Clinical Study Protocol	
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An Open-label Positron Emission Tomography (PET) Study to Determine Brain Exposure of Osimertinib after Intravenous Microdose Administration of [^{11}C]osimertinib and Therapeutic Oral Doses of Osimertinib to Patients with EGFR Mutated Non-Small Cell Lung Cancer and Brain Metastases

Sponsor: AstraZeneca AB. 151 85 Sodertalje. Sweden

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VERSION HISTORY

Version 1.0, 15 January 2018
INITIAL CREATION
Version 2.0, 24 September 2019
Changes of the protocol are summarized below: 3.1 Inclusion criteria: • 4. Updated to combine the criteria of the EGFR mutation T790M and the assessment by local laboratory via tissue/cytology or in plasma. • 5. Criteria removed and language incorporated into Inclusion criteria 4. • 6. Clarified confirmation of BM as having at least one non-measurable and/or measurable brain lesion at baseline as per CNS RECIST 1.1 • 7. Removed the following statement: with no deterioration over the previous 2 weeks • 7. Minimum life expectancy has been decreased from 12 weeks to 4 weeks to reflect the target population for the study more accurately. 3.2 Exclusion Criteria: • 3. Updated to exclude subjects that have had treatment with an EGFR-TKI within 10 days as opposed to 15 days, in order to avoid the risk of disease flare. • 5. Updated to exclude subjects with a history of brain metastases that is/are in the same hemisphere as the current brain metastases. • Cardiac criteria assigned as exclusion criteria 7. All numbering of subsequent criteria re-assigned accordingly. • 7. Language in Cardiac criteria updated as per most recent project specific safety requirements. Table 1: • Day (window) for Clinical Visit 3 and PET3 has been updated to reflect the maximum window for the PET and RECIST assessments following repeat dosing. Prior was 29 +/-7 days =36 days dosing. Updated to +25 (+/-4 days). • PK sampling times in footnote O updated from 1, 2, 4 and 6 hour(s) to 2, 4 and 7.5 hour(s). Table 4: Updated language in (cardiac section) as per project specific safety requirements.

6.8.4 QTc prolongation:

Updated language to align with the potential for QT changes.

8.5.4 PET imaging:

Clarified that this pertains to modified CNS RECIST 1.1 criteria.

9. 3 Study timetable and end of study:

Section 9.3.1 added detailing study and site closure as per ICH GCP requirements.

11 References:

Project specific safety requirements added as a reference along with the most recent versions of AZD9291 and [^{11}C]Osimertinib Investigator's Brochures.

Appendix C:

Updated as per most recent project specific safety requirements.

- Language updated throughout the document to ensure consistency that approximately 12 patients will be enrolled in order to obtain at least 8 evaluable patients.

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

CLINICAL STUDY PROTOCOL SYNOPSIS

An Open-label Positron Emission Tomography (PET) Study to Determine Brain Exposure of Osimertinib after Intravenous Microdose Administration of [^{11}C]osimertinib and Therapeutic Oral Doses of Osimertinib to Patients with EGFR Mutated Non-Small Cell Lung Cancer and Brain Metastases

Principal Investigator

PPD

Study centre and number of patients planned

This study will be conducted in Sweden. Recruitment and screening will take place at PPD and PPD. The study procedures will be conducted at the main study centre at PPD Approximately 12 patients with EGFR mutated non-small cell lung cancer with brain metastases will participate in this study. It is expected that at least 8 patients will complete all planned study assessment procedures.

Phase of development: Phase I

Study design

The study design includes 2 phases, the imaging phase and the continued access phase. Using high resolution positron emission tomography, this open-label study will examine brain distribution and retention of a microdose of [^{11}C]osimertinib in approximately 12 patients with epidermal growth factor receptor mutated non-small cell lung cancer and brain metastases. The imaging data analysis will include quantification of the maximum radioactivity concentration of [^{11}C]osimertinib in the brain after injection (percent of injected dose entering the brain).

The imaging phase of the study will include 3 single intravenous microdose administrations of [^{11}C]osimertinib and positron emission tomography examinations. Oral administration of osimertinib tablets (80 mg once daily) to patients will begin from the day of the second positron emission tomography for at least 21 days before the third positron emission tomography examination. The second phase, the continued access phase, will allow patients to continue to take osimertinib tablets (80 mg once daily) as a single agent depending on the agreement between the patient and the Investigator. Osimertinib administration will continue

until, in the opinion of the Investigator, the patients are no longer deriving clinical benefit, or the patients 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 that may be related to osimertinib, outcomes of pregnancy and IP dispensing/accountability.

Patients not participating in the continued access phase or who discontinue treatment during the imaging phase will return to the clinic for follow-up assessments 30 days (±7 days) after their last administration of osimertinib in the imaging phase. If the patient's last administration of osimertinib is in the continued access phase, the patient should be contacted 30 days after their last administration of osimertinib to follow up on any existing AEs/SAEs and monitor for new AEs/SAEs that may be related to the IP and record any sudden deaths of unknown cause.

Objectives

Primary Objective:	**Outcome Measure:**
To determine the brain exposure of [^{11}C]osimertinib in tumour regions of interest, (brain metastases, including leptomeningeal metastases) in patients with non-small cell lung cancer after a single intravenous microdose and after single and multiple therapeutic administrations of osimertinib.	The percent of injected dose in the whole brain and brain standard uptake value, to describe maximal radioactivity concentration in the brain. The time of the maximum radioactivity concentration in the brain. The brain to plasma partition coefficient (concentration brain/plasma ratio) as area under the concentration-time curve. All parameters of exposure will include the tumour region, whole brain and anatomical regions.

