disorders or significant gastrointestinal resection likely to interfere with the absorption of osimertinib and/or fexofenadine.

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

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

13. Women who are breastfeeding.

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

15. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days of the first administration of the IP until the final PK sample collection on Day 42 of the PK phase.

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

18. Previous allogenic bone marrow transplant.

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

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment

The Principal Investigator (PI) or designee will:

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

2. Assign potential patient a unique enrolment code (E-code) beginning with 'E#' after written informed consent has been obtained. The E-code (EWWXXYZZ) will consist of a 2-digit country number (WW), a 2-digit site number (XX), a 1-digit study number (Y) and a 2-digit patient number (ZZ, starting with 01) issued by the study centre in order of informed consent taken.

3. Determine patient eligibility. See Sections 3.1 and 3.2.

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

Patients who were enrolled, screened but not dosed (ie, withdrew from the study prior to dosing) may be re-enrolled and re-screened if, in the opinion of the Investigator, the reason(s) for earlier withdrawal no longer applies. Patients cannot re-enter the study if dosed and subsequently withdrawn from the study. Patients who discontinue their participation in the PK phase prematurely may still be eligible to continue to take osimertinib in continued access, if the Investigator believes it is in the patient's interest, ie, discontinuation from the PK phase may not necessarily result in withdrawal from the study.

3.4 Procedures for handling incorrectly enrolled patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study drug. There can be no exceptions to this rule.

Where patients who do not meet the selection criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post-initiation, a discussion should occur between the AstraZeneca Physician or his/her representative and the Investigator regarding whether to continue or discontinue the patient from treatment. Once a decision is made, Investigators need to ensure they comply with all applicable requirements for human patient protection and ethical review.

The AstraZeneca Physician or his/her representative is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study treatment stopped and be withdrawn from the study.

3.5 Methods for assigning treatment groups (Not applicable)

3.6 Methods for ensuring blinding (Not applicable)

3.7 Methods for unblinding (Not applicable)

3.8 Restrictions

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

1. Females of child-bearing potential should use reliable methods of contraception from the time of screening until 3 months after discontinuing study treatment. Acceptable methods of contraception include "true" abstinence (definition of "true" is when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence, eg, calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception]), tubal ligation, oral or transdermal contraceptives, copper-banded intra-uterine devices and vasectomised partner. All hormonal methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse. A reduction in the effectiveness of hormonal contraceptives cannot be excluded.

2. Male patients should be asked to use barrier contraceptives (ie, by use of condoms) during intercourse with all partners during the study and for a washout period of 6 months. Where a sexual partner of a male patient is a woman of child-bearing potential, patients should avoid procreation for 6 months after completion of study treatment. Patients should refrain from donating sperm from the start of dosing until 6 months after discontinuing study treatment. If male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

3. All patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known potent inducer effects on CYP3A4 and/or known inducer/inhibitor of P-gp (see Appendix G) whenever feasible, but patients may receive any medication that is clinically indicated for treatment of AEs during the study. 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 osimertinib. 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 in Appendix G.

4. Patients who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE Grade ≤2) while receiving treatment with osimertinib until at least one week after symptoms have resolved. If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE Grade ≥3) ocular events they must discontinue wearing their contact lenses until at least one week after treatment with osimertinib is permanently discontinued. Patients must

not use any eye drops or ointment for treatment of eye symptoms, unless agreed by a study doctor, at any time during the study until 1 week after osimertinib has been permanently discontinued. Patient should consult the clinic promptly if they have any concerns.

5. Patients should maintain a consistent diet during the PK phase of the study and should not change their diet between study periods.

6. On the days of fexofenadine administration, patients must abstain from taking any aluminium and magnesium containing antacids and any other metal containing drugs or products.

7. Patients are not to consume grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days of the first administration of the IP through the final PK sample on Day 42 of the PK phase.

8. On fexofenadine dosing days (ie, Day 1 of Treatment Period 1, Day 1 and Day 39 of Treatment Period 2), patients must fast from 1 hour before until 1 hour after dose administration.

Details of restrictions related to concomitant medications can be found in Section 7.7.

3.9 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance with the study protocol
- Worsened condition
- Disease progression
- The Investigator believes they are no longer deriving clinical benefit (continued access).
- Incorrectly enrolled patients

3.9.1 Procedures for discontinuation of a patients from investigational product

At any time, patients are free to discontinue IP or withdraw from the study (ie, IP and assessments – see Section 3.10), without prejudice to further treatment. A patient that decides to discontinue IP 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(s). Adverse events will be followed up (See Section 6.3.2); and all study drugs should be returned by the patients.

In the PK phase, any patient discontinuing IP should be seen at 30 days (±7 days) after their last dose for the evaluations outlined in the study plan (see Table 1). After discontinuation of IP, the Investigator will perform the best possible observations, tests, and evaluations, as well as give appropriate medication and ensure all possible measures for the safety of the patient. In addition, they will record on the eCRF the date of discontinuation, the reasons, manifestation, and treatment at the time of discontinuation. If patients discontinue IP, the AstraZeneca monitor or its representative must be informed immediately. The patient should return all IP.

After discontinuation of the IP in the PK phase, all ongoing AEs or SAEs must be followed until resolution unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease, or the patient is lost to follow up (see Section 6.3). All new AEs and SAEs occurring during the 30 calendar days after the last dose of IP or immediately before initiation of any other cancer therapy, whichever occurs first, must be reported (all SAEs must be reported to AstraZeneca or its representative within 24 hours as described in Section 6.4) and followed to resolution as above. Patients should be contacted at least 30 days after discontinuing IP to collect and/or complete AE information and collect IP. Any untoward event occurring subsequent to the 30 day follow-up AE reporting period that the Investigator assesses as possibly related to the IP should also be reported as an AE.

At the end of the PK phase, patients may continue to receive IP as continued access and undergo follow-up as part of their normal routine clinical care. After discontinuation of the IP in continued access, patients should be followed for 30 days to follow-up any existing SAEs and monitor for any new SAEs that may be related to IP.

If a patient is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

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

- Screen failures (see Section 3.10.1)
- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment (see Section 3.10.2)
- Risk to patients as judged by the Investigator and/or AstraZeneca or its representative.
- Severe non-compliance to protocol as judged by the Investigator and/or AstraZeneca or its representative.

- Incorrectly enrolled patients, ie, the patient does not meet the required inclusion/exclusion criteria for the study.
- The patient becomes pregnant.
- Patient lost to follow-up.

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be dosed. These patients should have the reason for study withdrawal recorded as 'Eligibility Criteria Not Fulfilled' (ie, patient does not meet the required inclusion criteria or meets an exclusion criterion). This reason for study withdrawal is only valid for screen failures (not dosed patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment (withdrawal of consent). Patients may withdraw from any aspects of the optional genetics research (see Sections 3.1 and 5.6) at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study.

If a patient wishes to withdraw their consent to further participation in the study entirely this should be clearly documented in the patient notes and in the clinical study database. Patients will always be asked about the reasons for withdrawal of consent for and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Section 6.3.2); and all study drugs should be returned by the patients.

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

3.11 Discontinuation of the study

The study will be stopped if, in the judgment of AstraZeneca, study participants 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 patients at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

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

4. STUDY PLAN AND TIMING OF PROCEDURES

The overall study plan is provided in Table 1 for the PK phase; PK sampling in the PK phase will be conducted as shown in Table 2.

Table 1 Study Plan – PK phase

Assessments	Screening	Treatment Period 1						Treatment Period 2												Follow-up[j]
Visits	1	2	3	4	5	6	-	7[b]	8	9	10	11	12	13	14	15	16	17	18	19
Day	-28 to -2 days before dosing	-1[a]	1	2	3	4	0 to 3 days[b]	1	2	3	4	11 ±1	18 ±1	25 ±1	32 ±1	39 ±3	40	41	42	30±7 days after last dose
Resident in clinic (optional)			←	→				←	→							←	→			
Outpatient visits	X	X			(X)	(X)				(X)	(X)	X	X	X	X			(X)	(X)	X
Written informed consent	X																			
Demography and baseline characteristics	X																			
Medical (including smoking)/ surgical history	X																			
Inclusion/exclusion criteria	X	X	X																	
ECOG performance status	X																			
Height/Weight[c]	X		X					X				X	X	X	X	X			X	
Ophthalmologic examination	X																			
Physical examination (full)	X																			X
Physical examination (abbreviated)		X														X			X	
Vital signs (blood pressure, pulse, body temperature)	X	X	X[d]					X[d]				X[d]	X[d]	X[d]	X[d]	X[d]			X	X
Resting standard 12-lead ECG	X		X[d]					X[d]				X[d]	X[d]	X[d]	X[d]	X[d]			X	X
ECHO/MUGA[e]	X																			
HBV and HCV Serology[f]	X																			
Haematology/coagulation[g]/ clinical chemistry	X	X						X[d]				X[d]	X[d]	X[d]	X[d]	X[d]			X	X
Urinalysis	X	X						X[d]				X[d]	X[d]	X[d]	X[d]	X[d]			X	X
Serum/urine pregnancy test	X	X						X[d]								X[d]			X	X
Pharmacogenetics blood sample - optional		X																		
Osimertinib administration[h]								X			Daily dosing osimertinib 80 mg →									
Fexofenadine administration[i]			X					X								X				
Diary								P			C	C/P	C/P	C/P	C/P	P	C	C		
Osimertinib PK blood sampling								X	X	X	X	X	X	X	X	X	X			
Fexofenadine PK blood sampling			X	X	X	X		X	X	X	X					X	X	X	X	

Table 1 Study Plan – PK phase

Assessments	Screening	Treatment Period 1						Treatment Period 2												Follow-up[j]
Visits	1	2	3	4	5	6	-	7[b]	8	9	10	11	12	13	14	15	16	17	18	19
Day	-28 to -2 days before dosing	-1[a]	1	2	3	4	0 to 3 days[b]	1	2	3	4	11 ±1	18 ±1	25 ±1	32 ±1	39 ±3	40	41	42	30±7 days after last dose
Resident in clinic (optional)		←	→					←	→							←	→			
Outpatient visits	X	X			(X)	(X)				(X)	(X)	X	X	X	X			(X)	(X)	X
Prior and concomitant meds	X	X[k]	X[k]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Osimertinib dispensed/returned											D			D/ R					R	

a. Day -1 is the day before dosing. All Day 1 procedures must be performed on Day -1 or pre-dose on Day 1 provided the results are reviewed before dosing. If the patient has been screened within 48 hours of Day 1, safety laboratory tests (haematology, coagulation, biochemistry and urinalysis) do not need to be repeated.

b. There will be a 3- to 7-day washout period between the first dose of fexofenadine administered in Treatment Period 1 and first dose administered in Treatment Period 2 ie, Visit 7 procedures can start on the day of Visit 6 or up to 4 days after Visit 6. If Visit 6 and Visit 7 are performed on the same day, the 72 hour sample for Treatment Period 1 may be used as the pre-dose PK sample for fexofenadine in Treatment Period 2.

c. Height to be assessed at screening only. Weight to be assessed at all designated timepoints; the same weighing scales should be used at each visit. For height and weight, indoor clothing may be worn but shoes should be removed.

d. Pre-dose.

e. ECHO/MUGA at baseline and repeated during the PK phase only if clinically indicated at any timepoint or subsequently at follow-up 30 (± 7) days after last dose of study medication (for example to follow up on a cardiac AE).

f. Includes HBsAg (hepatitis B surface antigen), anti-HBs (hepatitis B surface antibody), anti-HBc (hepatitis B core antibody) and anti-HCV (hepatitis C virus antibody).

g Coagulation (activated partial thromboplastin time [aPTT] and international normalised ratio [INR]) will be performed at baseline and if clinically indicated. For patients taking warfarin see Section 7.7.

h. Patients will take 80 mg osimertinib once on Day 1 of Treatment Period 2 and then continue with once daily dosing starting on Day 4 of Treatment Period 2 after the 72 hour sample through Day 41 of Treatment Period 2. The study treatments should be swallowed whole with approximately 240 mL of water, and not chewed, crushed, dissolved or divided. Osimertinib will be dispensed on Day 4 and Day 25 of Treatment Period 2. Compliance will be checked at subsequent visits.

i. Patients will take 120 mg fexofenadine once on Day 1 of Treatment Period 1, Day 1 of Treatment Period 2, and Day 39 of Treatment Period 2.

j. Follow-up assessments will only be performed for patients who permanently discontinue osimertinib treatment during the PK phase. On completion of the PK phase, patients may continue to take osimertinib tablets as a single agent until such time as the Investigator believes they are no longer deriving clinical benefit or they stop taking osimertinib for any other reason.

k Compliance with comedication and/or food/beverage restrictions related to CYP3A4 and P-gp activity must be maintained during Day -1 and Day 1.

C check; D = dug dispensed; ECG electrocardiogram; ECHO echocardiogram; ECOG Eastern Cooperative Oncology Group; HBV hepatitis B; HCV hepatitis C Virus; MUGA multiple gated acquisition scan; P provided; PK pharmacokinetics; R drug returned.

Table 2 Timing of PK samples – PK phase

Day		Fexofenadine PK blood	Osimertinib PK blood
Treatment Period 1	Day 1[a]	Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10	
	Day 2	24, 36	
	Day 3	48, 60	
	Day 4	72 (pre-dose)	
Treatment Period 2	Day 1[a]	Pre-dose[b], 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10	Pre-dose, 1, 2, 3, 4, 6, 8, 10
	Day 2	24, 36	24, 36
	Day 3	48, 60	48, 60
	Day 4	72 (taken prior to osimertinib administration)	72 (pre-dose)
	Day 11±1		Pre-dose
	Day 18±1		Pre-dose
	Day 25±1		Pre-dose
	Day 32±1		Pre-dose
	Day 39±3[a,c,e]	Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10	Pre-dose, 1, 2, 3, 4, 6, 8, 10
	Day 40 ±3[c]	24[d], 36	24 (pre-dose)
	Day 41 ±3[c]	48[d], 60	
	Day 42 ±3[c]	72[d]	

[a] Treatment will be administered fasted from at least 1 hour before dosing to at least 1 hour after dosing. Water is also restricted during this same time period with exception of the approximately 240 mL of water for drug administration.

[b] The 72 hour sample for Treatment Period 1 may be used as the pre-dose PK sample for fexofenadine in Treatment Period 2, if Treatment Period 2 (single dose of osimertinib plus fexofenadine) commences after a 3 day wash-out period (sites will still need to collect a predose sample for osimertinib)

[c] If the Day 39 visit window is applied, Days 40, 41, and 42 must occur subsequently in order to allow for 24, 36, 48, 60 and 72 hour PK samples to be drawn (ie, the samples are collected over a period of 3 consecutive days).

[d] The 24, 48, and 72 hour samples will, if possible, be taken before the next osimertinib dose on these days (for the 72 hour sample, this would be during continued access). The 24-hour osimertinib concentration must be taken prior to the next osimertinib dose on Day 40.

[e] None of the windows presented for Days 11, 18, 25, 32, and 39 will require prior agreement with AstraZeneca or representative.

4.1 Enrolment/screening period

Screening procedures will be performed according to the Study Plan for the PK phase (Table 1). At screening, consenting patients are assessed to ensure that they meet eligibility criteria (Sections 3.1and 3.2). Patients who do not meet these criteria must not be enrolled in the study.

Patients will be considered to be in the screening period until all Visit 1 assessments are completed and eligibility is confirmed. Patients will be considered to be in the treatment period after the first dose of fexofenadine has been administered.

The following assessments and procedures should be performed within 28 days prior to the first dose of IP:

- Signed informed consent for the study and pharmacogenetic informed consent (optional)
- Review inclusion/exclusion criteria; ensure that subject has documented an EGFR mutation known to be associated with EGFR-TKI sensitivity (eg, G719X, exon 19 deletion, L858R, L861Q)
- Demographics (sex, age, self-reported race/ethnicity)
- Medical/surgical history including smoking status
- Prior and concomitant medications including prescribed and over-the-counter preparations and previous cancer therapies (if applicable), check against exclusion criteria, restrictions (section 3.8) and Appendix G
- Physical examination, ECOG performance status, vital signs (supine blood pressure [BP] and pulse, body temperature), ECG, ECHO/ multiple gated acquisition scan (MUGA), body weight and height
- Haematology, clinical chemistry and coagulation, serology (hepatitis B and hepatitis C status) and urinalysis
- Serum or urine pregnancy test (pre-menopausal women of childbearing potential)
- Ophthalmology
- Adverse events

4.2 Treatment period

Descriptions of the procedures for this period are included in the Study Plan for the PK phase (Table 1). The timing of PK blood samples for osimertinib and fexofenadine is detailed in Table 2.

4.2.1 PK phase

It is important that PK sampling occurs as close as possible to the scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point. The sequence to be followed at a particular post-dose time point is:

1. ECGs
2. Vital signs
3. PK blood sample (at scheduled time)

4. Any other assessments

Pre-dose ECGs and vital signs assessments should be collected within 60 minutes prior to dosing.

A 30-minute window will be allowed for PK samples taken at pre-dose (sample must be taken prior to dose); a 5-minute window will be allowed for post-dose samples up to 1.5 hours; a 10-minute window for samples taken at 2 to 10 hours post-dose; a 1-hour window for samples taken from 24 hours through 36 hours post-dose; and a 2-hour window from 48 hours post-dose onwards. The window for visits with trough (pre-dose) samples is ±1 day; however, on a given day the trough sample must be collected prior to the next dose of IP. Similarly, the 24-hour osimertinib sample on Day 40 must be taken prior to the osimertinib dose on Day 40.

All Day -1 procedures in Treatment Period 1 must be performed in the clinic on Day -1 or pre-dose on Day 1; patients may be admitted on Day 1 if the Day -1 activities (see Table 1) can be completed on the same day. If the patient has been screened within 48 hours of Day 1, safety laboratory tests (haematology, coagulation, clinical chemistry and urinalysis) do not need to be repeated.

4.2.1.1 Treatment Period 1

On Day 1 (Visit 3), a single oral dose of fexofenadine hydrochloride 120 mg will be administered in the morning with approximately 240 mL of water. The patient is to fast from at least 1 hour before dosing to at least 1 hour after dosing. Water is also restricted during that time period with the exception of the water consumed for dose administration. Patients may remain resident until approximately 72 hours after the dose of fexofenadine (if agreed upon by the Investigator and patient), during which time PK blood samples and safety information will be collected.

4.2.1.2 Treatment Period 2

On Day 1 (Visit 6 or 7), after a washout of 3 to 7 days between fexofenadine doses, patients will receive osimertinib 80 mg and fexofenadine hydrochloride 120 mg (at the same time) having been fasted from at least 1 hour before dosing to at least 1 hour after dosing with approximately 240 mL of water. Water is also restricted during that time period with the exception of the water consumed for dose administration. Patients may remain resident until approximately 72 hours after the dose of osimertinib and fexofenadine (if agreed upon by the Investigator and patient), during which time PK blood samples and safety information will be collected.

On Day 4, after the 72 hour sample collection patients will start receiving daily doses of osimertinib 80 mg. From Day 5 to Day 38, patients will continue to receive daily doses of osimertinib 80 mg. No food or water restrictions apply. On Day 11 (±1 day), Day 18 (±1 day), Day 25 (±1 day), and Day 32 (±1 day) patients will return to the clinic prior to taking their daily osimertinib dose and trough (pre-dose) PK blood samples and safety information will be collected. It is important to record date/time of the last dose taken before the visit which includes trough (pre-dose) PK sampling and make sure that the trough

(pre-dose) sample is collected no less than 18 hours and no more than 30 hours after the last dose before the PK blood sample.

Patients will come into the clinic the morning of Day 39 (±3 days) prior to taking their daily osimertinib dose. It is important to record date/time of the last dose taken before the visit and make sure that the trough (pre-dose) sample is collected no less than 18 hours and no more than 30 hours after the last dose before the PK blood sample. On Day 39, in addition to receiving their daily dose of osimertinib, patients will receive fexofenadine hydrochloride 120 mg. Both drugs will be given at the same time with approximately 240 mL of water to the patient who is to have fasted from at least 1 hour before dosing to at least 1 hour after dosing. Water is also restricted during that time period with the exception of the water consumed for dose administration. The Day 39 treatment (osimertinib plus fexofenadine) may occur within a window of ±3 days. Patients may remain resident until approximately 72 hours after the dose of fexofenadine (if agreed upon by the Investigator and patient), during which time PK blood samples (fexofenadine: for 72 hours, osimertinib: for 24 hours) and safety information will be collected.

4.2.2 Continued Access

During continued access osimertinib can be taken with or without food. There are no water restrictions.

Following completion of the PK phase, patients may continue to take osimertinib as a single agent, if they and the Investigator deem it appropriate, until such time as the Investigator believes they are no longer deriving clinical benefit or they stop taking osimertinib for any other reason. Patients will be seen as per their normal routine clinical schedule; no further data will be recorded, other than the data specified in Section 7.8.

4.3 Follow-up period

Those patients who do not proceed into continued access will return to the clinic for follow-up assessments 30 days (±7 days) after their last dose in the PK phase; follow-up assessments are detailed in Table 1.

If the patient's last dose of osimertinib is in continued access (ie, after the PK phase), the patient should be contacted 30 days after their last dose of osimertinib to follow up on any existing SAEs and monitor for new SAEs that may be related to IP.

5. STUDY ASSESSMENTS

The InForm Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRF 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 eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy assessments (Not applicable)

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation and urinalysis parameters will be taken at the time given in the study plan (Table 1). If screening is undertaken within 48 hours of Day 1 of Treatment Period 1, safety laboratory tests do not need to be repeated.

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

The haematology, clinical chemistry, coagulation, and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Table 3 Laboratory safety variables

Clinical chemistry (2.7 mL sample)	**Haematology (2.7 mL sample)**
S/P-Albumin	B-Haemoglobin
S/P-ALT	B-Leukocyte
S/P-AST	B-Haematocrit
S/P-Alkaline phosphatase	B-Red blood cell count
S/P-Bilirubin, total	B-Absolute leukocyte differential count:
S/P-Calcium, total	Neutrophils
S/P-Creatinine	Lymphocytes
S/P-Glucose	Monocytes
S/P-Lactate dehydrogenase	Basophils
S/P-Magnesium	Eosinophils
S/P-Potassium	B-Platelet count
S/P-Sodium	B-Reticulocytes
S/P-Urea nitrogen or Blood urea nitrogen	
	Urinalysis (dipstick)[a]
Coagulation (1.8 mL sample)[b]	U-Glucose
B-Activated partial thromboplastin time	U-Protein
B-International normalised ratio	U-Blood
Serology screen (1.8 mL sample)[c]	**Pregnancy tests**
Hepatitis B and C (HBV, HCV)[d]	Blood or urine

ALT alanine aminotransferase; AST aspartate aminotransferase; B blood; HBV hepatitis B virus; HCV hepatitis C virus; P plasma; S serum; U urine.

[a] Microscopic analysis should be performed by the clinic's local laboratory if required.

[b] For patients taking warfarin see Section 7.7.

[c] Serology results will not be captured in the eCRF.

[d] HBV DNA and HCV RNA if required to confirm active disease

Pre-menopausal women of childbearing potential must have a negative urine or serum pregnancy test within 28 days prior to starting study treatment, and a confirmatory test before treatment on Day 1 of Treatment Period 1. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately. The pregnancy test will be repeated on Day 1 of Treatment Period 2, Day 39 of Treatment Period 2 and at the follow-up visit 30 (±7) days after the last dose of study drug (in the PK phase). Tests will be performed by the clinic's local laboratory. If results are positive, the patient is ineligible/must be discontinued from the study.

Routine urinalysis should be performed if clinically indicated. Microscopic analysis should be performed by the clinic's local laboratory if required.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

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

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

5.2.2 Volume of blood

The maximum volume of blood that will be taken for any given patient for the purposes of the study is shown in Table 4.

Table 4 Volume of blood to be drawn from each patient: PK phase

Assessment		Sample volume (mL)	No. of samples			Total volume (mL)
			Screening	TP1	TP2	
Safety	Clinical chemistry	2.7	1	1	7	24.3
	Haematology	2.7	1	1	7	24.3
Coagulation[a]	aPTT/INR	1.8	1	0	0	1.8
PK	osimertinib and metabolites	2.0	0	0	26	52
	Fexofenadine	2.0	0	17	34	102
Serology	HBV/HCV[b]	1.8	1	0	0	1.8
Pharmacogenetics sample		10.0		1	0	10.0
Total volume (mL)		**23**	**9**	**49.4**	**152.4**	**216.2**

aPTT activated partial thromboplastin time; HBV hepatitis B virus; HCV hepatitis C virus; INR international normalised ratio; TP1 Treatment Period 1; TP2 Treatment Period 2.

[a] Coagulation (aPTT and INR) will be performed at baseline and if clinically indicated

[b] HBV DNA and HCV RNA if required to confirm active disease.

Note: Table is for guidance. Exact blood volumes may differ depending on local requirements.

5.2.3 Physical examination

Physical examinations will be conducted at the times specified in the Study Plan (Table 1) and any findings recorded on the eCRF.

The physical examination will include a whole body inspection as follows: general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, respiratory, abdomen, neurological, genital / rectal and breast.

A brief physical examination will be conducted at Day -1 and Day 39; this should include general appearance, cardiovascular, respiratory, abdomen, and a brief neurological examination, and would exclude for example genital/rectal/breast examinations.

If new or aggravated physical findings imply deterioration compared with baseline, the finding should be reported as an AE (see Section 6.3.6).

Performance status will be assessed at screening using the ECOG scale (see Appendix F).

5.2.4 ECG

5.2.4.1 Resting 12-lead ECG

A 12-lead safety ECG (paper ECG printout of 10 seconds for Investigator review) will be taken at the times specified in the Study Plan (Table 1).

For each time point, three ECG recordings should be taken within an approximate 5 minute period. Additional ECGs may be taken at any other time the Investigator deems necessary for safety during the dosing period. The patients will rest for at least 10 minutes before the start of each recording and they must be in the same supine body position (maximum 30 degrees flexion in the hip and feet not in contact with the footboard) at each recording time point during all visits.

The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant. The paper copy of each ECG reading will be retained with the patient's completed source documents. Only overall evaluation (normal/abnormal) will be recorded in the eCRF. If there is a clinically significant abnormal ECG finding during the treatment period, this should be recorded on the AE eCRF, according to standard AE collection and reporting processes (see Section 6.3.6). The investigator or designated physician will review each ECG prior to discharge from the clinic and may refer to a local cardiologist if appropriate for immediate management of the patient.

5.2.5 Echocardiogram/MUGA scan

An echocardiogram or MUGA scan to assess left ventricular ejection fraction (LVEF) will be performed at baseline and repeated during the PK phase only if clinically indicated. The modality of the cardiac function assessments must be consistent within a patient ie, if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans. The patients should also be examined using the same machine and operator whenever possible. The LVEF value (%) should be recorded on the eCRF.

5.2.6 Vital signs

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

Deterioration as compared with baseline in protocol-mandated vital signs should only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP, or the Investigator insists the abnormality should be reported as an AE (see Section 6.3.6).

5.2.6.1 Pulse and blood pressure

Supine BP and pulse will be measured at the times specified in the Study Plan (Table 1) using a semi-automatic BP recording device with an appropriate cuff size after the patient has been resting in bed for 10 minutes.

5.2.6.2 Body temperature

Body temperature will be measured at the times specified in the Study Plan (Table 1) using a semi-automatic body temperature recording device.

5.2.6.3 Weight and height

Height (screening only) and weight will be assessed at the visits as shown in the Study Plan (Table 1). Indoor clothing may be worn but shoes should be removed. For weight assessment, the same weighing scales should be used at each visit.

5.2.7 Other safety assessments

5.2.7.1 Ophthalmologic exam

Full ophthalmic assessment, including slit lamp examination, should be performed at Screening and if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Ophthalmology examination results at Screening and for additional ophthalmic assessments during the study should be collected in the eCRF.

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

Patients experiencing corneal ulceration will not be permitted to restart study treatment (see Section 6.7.5)

5.3 Other assessments (not applicable)

5.4 Pharmacokinetics

5.4.1 Collection of samples

Venous blood samples for determination of concentrations of osimertinib and its metabolites (AZ5104 and AZ7550) (2 mL) and fexofenadine (2 mL) will be taken at the times presented in Table 2. Although every attempt should be made to collect all samples as per the protocol-defined time points, it is accepted that this will not always be possible and therefore it is essential that the actual time and date of collection of each blood sample (whether collected as per protocol or not) is recorded in the eCRF. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

For blood volumes see Section 5.2.2.

5.4.2 Determination of drug concentration

Samples for determination of concentration of osimertinib and its metabolites (AZ5104 and AZ7550) and fexofenadine in plasma will be analysed by Covance on behalf of AstraZeneca R&D, using appropriate bioanalytical methods. 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 at the time of receipt by the bioanalytical laboratory will be analysed.

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 osimertinib metabolites. 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.

5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses. Any such samples will be retained for a maximum of 15 years. At this time, all remaining samples collected and stored by the Sponsoring Company will be destroyed.

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

Any residual PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be retained at 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 optional pharmacogenetics research component of the study a blood sample will be collected (see Section 5.6.1).

AstraZeneca may perform genetic research in the osimertinib clinical pharmacology development programme to explore how genetic variations may affect the clinical PK of osimertinib.

For this clinical study, pharmacogenetic research will be limited to analysis of genes that may affect osimertinib PK (for example, but not limited to, drug metabolising enzymes and drug transporters) may be performed if the results from the clinical study cannot be explained by the current level of drug metabolism and PK understanding, or if patients with outlying PK behaviour are observed.

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

5.6.1 Collection of pharmacogenetic samples

Written consent is mandatory for those patients who agree to participate in the pharmacogenetic research components of the study.

The single blood sample for genetic research will be obtained from the patients on Day -1, prior to the first administration of fexofenadine 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 at Day -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.

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 Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported separately in a scientific report or publication.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal

details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA).

The samples and data for genetic analysis in this study will be single coded. The link between the patient's enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access within the relevant sample tracking system 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 when the patients has requested disposal/destruction of collected samples not yet analysed.

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

5.7 Biomarker analysis (Not applicable)

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

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

6.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions

- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patients or may require medical intervention to prevent one of the outcomes listed above.

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse events will be collected from the time of signature of informed consent, throughout the PK phase treatment period and including the follow-up period. SAEs will be recorded from the time of informed consent.

For these patients who are continuing to receive osimertinib and are being followed as part of their routine clinical care, AstraZeneca will collect limited information only (see Section 7.8).

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment or other assessment/visit as appropriate in the study will be 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.

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 osimertinib, the Investigator should notify AstraZeneca.

If patients who are gaining clinical benefit are allowed to continue IP following data cut-off and/or post study completion then, as a minimum, all SAEs must continue to be collected and reported to Astra Zeneca Patient Safety or its representative within the usual timeframe (Section 6.4).

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date and time 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
- Outcome.

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

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

Severity of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, 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.

The grading scales found in the revised National Cancer Institute CTCAE Version 4.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation is the CTCAE criteria that convert mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

For each episode, the highest severity grade attained should be reported.

6.3.4 Causality collection

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

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

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

6.3.5 Adverse events based on signs and symptoms

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

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the 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 is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

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

6.3.7 Hy's Law

Cases where a patient shows an AST or ALT ≥3×ULN and total bilirubin ≥2×ULN may need to be reported as SAEs. Prompt reporting of cases meeting Hy's law criteria (via the SAE

expedited reporting system) is required for compliance with regulatory guidelines. The Investigator is responsible for, without delay, determining whether a patient meets potential Hy's law (PHL) criteria.

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

6.3.8 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Expected progression of the patient's cancer and/or expected progression of signs and symptoms of the cancer, unless more severe in intensity or more frequent than expected for the patient's condition should be considered as disease progression and not as an AE.

Events that are unequivocally due to disease progression should not be reported as an AE during the study.

6.3.9 New cancers

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

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 IP, should be reported as follows:

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

- Where death is not clearly due to progression of the disease under study the AE causing the death should be reported in the WBDC system 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. This information can be captured in the 'death eCRF'.

- 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

During the PK phase, all SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedures, and should be recorded in the eCRF. During the continued access phase, SAEs that may be related to IP have to be reported and will be collected on paper SAE forms (see Section 7.8).

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

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

For fatal or life-threatening 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 ie, immediately but **no later than 24 hours** of when he or she becomes aware of it and updates the information on the Adverse Event eCRF.

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

The reference document for definition of expectedness is the current IB for the AstraZeneca drug.

The sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations. The investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular deaths) involving his/her subjects to the Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the trial. In accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the sponsor will inform the investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the IEC's/IRB's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the sponsor will inform the investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" [SUSARs]). The investigator should place copies of Safety reports in the Investigator Site File. National regulations with regard to Safety report notifications to investigators will be taken into account. When specifically required by regulations and guidelines, the sponsor will provide appropriate Safety reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting by the sponsor is not clearly defined by national or site-specific regulations, the investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety

reports provided by the sponsor and of filing copies of all related correspondence in the Investigator Site File. For trials covered by the European Directive 2001/20/EC, the sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidances.

6.5 Overdose

There are no data on overdosing with osimertinib. An overdose of osimertinib is defined as any dose greater than the highest daily dose included in the Clinical Study Protocol. 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 CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it and enters this into the Overdose eCRF within the same timeline.

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting to the AstraZeneca Patient Safety data entry site must occur within 30 days.

During continued access, only overdoses associated with a SAE must be reported.

6.6 Pregnancy

The outcome of any pregnancy occurring from the date of the first dose until 6 months after dosing with osimertinib should be followed up and documented.

Please refer to Section 6.6.1 and Section 6.6.2 for further details.

6.6.1 Maternal exposure

If a patients becomes pregnant during the course of the study, osimertinib should be discontinued immediately.

Pregnancy itself is not regarded as an AE 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 (normal birth, spontaneous miscarriage, elective termination, ectopic pregnancy, or congenital abnormality) from the date of first dose until 6 months after the last dose of osimertinib should be followed up and documented even if the patients was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it and enters this into the Pregnancy Report eCRF.

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.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 6 months following the last dose.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (normal birth, spontaneous miscarriage, elective termination, ectopic pregnancy, 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. The outcome of any conception occurring from the date of the first dose until 6 months after the last dose should be followed up and documented.

6.7 Management of IP related toxicities

Patients who have IP-related toxicities requiring dose interruption or dose reduction may be discontinued from the PK phase and entered into continued access following discussion with an AstraZeneca representative. Dose reduction is not allowed in the PK phase of the study; if the investigator feels that they need to reduce the IP dose due to toxicity, then the patient should be discontinued from the PK phase and may be entered into continued access.

The following text is guidance for investigators who treat patients with osimertinib in continued access:

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

If dose reduction is necessary, then the dose of osimertinib should be reduced to 40 mg taken once daily. Patients who reduce to the 40 mg dose must remain on the 40 mg dose for the remainder of the study.

Dose interruption and reduction guidelines are provided in Table 5.

Table 5 Osimertinib dose adjustment information for adverse reactions

Target organ	Adverse reaction	Dose modification
Pulmonary	ILD/pneumonitis	Permanently discontinue osimertinib
Ocular	Corneal ulceration	Permanently discontinue osimertinib
Cardiac	QTc interval >500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc interval is <481 msec or recovery to baseline if baseline QTc is ≥481 msec, then restart at the reduced dose (40 mg)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib
Other	Grade 3 or higher adverse reaction	Withhold osimertinib for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding osimertinib for up to 3 weeks	osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding osimertinib for up to 3 weeks	Permanently discontinue osimertinib

ECG electrocardiogram; ILD interstitial lung disease

6.7.1 Skin reactions

Recommendations for appropriate management of skin reactions, including guidance on dose adjustments for clinically significant and/or intolerable skin reactions that are considered by the Investigator to be causally related to osimertinib are available in Appendix H.

The following is not applicable to continued access:

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

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

Photographs of skin reactions may be collected and these photographs should be available for central review by AstraZeneca and for external expert dermatological review if required. Skin biopsies may be taken of skin reactions.

6.7.2 Diarrhoea

Recommendations for appropriate management of diarrhoea, including dose-adjustments for AEs of diarrhoea that are of CTCAE Grade ≥3 or that are clinically significant and/or intolerable and considered by the Investigator to be causally related to osimertinib are available in Appendix H. During the PK phase, changes in CTCAE grade of diarrhoea will be captured in the AE eCRF.

6.7.3 Worsening pulmonary symptoms

If new or worsening pulmonary symptoms (eg, dyspnoea) or a radiological abnormality suggestive of ILD/pneumonitis is observed, an interruption in study treatment dosing is recommended. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, haematological parameters) will be captured in the eCRF during the PK phase. During the continued access phase, a questionnaire regarding the results of the full diagnostic workup may be sent to Investigators. All image data should also be provided to AstraZeneca. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary haemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should be considered and study treatment permanently discontinued (per Table 5 above).

Patients experiencing ILD/pneumonitis will not be permitted to restart study treatment.

In the absence of a diagnosis of ILD/pneumonitis, study treatment may be restarted.

An AstraZeneca or representative study team physician must be contacted.

6.7.4 QTc prolongation

Refer to Table 5 above. The Investigator or designated physician should review each ECG prior to discharge and may refer to a local cardiologist if appropriate for immediate management of the patient.

6.7.5 Corneal ulceration

Any patient developing corneal ulceration will be permanently discontinued from study treatment (per Table 5 above) and should be followed regularly until resolution of the event. Corneal ulceration should be treated according to local guidance.

6.8 Study governance and oversight

No Data Monitoring Committee is planned, as this study is an open-label non randomised Phase I study. In addition the safety profile of osimertinib from the ongoing Phase I study in a similar NSCLC patient population is modest and predictable. There is therefore no requirement for pre-planned specified expert independent safety reviews in this study.

Safety data will be reviewed on an ongoing basis by the internal AstraZeneca and delegated Contract Research Organisation (CRO) study team as appropriate. The internal Study Team will evaluate progress of the study, assess safety and other relevant information for the study, and will make decisions on continuation, modification or discontinuation of the study.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply osimertinib and fexofenadine to sites.

Investigational product	Dosage form and strength	Manufacturer
Osimertinib	40 and 80 mg film-coated tablets	AstraZeneca

Fexofenadine will be supplied as 120 mg fexofenadine hydrochloride tablets (equivalent to 112mg of fexofenadine) for oral administration.

7.2 Dose and treatment regimens

7.2.1 PK phase

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

If a patient vomits on Day 1 of Treatment Period 1 (fexofenadine), Day 1 and/or Day 39 of Treatment Period 2 (osimertinib plus fexofenadine) within approximately 2.5 hours of fexofenadine administration, the AstraZeneca representative should be contacted for advice regarding the evaluability of the patient or whether the patient may return to the clinic on a subsequent day to repeat the treatment (return to clinic only applicable for Day 39). If a patient is discontinued from the PK phase, the Investigator may contact an AstraZeneca representative to determine if it is appropriate for the patient to proceed into continued access.

Starting on Day 4 of Treatment Period 2, doses of osimertinib should be taken approximately 24 hours apart at the same time point each day. Doses should not be missed. The patient should inform the Investigator of any doses missed prior to any of the outpatient visits for PK trough collections. In case the patient misses any doses of osimertinib during the 7-day period before each scheduled serial sample collection day (within 7 days of receiving osimertinib plus fexofenadine [Day 39]), please contact the AstraZeneca representative for advice regarding the evaluability of the patient and appropriate timing of the PK assessments. Outside of this timeframe, if a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time.

At each dispensing visit, sufficient osimertinib for each study period, plus overage, will be dispensed. Individual bottles will be dispensed in accordance with local practice.

Osimertinib 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 study drug to a patient.

Additional information about osimertinib may be found in the IB.

Treatment Period 1: On Day 1, a single dose of 120 mg fexofenadine treatment will be administered under fasted conditions.

Treatment Period 2: There will be a 3-day (72 hour) to 7-day washout period between the fexofenadine dose on Day 1 of Treatment Period 1 and the fexofenadine + osimertinib dose on Day 1 of Treatment Period 2. On Day 1 of Period 2, 120 mg fexofenadine and 80 mg osimertinib will be administered together under fasted conditions.

From Day 4 onwards through to Day 38, patients will receive a daily 80 mg dose of osimertinib. The Day 4 dose may be taken in the clinic. Based on results from the PK phase of Study D5160C00009, osimertinib exposure is not affected by a high fat, high calorie meal (AUC and C_{max} changes were within the no effect limit of 70% to 143%); therefore, no food or water restrictions apply for osimertinib. The study treatment should be swallowed whole with approximately 240 mL of water, and not chewed, crushed, dissolved or divided. On Day 11 (±1 day), Day 18 (±1 day), Day 25 (±1 day), and Day 32 (±1 day) the daily osimertinib dose will be withheld until after trough (pre-dose) PK blood samples and safety information have been collected. Osimertinib may be taken in the clinic on these days.

On Day 39 ±3 days, the daily osimertinib dose will be withheld until after trough (pre-dose) PK blood samples have been collected. Following completion of all predose procedures, 120 mg fexofenadine and 80 mg osimertinib will be administered together under fasted conditions. Osimertinib administration will continue through to Day 41 without any food or water restrictions.

All study treatments should be swallowed whole with approximately 240 mL of water, and tablets should not be not chewed, crushed, dissolved or divided. On the serial PK sampling days associated with fexofenadine administration (Day 1 of Period 1 and Period 2) and Day 39, food will be withheld from at least 1 hour before dosing to at least 1 hour after dosing. With exception of the 240 mL of water during study drug administration, water will also be withheld from 1 hour before and after fexofenadine administration. There are no food and water restrictions for any of the other osimertinib doses taken in the PK phase.

A Patient Diary Card will be issued to the patient on Day 4 of Treatment Period 2 (see Section 7.5). The patient should record in the Patient Diary Card the date and time all doses of osimertinib taken at home, as well as any missed doses and any possible episodes of vomiting with exact start and stop time. Any change from dosing schedule, dose interruptions, and dose reductions should be recorded in the eCRF.

7.2.2 Continued Access

At the end of the PK phase (after collection of the 72 hour PK sample on Day 42), those patients who are deemed to be gaining clinical benefit from osimertinib may enter continued access and may continue to take osimertinib 80 mg once daily.

No food or water restrictions apply. The study treatments should be swallowed whole with approximately 240 mL of water, and not chewed, crushed, dissolved or divided.

Doses of osimertinib should be taken approximately 24 hours apart at the same time point each day. Doses should not be missed. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their osimertinib, they should not make up for this dose, but should take the next scheduled dose. Any change from dosing schedule, dose interruptions, dose reductions should be recorded per local site practice during continued access.

At each dispensing visit, sufficient osimertinib for each study period, plus overage, will be dispensed. Individual bottles will be dispensed in accordance with local practice.

Osimertinib tablets will be packed in high-density polyethylene 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 study drug to a patient.

Additional information about the IP may be found in the IB.

7.3 Labelling

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

Specific dosing instructions will not be included on the label. The site must complete the 'Patient Dispensing Card' with the details of the dosing instructions at the time of dispensing.

The patient emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Dispensing Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.

7.4 Storage

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

7.5 Compliance

The administration of all study drugs (including IP) should be recorded in the appropriate sections of the eCRF.

For the PK phase, patients will report any self-administered medications for the periods when they are not resident in the clinic. Patients will be issued with a Patient Diary Card, which contains clear instructions on how and when to take their study drug, and the date of their next clinic appointment. Patients will need to complete diaries, which will record the date and time of each dose.

For the PK phase, when patients are at the study site, compliance will be assured by supervised administration of IP by the Investigator or his/her delegate. Date and time of the dose(s) will be recorded in the eCRF.

When patients self-administer their osimertinib, they should be given clear instructions on how and when to take their study treatment. Patients should aim to take their doses at similar times each day, approximately 24 hours apart. They should be instructed that the dose is to be swallowed whole with a glass of water and not chewed, crushed, dissolved or divided.

Study site pharmacy staff will make tablet counts at regular intervals during treatment. For the PK phase, diaries should be reviewed and tablet counts be performed at each outpatient visit and at check-in on Day 39 in addition to the final visit on Day 42.

Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the Investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of osimertinib at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded on the eCRF. Patients must return all bottles and any remaining tablets when they discontinue IP.

7.6 Accountability

The IP provided for this study is for use only as directed in the study protocol. It is the Investigator/institution's responsibility to establish a system for handling study treatments, including IPs, so as to ensure that:

- Deliveries of such products from AstraZeneca or its representative are correctly received by a responsible person
- Such deliveries are recorded
- Study treatments are handled and stored safely and properly as stated on the label
- Study treatments are only dispensed to study patients in accordance with the protocol

The study personnel will account for all IP dispensed and returned.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the IP was dispensed, the quantity and date of dispensing, and unused IP returned to the Investigator. This record is in addition to any IP accountability information recorded on the eCRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the Investigator or a pharmacist, and copies retained in the Investigator site file. Dispensing and accountability records will continue to be collected after the end of the PK phase for as long as patients continue to receive IP.

7.7 Concomitant and other treatments

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study, with reasons for the treatment, will be recorded in the eCRF. Concomitant use of regular medications that may prolong the QT interval will be restricted whenever feasible, but patients may receive any medication that is clinically indicated for the treatment of AEs. Guidance on medications that are contraindicated or require close monitoring is given in Appendix G.

If medically feasible, patients taking regular medication, with the exceptions shown in the table below, should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon BCRP and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving osimertinib.

Prohibited Medication/Class of drug:	Usage:
Other anticancer agents (including any listed in Appendix G), investigational agents and radiotherapy (ie, radiotherapy specifically for treatment of asymptomatic lesions, irrespective of whether progressing or not)	Should not be given while the patient is on study treatment.

Restricted Medication/Class of drug:	Usage:
PK phase: All patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known potent inducer effects on CYP3A4 and inducer/inhibitory effects on P-gp (see Appendix G) 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 osimertinib.	Whenever feasible, but patients may receive any medication or adjustments to medication that are clinically indicated for treatment of AEs.
On the days of fexofenadine administration, patients must abstain from taking any aluminium and magnesium containing antacids and any other metal containing drugs or products.	Prohibited on Day 1 of Treatment Period 1, Day 1 and Day 39 of Treatment Period 2
Continued access: All patients must avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known potent inducer effects on 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 osimertinib.
Statins:	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.

Rescue/Supportive Medication/Class of drug:	Usage:
Anticoagulant therapy: Patients who are taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and aPTT) be monitored carefully at least once per week for the first month of daily osimertinib administration, then monthly if the INR is stable. Subcutaneous heparin is permitted.	Allowed at any time during the study.
Pre-medication will be allowed after, but not before the first dose of study treatment.	To be administered as directed by the Investigator. This includes management of diarrhoea, nausea and vomiting.
Blood transfusions	Allowed at any time during the study.
Granulocyte colony stimulating factors	Should not be used prophylactically during the PK phase. Use of prophylactic colony stimulating factors may be considered after the PK phase following discussion with the AstraZeneca Study Team Physician.
Corticosteroids and/or bisphosphonates	Patients may receive treatment with corticosteroids and/or bisphosphonates for the treatment of bone metastases.
Palliative radiation	Patients may receive radiotherapy for painful bony metastases. In continued access, the AstraZeneca Study Team Physician should be consulted when considering irradiation to brain or thorax for treatment of symptomatic lesions.
Supportive care and other medications that are considered necessary for the patient's well-being	To be administered as directed by the Investigator.

Patients should be instructed to inform the Investigator if they take any restricted medications.

7.7.1 Other concomitant treatment

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

7.8 Continued Access to Study Treatment

Patients who have not discontinued osimertinib at the end of the PK phase may continue to receive osimertinib as a single agent, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment (continued access).

After the end of the PK phase, the clinical study database will be closed. No further data will be recorded during continued access other than SAEs that may be related to IP and drug dispensing/accountability, until osimertinib is permanently discontinued. For pregnancy reporting during continued access, see Section 6.6. Investigators will continue to follow up any existing SAEs, and report all SAEs that may be related to IP to AstraZeneca Patient Safety, until 30 days after IP is permanently discontinued, in accordance with Section 6.4 (Reporting of SAEs). Investigators should complete paper SAE forms and fax them directly to the AstraZeneca Patient Safety data entry site for entering onto the AstraZeneca Patient Safety database. Also refer to Section 6.7.3 if an SAE of new or worsening pulmonary symptoms that may be related to IP is reported during the continued access phase.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

Statistical analyses will be performed by using SAS® Version 9.2 or higher and, where appropriate, additional validated software.

A comprehensive Statistical Analysis Plan (SAP) will be prepared by the biostatistician and any subsequent amendments will be documented, with final amendments completed prior to database lock.

8.2 Sample size estimate

The number of patients planned to be enrolled in this study is to provide adequate pharmacokinetic information to assess the effects of osimertinib on the pharmacokinetics of fexofenadine, whilst exposing as few patients as possible to the IP and procedures. Eighteen patients would provide adequate PK data. To allow for completion of at least 18 patients, a total of 24 patients will be enrolled.

Interpretation of results will be based on the estimated effect of single dose osimertinib on fexofenadine, and multiple dose osimertinib on fexofenadine (geometric mean ratio) and associated 90% CI. For example, if the estimated treatment ratio (test/reference) is 1.00 and the true intra-subject CV is 30%, then 18 evaluable subjects will provide a CI within 0.70 to 1.43 with a probability of 90%.

8.3 Definitions of analysis sets

8.3.1 Efficacy analysis set

Not applicable.

8.3.2 Safety analysis set

The safety analysis set will include all patients who receive at least 1 dose of osimertinib or fexofenadine.

8.3.3 PK analysis set

The PK analysis set will include all patients who receive a fexofenadine and/or an osimertinib dose and have at least 1 quantifiable plasma concentration collected post-dose without important protocol deviations/violations or events thought to significantly affect the PK of the IP.

The pharmacokineticist will agree on the strategy for dealing with data affected by important protocol deviations or events before any formal statistical analysis is performed. Important protocol deviations or events 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 may not be 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 or timing of the dose, incomplete PK profile collected and/or changes in concomitant medications affecting P-gp that may affect the PK results, 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.

8.3.4 PRO analysis set

Not applicable.

8.4 Outcome measures for analyses

The following outcome measures are to be assessed in relation to the study objectives:

Table 6 Outcome measures

Analysis: PK phase	Outcome Measures:
Primary fexofenadine	Fexofenadine AUC and C_{max} (alone and in combination with osimertinib)
Secondary fexofenadine	Fexofenadine t_{max}, AUC_{0-t}, CL/F,V_z/F, λ_z, $t_{1/2\lambda z}$ (alone and in combination with osimertinib)
Secondary osimertinib and metabolites (AZ5104 and AZ7550)	Osimertinib and metabolites (AZ5104 and AZ7550): Single dose: AUC_{0-72}, C_{max}, t_{max}, and the metabolite ratio (AZ5104:osimertinib, AZ7550:osimertinib) MRC_{max} Multiple dose: AUC_{tau}, $C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$ and CL_{ss}/F (osimertinib only). In addition, the metabolite ratios (AZ5104:osimertinib, AZ7550:osimertinib) $MRAUC_{tau}$ and $MRC_{ss,max}$ Trough concentrations on D11, D18, D25, and D32 for osimertinib and metabolites
Secondary safety	Adverse events, graded by CTCAE Version 4.0, physical examination, vital signs (blood pressure, pulse, temperature, height, weight), standard 12-lead ECG and evaluation of laboratory parameters (haematology, coagulation, clinical chemistry and urinalysis), ophthalmology.

AZ5104 and AZ7550 are metabolites of osimertinib
AUC area under the plasma concentration-time curve from zero extrapolated to infinity; AUC_{0-72} area underplasma concentration-time from time zero to 72 hours post-dose; AUC_{0-t} area under plasma concentration-time from time zero to the last quantifiable concentration; AUC_{tau} area under plasma concentration-time from time zero to the end of the dosing interval; CL/F apparent plasma clearance following oral administration; CL_{ss}/F apparent plasma clearance at steady state; C_{max} maximum plasma concentration; $C_{ss,max}$ maximum plasma concentration after multiple dosing; $C_{ss,min}$ minimum plasma concentration at steady state; $MRAUC_{tau}$ metabolite-parent ratio of AUC_{tau}; MRC_{max} metabolite-parent ratio of C_{max}; $MRC_{ss,max}$ metabolite-parent ratio of $C_{ss,max}$; λ_z terminal rate constant; $t_{1/2\lambda z}$ terminal half-life; t_{max} time to C_{max}; $t_{ss,max}$ time to $C_{ss,max}$; V_z/F apparent volume of distribution.

8.4.1 Calculation or derivation of pharmacokinetic variables

The PK analyses of plasma data for fexofenadine as well as osimertinib and metabolites (AZ5104 and AZ7550) will be performed at

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 6.4 or higher (Certara, L.P. Princeton, New Jersey, United States) and/or SAS® Version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina, United States). Actual elapsed time from dosing will be used for the plasma PK parameter calculations. All descriptive and inferential statistical computations will be performed using SAS® version 9.2, or higher.

The following single-dose plasma PK parameters will be determined for plasma fexofenadine, on Day 1 (Treatment Period 1), Day 1 and Day 39 (Treatment Period 2), when possible:

- AUC: Area under the plasma concentration-time curve from time zero extrapolated to infinity, calculated by linear up/log down trapezoidal summation
- AUC_{0-t}: Area under the plasma concentration-time from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation
- C_{max}: Maximum concentration, obtained directly from the observed concentration versus time data
- t_{max}: Time to reach observed maximum concentration, taken directly from the individual concentration-time curve
- CL/F: Apparent oral plasma clearance
- V_z/F: Apparent volume of distribution
- $t_{½\lambda z}$: Terminal half-life
- λ_z: Terminal rate constant

The following single-dose plasma PK parameters will be determined for plasma osimertinib and metabolites (AZ5104 and AZ7550), on Day 1, Treatment Period 2 when possible:

- AUC_{0-72}: Area under the plasma concentration-time from time zero to 72 hours post-dose, calculated by linear up/log down trapezoidal summation
- C_{max}: Maximum concentration, obtained directly from the observed concentration versus time data
- t_{max}: Time to reach observed maximum concentration, taken directly from the individual concentration-time curve
- MRC_{max}: Ratio of metabolite (AZ5104 and AZ7550) C_{max} to parent C_{max}

The following multiple-dose plasma PK parameters will be determined for plasma osimertinib and metabolites (AZ5104 and AZ7550), on Day 39, when possible:

- AUC_{tau}: Area under the plasma concentration-time curve during a dosing interval
- $C_{ss,max}$: Observed maximum concentration at steady state, taken directly from the individual concentration-time curve
- $t_{ss,max}$: Time to reach observed maximum concentration, taken directly from the individual concentration-time curve

- $C_{ss,min}$: Observed minimum concentration at steady state, tau, taken directly from the individual concentration-time curve
- CL_{ss}/F: Apparent clearance estimated as dose divided by AUC_{tau} (osimertinib only)
- $MRAUC_{tau}$: Ratio of metabolite (AZ5104 and AZ7550) AUC_{tau} to parent AUC_{tau}
- $MRC_{ss,max}$: Ratio of metabolite (AZ5104 and AZ7550) $C_{ss,max}$ to parent $C_{ss,max}$.

8.5 Methods for statistical analyses

8.5.1 Pharmacokinetic analysis (PK phase only)

The sample bioanalysis will be performed by Covance. The merging of PK concentration data with actual PK sampling times will be performed by Data Management. The PK analysis will be the responsibility of the pharmacokineticist at Early Clinical Development, Overland Park, Kansas, United States. The PK summaries, figures, and data listings, as well as the statistical analysis of the PK variables, will be the responsibility of the biostatistician.

All data received will be presented in data listings. Pharmacokinetic summaries will be presented for patients in the PK analysis set, as defined in Section 8.3.3. Data from patients excluded from the PK analysis set will be included in the data listings, but not in the summaries. Extra measurements (such as unscheduled or repeat assessments) will also not be included in summary tables, but will be included in patient listings.

Quantitative variables will be summarised using descriptive statistics, including n, arithmetic mean, standard deviation (SD), coefficient of variation (%CV), median, minimum and maximum values. Additionally, geometric means, geometric coefficient of variation (%GCV), and geometric SD (back transformed), geometric mean – geometric SD (back transformed) and geometric mean + geometric SD (back transformed), will be reported for PK analyte concentrations, and all PK parameters, except for t_{max} and $t_{ss,max}$. After the recruitment and confirmation of evaluability of first 3 severe renal patients, plasma PK parameters will be calculated and an analysis conducted. This analysis will incorporate historical exposure data from matched normal function and severe renal patients from other osimertinib clinical studies. An analysis will be conducted to estimate the ratio of osimertinib exposure metrics between severe renal and normal renal function patients and the results from this analysis may be used to discuss with the regulatory agencies, as appropriate. Any results from this analysis will be conducted and reported separately from the CSR.

8.5.2 Analysis of the pharmacokinetic variable(s)

Plasma concentrations of osimertinib, AZ5104, AZ7550, fexofenadine and the derived PK parameters will be summarised by treatment using descriptive statistics and displayed graphically as appropriate.

To assess the effect of osimertinib on the PK of fexofenadine, natural log-transformed C_{max} and AUC (or AUC_{0-t}, if AUC is not adequately estimable) will be compared between treatments separately using a linear mixed effects model, with treatment as a fixed effect and patient as a random effect. The following comparisons will be performed:

- Fexofenadine and osimertinib single doses (Treatment Period 2 Day 1) versus fexofenadine single dose (Treatment Period 1).

- Fexofenadine single dose and osimertinib at steady state (Treatment Period 2 Day 39) versus fexofenadine single dose (Treatment Period 1).

Estimates of the mean difference between treatments and corresponding 90% CIs will be calculated. The mean differences and the CIs will be back-transformed to the original scale in order to give estimates of the ratios and the associated 90% CIs. Additionally, back-transformed geometric means together with 95% CIs for AUC and C_{max} will be estimated and presented for each treatment.

Furthermore, for fexofenadine, analyses of t_{max} will be performed using the Wilcoxon Signed Rank Test. The Hodges-Lehmann median estimator of the difference in treatments (fexofenadine plus osimertinib –fexofenadine alone) and 90% CIs will be presented.

Steady state of osimertinib and its metabolites will be assessed graphically.

8.5.3 Demographic and safety analyses

For qualitative demographic and safety variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarised using descriptive statistics, including n, mean, SD, median, minimum, and maximum values. Where appropriate, assessments will be summarised by visit. All data will be summarised and listed appropriately.

The number of patients screened and included in the Safety analysis set will be summarised. Demographic and baseline characteristics will be summarised and listed for the Safety analysis set.

Treatment duration will be summarised. Treatment duration is based on the dates of first and last dose.

Study day will be calculated as follows:

- Days prior to first dose: Study day = date – first dose date.

- Days on or after first dose: Study day = date – first dose date + 1.

The “dose” used to determine the first dose date will be fexofenadine for Treatment Period 1, and osimertinib for Treatment Period 2.

Safety profiles will be assessed using the Safety set, in terms of AEs, vital signs (including BP, pulse and temperature), ECG, laboratory data (clinical chemistry, haematology and urinalysis), physical examinations and echocardiogram.

Appropriate summaries of AEs, laboratory data, vital signs, and ECGs will be produced. Adverse events will be summarised separately for Treatment Periods 1 and 2. Laboratory data, vital signs, temperature, and ECGs will be summarised for Treatment Period 2. Summaries will be presented for scheduled visits only. Any unscheduled assessments will be listed. Physical examinations and echocardiogram data will only be listed.

The baseline value for laboratory data, vital signs and ECGs is defined as the latest result obtained prior to the start of Treatment Period 1.

The number of patients experiencing AEs following administration of osimertinib as well as the number of AEs experienced will be summarised. Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) system of nomenclature (preferred term and system organ class [SOC]). Adverse events reported before administration of study treatment will be listed only and be referred to as "pre-treatment". Treatment emergence will be defined for each part of the study (Treatment Periods 1 and 2).

For Treatment Period 1, a treatment emergent AE (TEAE) will be defined as an AE with the start date and time on or after the first dose date and time, and up to (not including) the date and time of the first dose in Treatment Period 2, or up to (and including) 30 days after dosing in Treatment Period 1.

For Treatment Period 2, a TEAE will be defined as an AE with the start date and time on or after the first dose date and time in Treatment Period 2, and up to (and including) 30 days after the last Treatment Period 2 dose date.

Similarly, the number of patients experiencing SAEs, other significant AEs (OAEs), AEs that led to discontinuation of IP (DAEs), AEs that led to death, and treatment-related AEs and the number of such events will be summarised by study period.

All AE data will be listed for all patients. In addition, SAEs, OAEs, and AEs that led to withdrawal or death, and treatment-related AEs will be listed.

Laboratory data (haematology, clinical chemistry and urinalysis) will be summarised and listed. Shift tables will be provided for select tests, where shift from baseline to the worst value for Treatment Period 2 will be summarised. Laboratory data outside the reference ranges should be indicated in the listings.

Concomitant medications will be summarised by the coded terms for both Treatment Periods 1 and 2. The number of patients receiving a medication will be summarised overall and for each period of the study. A medication taken during the course of the study is considered concomitant. A patient is only counted once even if they receive the medication more than once within that period of the study.

The impact of any important protocol deviations, missing data and the use of rescue or concomitant medication on the robustness of study results will be investigated and any methods employed to deal with these will be documented.

Further details of summaries of the safety data will be given in the SAP.

8.5.4 Subgroup analysis (if applicable)

Not applicable.

8.5.5 Interim analysis

No interim analysis is planned.

8.5.6 Sensitivity analysis (if applicable)

Not applicable.

8.5.7 Exploratory analysis (if applicable)

The relationship between PK and treatment period and other variables may be assessed, as deemed appropriate. Results will be reported separately from the CSR.

The PK, demographic, treatment and safety data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK methods if deemed appropriate. The results of any such analyses will be reported separately from the CSR.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

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

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

9.2 Monitoring of the study

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the 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 patients (eg, 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 patients.

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

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The PI at each/the centre 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 Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the PI 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.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patients undergoing the study'. This will occur when the last patient receiving treatment as continued access has permanently discontinued osimertinib and had their 30 day safety follow-up contact.

The study is expected to start in Q1 2017 and the PK phase is expected to end by Q2 2017.

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

9.4 Data management by

Data management will be performed by Data Management, according to the Data Management Plan (DMP).

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

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary.

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 DMP. 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 DMP will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all patients have completed the PK phase of the study (or at the request of AstraZeneca), a database lock will be carried out. All PK phase data for patients who have completed by the time of the database lock transfer will be cleaned and validated as defined in the DMP. A CSR will be produced reporting the PK phase data.

Data from continued access phase of the study will only be recorded in the source documents; these data will not be entered into the study database (see also Section 7.8), nor reported as an addendum to the CSR.

Serious Adverse Event (SAE) Reconciliation

Serious AE 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 within the relevant sample tracking system at AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples.

The results from this genetic research will be reported separately from the main CSR.

Data associated with human biological samples

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

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Subject data protection

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

AstraZeneca 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**.**

Precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patients. 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 subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

An Ethics Committee (EC) 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, and to the study site staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study. The EC should approve all advertising used to recruit patients for the study. AstraZeneca 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 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 will handle

the distribution of any of these documents to the national regulatory authorities. AstraZeneca will provide Regulatory Authorities, ECs and PIs with safety updates/reports according to local requirements.

Each PI is responsible for providing the EC/Institutional Review Board (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 PI so that he/she can meet these reporting requirements.

10.4 Informed consent

The PI(s) or Sub-investigator(s) at each centre 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 ICF before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International Co-ordinating Investigator, 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 and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

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

If a protocol amendment requires a change to a centre's ICF, AstraZeneca and the centre's EC 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.

10.6 Audits and inspections

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

11. LIST OF REFERENCES

Bonomi 2010
Bonomi PD. Implications of key trials in advanced non-small cell lung cancer. Cancer 2010; 116:1155-1164.

EMA 2012
European Medicine Agency (EMA), Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions. 21 June 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf

Ferlay et al 2010
Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010:127(12);2893-917. DOI:10.1002/ijc.25516.

Fukuoka et al. 2011
Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS, Sriuranpong V, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol. 2011;29:2866-74.

Herbst et al. 2008
Herbst RS, Heymach JV, Lippman SM. Lung cancer. N Engl J Med. 2008;359:1367-80.

Heuckmann et al 2012
Heuckmann JM, Rauh D, Thomas RK. Epidermal growth factor receptor (EGFR) signaling and covalent EGFR inhibition in lung cancer. J Clin Oncol 2012, 30(27);3417-3420 DOI:10.1200/JCO.2012.43.1825

NCCN 2012
National Comprehensive Cancer Network Guidelines for Treatment of Cancer by Site. 2012. Available from URL: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site.

NCCN 2016
National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Non-small cell lung cancer. Version 4.2016. Available from: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed on 4 May 2016.

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

Pisters and Le Chevalier 2005
Pisters KMW, Le Chevalier T. Adjuvant chemotherapy in completely resected non-small-cell lung cancer. J Clin Oncol 2005;23:3270-3278.

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

Su et al. 2012
Su KY, Chen HY, Li KC, Kuo ML, Yang JCH, Chan WK, et al. Pretreatment epidermal growth factor receptor (EGFR) T790M mutation predicts shorter EGFR tyrosine kinase inhibitor response duration in patients with non-small-cell lung cancer. J Clin Oncol. 2012;30:433-40.

Travis et al. 2011
Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thor Oncol. 2011;6: 244-85.

Wang et al. 2012
Wang M, Zhao J, Zhang LM, Li H, Yu JP, Ren XB, et al. Combined erlotinib and cetuximab overcome the acquired resistance to epidermal growth factor receptors tyrosine kinase inhibitor in non-small-cell lung cancer. J Cancer Res Clin Oncol. 2012;138:2069-77.

Wu et al. 2010
Wu JY, Wu SG, Yang CH, Chang YL, Chang YC, Hsu YC, et al. Comparison of gefitinib and erlotinib in advanced NSCLC and the effect of EGFR mutations. Lung Cancer. 2011;72:205-12.

Yu et al. 2013
Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res. 2013;19:2240-7.

Appendix A Additional Safety Information

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

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the 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.

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

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the 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?

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

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

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

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

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

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

- Is there a known mechanism?

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

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

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B 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 study samples will fall into Category B or exempt under IATA regulations

- Clinical study 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.

Appendix C Pharmacogenetics Research

Background and Rationale

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

It is emphasised that AstraZeneca will only look for markers within genes relevant to the mode of action of, and response to osimertinib, and the disease under study within the current Clinical Study Protocol. No other research will be performed on the samples.

Genetic Research Objectives

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to osimertinib and/or the disease under study within the current Clinical Study Protocol.

Genetic Research Plan and Procedures

Selection of genetic research population

Study selection record

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

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 **and**:

- Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

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 Sections 3.9 and 3.10 of the main Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at Visit 1. 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 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 5.2.2 of the Clinical Study Protocol.

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 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 relevant sample tracking system 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.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

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 PI(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.

Subject 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.

Data management

Any genotype data generated in this study will be stored within the relevant tracking system at AstraZeneca and/or third party contracted to work with AstraZeneca to analyse the samples.

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

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

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.

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

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

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

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3×ULN **together with** total bilirubin ≥ 2×ULN at any point during the study following the start of study drug irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3×ULN **together with** total bilirubin ≥ 2×ULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

Identification of Potential Hy's Law Cases

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

- ALT ≥ 3×ULN
- AST ≥ 3×ULN

- Total bilirubin ≥ 2×ULN

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

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

Follow-up

Potential Hy's Law Criteria not met

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

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

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 (See Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)
- Notify the AstraZeneca representative who will then inform the central Study Team

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

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

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 Study Physician 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 total bilirubin (TBL) elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

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

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

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

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

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

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

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required
  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Potential Hy's Law Criteria met of this Appendix

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

Actions Required for Repeat Episodes of Potential Hy's Law

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

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

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

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

If No: follow the process described in Potential Hy's Law Criteria met of this Appendix

If Yes:

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

- If there is no significant change no action is required

- If there is a significant change follow the process described in Section 4.2 of this Appendix

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

References

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

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

Appendix E Acceptable Birth control Methods

Osimertinib is regarded as a compound with medium/high foetal risk

Patients of childbearing potential and their partners, who are sexually active, must agree to the use of 2 highly effective forms of contraception throughout their participation in the study and for 3 months (females) and 6 months (males) after last dose of study drug.

Acceptable non-hormonal birth control methods include:

- True sexual abstinence. When this is in line with the preferred and usual lifestyle of the patient. *[Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]*. . Abstinence must be for the total duration of the study and until 3 months (females) and 6 months (males) after discontinuation of study treatment.

- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.

- Tubal occlusion plus male condom with spermicide

- Intrauterine device (IUD) plus male condom + spermicide. Provided coils are copper-banded.

Acceptable hormonal methods:

- IUS Levonorgestrel Intra Uterine System (Mirena) + male condom with spermicide

- Medroxyprogesterone injections (Depo-provera) + male condom with spermicide.

Appendix F Eastern Cooperative Oncology Group (ECOG) Performance Status

Patient ability	Score
Fully active, able to carry on all pre-disease performance without restriction	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work	1
Ambulatory and capable of all self-care, but unable to work. Up and about more than 50% of waking hours	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	3
Completely disabled, unable to carry out any self-care and confined totally to bed or chair	4

Appendix G 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.

Drugs Inducing CYP3A4 Metabolism that AstraZeneca Strongly Recommend are Not Combined with Osimertinib

Osimertinib is metabolised by CYP3A4 and CYP3A5 enzymes.

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

The following potent inducers of CYP3A4 must not be used during this study for any patient receiving osimertinib (Table 7).

Table 7 Drugs inducing CYP3A4

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

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

Medicines Whose Exposures May be Affected by Osimertinib that AstraZeneca Considers May be Allowed with Caution

Osimertinib may increase the concentration of sensitive breast cancer resistance protein (BCRP) substrates (concentration of the sensitive BCRP substrate, rosuvastatin, is increased). This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to be modulated BCRP activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

Table 8 Exposure, pharmacological action and toxicity may be increased by osimertinib

Warning of possible interaction	Advice
Rosuvastatin Sulfasalazine	Drugs are permitted but caution should be exercised and patients monitored closely for

Table 8 Exposure, pharmacological action and toxicity may be increased by osimertinib

Warning of possible interaction	Advice
Doxorubicin Daunorubicin Topotecan	possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with osimertinib.

Drugs that May Prolong QT Interval

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

Drugs Known to Prolong QT Interval

The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with osimertinib. Recommended withdrawal periods following cessation of treatment with these agents are provided in Table 9.

Table 9 Drugs prolonging QT interval

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

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

Drugs that may possibly prolong QT interval

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated (Table 10).

Table 10 Drugs that may prolong QT interval

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

Drugs Contraindicated for Administration with Fexofenadine (PK phase)
Inducers of p-glycoprotein (P-gp) and inhibitors of P-gp known to increase the exposure as defined by the area under the concentration versus time curve by more than 1.25 fold should not be administered within 3 weeks of the first administration of fexofenadine through collection of the final PK sample on Day 42 of Part A

The following inducers of P-gp must not be used during this study for any patient in Part A of the study (Table 11).

Table 11 Drugs inducing P-gp

Contraindicated drugs	Withdrawal period prior to fexofenadine start
Avasimibe, carbamazepine, efavirenz, genistein (found in food products), phenytoin, quercetin (found in food products), rifampicin, St John's Wort, tipranavir/ritonavir	3 weeks

The following inhibitors of P-gp must not be used during this study for any patient in Part A of the study or should not be changed during the treatment period (Table 12).

Table 12 Drugs inhibiting P-gp

Contraindicated drugs	Withdrawal period prior to fexofenadine start
Alogliptin, amiodarone, , azithromycin, captopril, carvedilol, clarithromycin, clopidogrel, conivaptan, curcumin, cyclosporine, diltiazem, dronedarone, eliglustat, erythromycin, felodipine, fluvoxamine, indinavir, indinavir/ritonavir, itraconazole, ivacaftor, ketoconazole, lapatinib, lopinavir/ritonavir, mibefradil, milk thistle, nelfinavir, paroxetine, propafenone, quercetin (found in food products), quinidine, quinine, ranolazine, rifampicin, ritonavir, saquinavir/ritonavir, schisandra chinensis extract, simeprevir, St John's Wort (single dose), suvorexant, telaprevir, ticagrelor, tipranavir/ritonavir, valspodar (PSC 833), verapamil, vorapaxar	3 weeks
Allowed drugs	
Canagliflozin, cremophor RH40, ginkgo, mirabegron, nifedipine, nitrendipine, talinolol, telmisartan, tolvaptan, vandetanib, voclosporin	Medication should not be changed (adjusted or discontinued) within 10 days of Day 1, Period 1 in Part A through collection of the last planned PK sample in Part A (Day 42, 72 hours) unless medically necessary.

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

Appendix H Guidance for the Management of Adverse Events in Studies using 80 mg AZD9291

Guidance for the Management of Adverse Events in Studies using 80mg AZD9291

Skin Reactions

Diarrhoea

Ophthalmic Assessments

LVEF

ILD / Pneumonitis

A Guide for Investigators

Version 4.0: 28 June 2016

Contents

Introduction

AZD9291 is a potent irreversible small molecule inhibitor of both the single EGFRm+ (tyrosine kinase inhibitor (TKI) sensitivity conferring mutations) and dual EGFRm/T790M (TKI resistance conferring mutation) receptor forms of EGFR, with weaker inhibition towards wild type EGFR (compared with gefitinib or erlotinib). The development programme focuses on the treatment of patients with Non Small Cell Lung Cancer (NSCLC) which have the EGFRm and T790M mutations.

Clinical experience with 80mg AZD9291 has shown an association with the occurrence of dermatological adverse events (particularly rash and dry skin) and diarrhoea. The considerable majority of these events have been mild, transient events that have not always required treatment.

Based on experience with other EGFR and HER2 inhibitors, decreases in LVEF; anterior ocular effects and ILD/pneumonitis should be monitored for.

Some guidance is provided in this document regarding these events.

The purpose of these treatment guidelines is:

- To prevent tolerable adverse events becoming intolerable for the patient and leading to discontinuation of treatment.
- To promote consistency of treatment for specific adverse events across the AZD9291 clinical development programme.

Skin Effects – Rashes & Acnes

- Skin effects may occur at any time, but most likely to start within 2 weeks of starting study treatment
- **Patients may consider applying over-the-counter moisturising cream to face, hands and feet twice daily from the start of study.**
- Treatment administered should be recorded in the **MED** module
- Any occurrence of a skin event should be recorded as an Adverse Event by completing the **AELOG** CRF, and the severity captured using the CTCAE(v4) grading system.
- Please also complete the **SKNREAC** CRF to record details of the rash. This will help future management of these events.
- AstraZeneca will be reviewing dermatological adverse events on an ongoing basis and may ask for additional information to be provided

You can request additional expert advice on management of dermatological reactions via the Study Medical Monitor, particularly if:

A patient has not responded to dermatological intervention and permanent discontinuation of AZD9291 is being considered

Please provide anonymised

- description of reaction: time to onset, anatomical location, associated symptoms, dermatological interventions already implemented
- patient age, comorbidities and concomitant medications

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Skin Effects - Rash Treatment Guidance

Patients may consider applying over-the-counter moisturising cream to face, hands & feet twice daily from start of study.

CTCAE(v4) Grade 1

- **<10% body surface area (BSA)** papules/pustules
- with or without symptoms of pruritus or tenderness

Emollient cream application
and/or
Topical steroid moderate strength bid
and/or
Topical antibiotic bid

CTCAE(v4) Grade 2

- **10 to 30% BSA** papules/pustules with or without symptoms of pruritus or tenderness
- **psychosocial impact**
- **limiting instrumental activities of daily living (ADL)**

- Treatment same as Grade 1
- Consider using oral antibiotic for 6 weeks

CTCAE(v4) Grade ≥3

- **>30% BSA** papules/pustules with or without symptoms of pruritus or tenderness
- **limiting self-care ADL**
- **associated with local superinfection**

Topical steroid moderate strength bid
and
Oral antibiotic for 6 weeks
Switch to broad spectrum/gram negative cover if infection suspected (yellow crusts, purulent discharge, painful skin / nares)
Consider skin swab for bacterial culture

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Dry Skin / Xerosis Treatment Guidance

Patients may consider applying over-the-counter moisturising cream to face, hands & feet twice daily from start of study.

CTCAE(v4) Grade 1

- <10% body surface area (BSA)
- No associated erythema or pruritus

- Face/Hands/Feet: over-the-counter moisturising cream or ointment bid
- Body: ammonium lactate 12% cream bid or salicylic acid 6% cream bid

CTCAE(v4) Grade 2

- 10 to 30% BSA
- Associated with erythema or pruritus
- Limiting instrumental activities of daily living (ADL)

- Treatment same as Grade 1

CTCAE(v4) Grade ≥3

- >30% BSA
- Associated with erythema or pruritus
- Limiting self-care ADL

- Treatment same as Grade 1/2, plus:
- Eczematous areas of body: topical steroid moderate strength bid

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Pruritus Treatment Guidance

Patients may consider applying over-the-counter moisturising cream to face, hands & feet twice daily from start of study.

CTCAE(v4) Grade 1

- Mild or localised
- Topical intervention indicated

- Topical steroid moderate strength bid or topical antipruritic bid

CTCAE(v4) Grade 2

- Intense or widespread
- Intermittent
- Skin changes from scratching (e.g. oedema, papulation, excoriation, lichenification, oozing/crusts)
- Oral intervention indicated
- Limiting instrumental ADL

- Topical steroid moderate strength bid or topical antipruritic bid
- Oral antihistamine

CTCAE(v4) Grade ≥3

- Intense or widespread
- Limiting self-care ADL or sleep
- Oral corticosteroid or immunosuppressive therapy indicated

- Oral antihistamine
- GABA agonist (gabapentin 300 mg or pregabalin 50-75 mg every 8 hours)

Paronychia Treatment Guidance

Patients may consider applying over-the-counter moisturising cream to face, hands & feet twice daily from start of study.

CTCAE(v4) Grade 1

- Nail fold oedema or erythema
- Disruption of the cuticle

- Topical antibiotic bid and vinegar soaks#

CTCAE(v4) Grade 2

- Localised intervention indicated
- Nail fold oedema or eythema with pain
- Associated with discharge or nail plate separation
- Limiting instrumental activities of daily living (ADL)

- Topical antibiotic bid and vinegar soaks#
- Topical silver nitrate weekly

CTCAE(v4) Grade ≥3

- Surgical intervention or IV antibiotics indicated
- Limiting self-care ADL

- Topical antibiotic bid and vinegar soaks#
- Topical silver nitrate weekly
- Consider nail avulsion / removal

Soaking fingers or toes in a 1:1 solution of white vinegar in water for 15 minutes every day

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Key Points for Dermatological Guidance

- Patients may consider applying over-the-counter moisturising cream to face, hands and feet bid from the start of study.
- Investigators may consider issuing a prescription for topical treatment to patients. However, topical steroids and topical or oral antibiotics should not be implemented prophylactically and treatment should only be started when confirmed with Investigator.
- **As soon as an acneiform / papulopustular rash occurs, treatment with moderate strength topical steroids and antibiotics should be implemented.**
- Use of topical benzoyl peroxides and other irritating anti-acne agents should be avoided.
- **Patients should be instructed to contact the site if the skin reaction changes (e.g. if it spreads or becomes painful)**
- Investigators should record skin effects in the **AELOG** and **SKNREAC** CRF modules.
- The occurrence of non-papulopustular skin reactions should be treated appropriately, as defined by the treating physician, and in consultation with a dermatologist where necessary
- Photographs of skin reactions should be sent to the AstraZeneca study team, which may be used for external expert dermatological review if required.

Diarrhoea Treatment Guidance

Uncomplicated CTCAE (v4) Grade ≤2 diarrhoea:

- Dietetic measures:
  - Stop all lactose-containing products
  - Drink 8 to 10 large glasses of clear liquids per day
  - Eat frequent small meals
  - Recommend low fat regimen enriched with rice, bananas, and apple sauce
- Pharmacological treatment:
  - Administer loperamide: initial dose 4mg, followed by 2mg every 4 hours or after every unformed stool.
  - Grade 1 intermittent diarrhoea may not require treatment
  - Consider continuation of loperamide until diarrhoea-free for 12h
  - Consider electrolyte replacement, as appropriate

CTCAE (v4) Grade ≥3 or any Grade with complications (dehydration, fever and/or Grade ≥3 neutropenia):

- Dietetic measures:
  - As per Grade ≤2 diarrhoea
- Pharmacological treatment:
  - As per Grade ≤2 diarrhoea
  - If dehydration is severe, administer octreotide and use intravenous fluids as appropiate.
  - Consider prophylactic antibiotics, especially if diarrhoea is persistent beyond 24h or there is fever or Grade 3-4 neutropenia
  - Consider electrolyte replacement, as appropriate, and consider more frequent measurement of electrolytes until AE resolves

Advice for Patients: Skin Reactions and Diarrhoea

- It is important that patients are fully informed that skin reactions or diarrhoea may occur during treatment with AZD9291
- Patients should be informed that skin reactions and diarrhoea:
  - Are not contagious
  - Do not result from allergy to treatment
- Patients should be encouraged to report any instances of skin reaction or diarrhoea as soon as they arise so that appropriate treatment can be promptly initiated
- Patients should be instructed to contact the site if a skin reaction changes (e.g. if it spreads or becomes painful)
- It may be beneficial to avoid irritating skin products (e.g. irritating soaps, products containing retinol or retinoic acid)
- Camouflage make-up (non-comedogenic or non-pore blocking) can be used during study treatment

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Introduction – Ophthalmic Assessments

AZD9291 is a potent irreversible small molecule inhibitor of both the single EGFRm+ (tyrosine kinase inhibitor (TKI) sensitivity conferring mutations) and dual EGFRm/T790M (TKI resistance conferring mutation) receptor forms of EGFR, with weaker inhibition towards wild type EGFR (compared with gefitinib or erlotinib). The development programme focuses on the treatment of patients with Non Small Cell Lung Cancer (NSCLC) which have the EGFRm and T790M mutations.

There have been no keratitis or ulcerative events with **clinical experience with AZD9291**, but an association between the use of other EGFR TKIs and the occurrence of ophthalmic adverse events has been reported.[1]

As a result, AstraZeneca has chosen to include the following in the clinical study:

- baseline slit-lamp assessments for all patients
- follow-up assessments for those patients reporting any clinically significant and/or persistent ophthalmic symptom

The purpose of these guidelines is to:

- provide guidance on when to perform follow-up ophthalmic assessments
- promote consistency of assessment across the study

[1] Tullo et al., Eye, 2005; 19:729-738

Ophthalmic Assessments

Baseline

- Slit lamp examination performed by an ophthalmologist (or appropriately qualified individual)
- Date of assessment should be recorded on the **VISUAL** CRF
- Results should be recorded in the patient's notes

Follow-up

- If the patient reports any eye symptoms during treatment with AZD9291 or if signs are observed during a study visit, the Investigator should perform a clinical examination including a repeat best corrected near and distant visual acuity assessment if appropriate
- Findings should be documented in the patient's notes

Referral to Ophthalmologist

- Patients with ophthalmic AEs of CTCAE Grade ≥ 3 or eye symptoms that are clinically significant and/or persistent (>7 days) should be referred to the ophthalmologist. For example:
  - Deterioration in near or distant visual acuity by more than one level
  - Persistence or worsening of:
    - Burning/ irritation/ smarting
    - Itching
    - Redness with or without discharge
    - Light sensitivity (photophobia)
    - Blurred vision
- Ophthalmology examination findings should be documented in the patient's notes and reported to AstraZeneca if required

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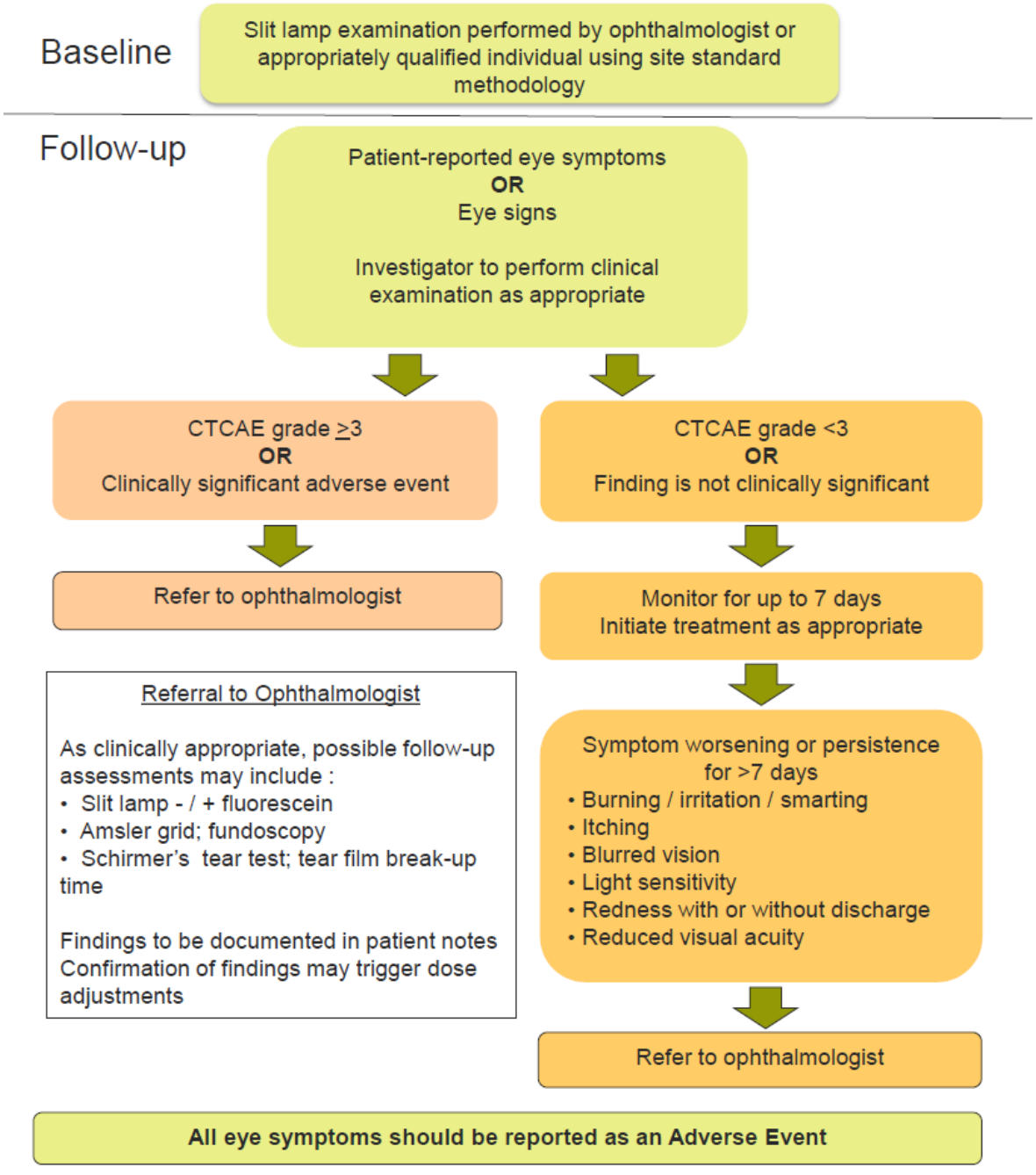
Post-baseline Ophthalmic Findings

- Any clinically significant post-baseline ophthalmic findings, including those confirmed by the ophthalmologist, must be recorded as an Adverse Event by completing the **AELOG** module, and the severity captured using the CTCAE(v4) grading system.
- In addition, a report should be provided to AstraZeneca detailing:
  - ophthalmic examinations performed
  - findings
  - photographic record of appropriate findings
- Treatment administered should be captured on the **MED** CRF

Ophthalmic Assessments Flow Chart



Guidance on Ophthalmic Dose Adjustments

Confirmed CTCAE Grade ≥3
OR
clinically significant or persistent (present for >7 days) Adverse Event
and considered causally related to AZD9291

Initiate ophthalmic treatment as appropriate and withhold dose for up to 3 weeks

- **If adverse event improves to CTCAE Grade ≤1 within 3 weeks reinstate AZD9291 at the current dose maintaining treatment as appropriate**
- **If adverse event improves to CTCAE Grade 2 within 3 weeks, consider reinstating AZD9291 at a reduced dose* (1 dose level) maintaining treatment as appropriate**
- **Where a CTCAE Grade ≥3 or clinically significant or persistent adverse event does not improve to a lower CTCAE Grade within 3 weeks of AZD9291 interruption, AZD9291 should be permanently discontinued.**

*** Note dose reduction requirements in CSP**

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Summary of Ophthalmic Guidance

- It is important that patients are fully informed that ophthalmic events may occur during treatment with AZD9291.
- AZD9291 should not be administered on the first scheduled day if the patient has any clinically significant eye symptoms.
- Patients should be encouraged to report any instances of ophthalmic symptoms and/or vision changes to allow the appropriate treatment to be initiated. Symptoms may include:
  - Burning / itching / irritation / smarting
  - Redness with / without discharge
  - Blurred vision
  - Light sensitivity
- Patients who wear contact lenses must discontinue wearing them if they have any mild to moderate eye symptoms (CTCAE grade ≤2) until at least one week after symptoms have resolved.
- Patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed by a study doctor, at any time during the study until 1 week after AZD9291 has been permanently discontinued.
- If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade ≥3) ocular events they must discontinue wearing their contact lenses until at least one week after treatment with AZD9291 is permanently discontinued.
- **Ulcerative events must result in permanent discontinuation from study**

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LVEF Guidance

- AZD9291 is a potent irreversible small molecule inhibitor of both the single EGFRm+ (tyrosine kinase inhibitor (TKI) sensitivity conferring mutations) and dual EGFRm/T790M (TKI resistance conferring mutation) receptor forms of EGFR, with weaker inhibition towards wild type EGFR (compared with gefitinib or erlotinib). The development programme focuses on the treatment of patients with Non Small Cell Lung Cancer (NSCLC) which have the EGFRm and T790M mutations.

- AZD9291 and its active metabolite may also inhibit HER2. For this reason, LVEF measurements are being taken at baseline and every 12 weeks to monitor for potential decreases in LVEF.

- For high quality data and best assessment of risk:
  - The same method must be used for each patient (i.e. ECHO throughout, or MUGA throughout)
  - Please use the same machine for each assessment
  - Wherever possible, the scans must be performed by the same operator

- Consult cardiologist or AstraZeneca for abnormal LVEF results, at the Investigator's discretion

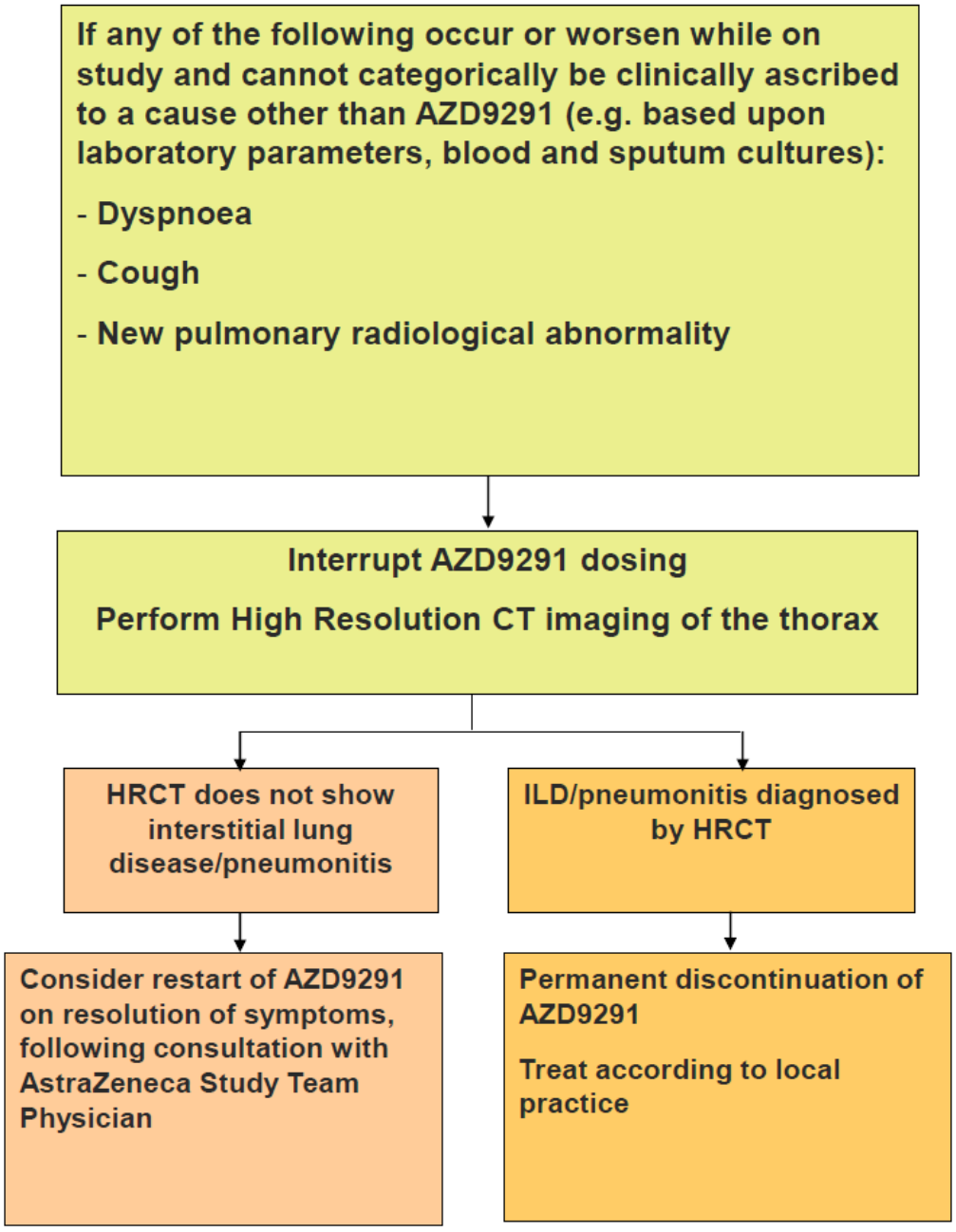
- *ad hoc* measurement of LVEF should be performed if the investigator has clinical suspicion of new onset impaired cardiac function

- Patients are to be managed clinically according to local practice

ILD / Pneumonitis Guidance

- AZD9291 is a potent irreversible small molecule inhibitor of both the single EGFRm+ (tyrosine kinase inhibitor (TKI) sensitivity conferring mutations) and dual EGFRm/T790M (TKI resistance conferring mutation) receptor forms of EGFR, with weaker inhibition towards wild type EGFR (compared with gefitinib or erlotinib). The development programme focuses on the treatment of patients with Non Small Cell Lung Cancer (NSCLC) which have the EGFRm and T790M mutations.
- A number of unconfirmed pneumonitis like events have been seen in patients dosed with 80mg AZD9291. Causality has not been established.
- If you have clinical suspicion of interstitial lung disease (ILD), dosing with AZD9291 should be interrupted whilst further investigations are performed.
- Please complete the eCRF and inform AstraZeneca as soon as a potential pneumonitis event is identified. The Study Team will send a pneumonitis questionnaire to you, in order to collect more information about the event for full review and reporting.
- All Imaging conducted throughout the study (including High Resolution CTs (HRCT) at time of pneumonitis diagnosis and follow up) will be requested to be sent to AstraZeneca for independent review.
- A diagnostic workup (including HRCT, blood and sputum culture, laboratory parameters) should be performed, to exclude conditions such as lymphangitic carcinomatosis, infection, allergy or pulmonary haemorrhage.
- In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded a diagnosis of interstitial lung disease should be considered and study treatment permanently discontinued.

ILD & Pneumonitis Guidance



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