Secondary Objective:	**Outcome Measure:**
To determine the pharmacokinetics of osimertinib and its metabolite (AZ5104) after multiple administrations of osimertinib.	The following variables will be calculated where the data allow: maximum plasma concentration, time to reach maximum plasma concentration, area under the plasma concentration-time curve from zero to the last measurable time point. Also, the metabolite to parent ratio of the area under the plasma concentration-time curve and maximum concertation after a single administration will be calculated, as appropriate.

Safety Objective:	Outcome Measure:
To examine the safety and tolerability of [11C]osimertinib intravenous administration and multiple oral administrations of osimertinib in non-small cell lung cancer patients with brain metastases.	Assessment of adverse events graded by the Common Terminology Criteria for Adverse Events (version 4.03), standard 12-lead electrocardiograms, physical examination, vital signs (including blood pressure, pulse) and evaluation of laboratory parameters (clinical chemistry, haematology, and urine analysis).

Target patient population

The target population for this study will be patients who have epidermal growth factor receptor mutation-positive non-small cell lung cancer with brain metastases.

Duration of treatment

The study consists of 2 phases, an imaging phase and a continued access phase. The patient's participation in the imaging phase of the study will be approximately 32 days. The imaging phase of the study will include 3 single intravenous microdose administrations of [11C]osimertinib and positron emission tomography examinations on: Day 1, Day 2 (or up to Day 8) and Day 29. Osimetrinib 80 mg tablets will be taken once a day by the patient from the day of the second positron emission tomography for at least 21 days before the third positron emission tomography examination. During the continued access phase patients will continue to take osimertinib tablets (80 mg once daily) as a single agent depending on the agreement between the patient and the Investigator. Osimertinib administration will continue until, in the opinion of the Investigator the patient is no longer deriving clinical benefit or the patient has stopped taking osimertinib for any other reason.

Investigational product, dosage and mode of administration

Osimertinib

Osimertinib 40 mg and 80 mg film-coated oral tablets, manufactured by AstraZeneca will be provided for the study. Osimertinib 40 mg film-coated tablets will be provided to be used only in the case where dose reduction is necessary.

[11C]osimertinib

The radiolabelled [11C]osimertinib will be manufactured *ex tempore* by the positron emission tomography centre, Radiochemistry Laboratory at the Karolinska Institutet, PPD , Solna, Sweden, from a precursor "AZ13774738" supplied by PharmaSynth AS (Tartu, Estonia) and close in time to each positron emission tomography measurement. After synthesis, the [11C]osimertinib will be dissolved in a sterile buffer solution and sterile filtered and the final product will undergo quality control prior to release for human administration.

Statistical methods

All patients who receive at least 1 administration of either [11C]osimertinib or osimertinib will be included in the assessment of imaging and safety. Pharmacokinetic parameters will be

summarised for all patients who had post-administration pharmacokinetic assessments without any Clinical Study Protocol deviations or dosing deviations that might have affected the pharmacokinetic analysis. Given the exploratory nature, no formal statistical analysis will be performed in this study. The statistical analysis will be descriptive. Demographic and baseline characteristics, imaging outcomes, safety outcomes, and treatment duration will be summarised using descriptive statistics, as appropriate.

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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
ABSS	Automatic blood sampling system
AE	Adverse event (see definition in Section 6.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Absolute partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUCss	Area under the concentration-time curve at steady state
BBB	Blood brain barrier
BCRP	Breast cancer resistance protein
BP	Blood pressure
BM	Brain metastases
BMI	Body mass index
^{11}C	Carbon-eleven
C_{max}	Maximum concentration after single dose
Css_{max}	Maximum concentration at steady state
CAP	Continued access phase
CNS	Central nervous system
CRF	Case report form (paper)
CSA	Clinical study agreement
CSF	Cerebrospinal fluid
CSP	Clinical Study Protocol
ctDNA	Circulating tumour DNA
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DWI	Diffusion-weighted imaging
EC	Ethics Committee
ECHO	Echocardiogram

Abbreviation or special term	Explanation
ECG	Electrocardiogram
ED	Effective dose
EGFR	Epidermal growth factor receptor
EGFRm	Epidermal growth factor receptor mutation positive
EMA	European Medicines Agency
FSH	Follicle-stimulating hormone
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRRT	High resolution research tomograph
HL	Hy's Law
IATA	International Air Transport Association
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ILD	Interstitial lung disease
IP	Investigational product
IV	Intravenous
Kpu,u	Brain/plasma partition coefficient
LH	Luteinising hormone
LM	Leptomeningeal metastases
MBq	Megabecquerel
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition angiogram
NSCLC	Non-small cell lung cancer
%ID	Percent of radioactive drug injected
PET	Positron emission tomography
PCV:	Packed cell volume
PHL	Potential Hy's law

Abbreviation or special term	Explanation
PI	Principal Investigator
PK	Pharmacokinetics
PTT	Partial thromboplastin time
QTc	QT interval corrected
RECIST	Response Evaluation Criteria In Solid Tumours
ROI	Region of interest
RNA	Ribonucleic acid
SAE	Serious adverse event (see definition in Section 6.2)
SD	Standard deviation
SUV	Standardised uptake value
SV	Sievert
TKI	Tyrosine kinase inhibitor
T790M	Substituition of threonine to methionine at amino acid position 790
T_{max}	Time of maximum drug concentration after single dose
Tss_{max}	Time of maximum drug concentration at steady state
TT	Thrombin time
ULN	Upper limit of normal
WBDC	Web Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

1.1 Background and rationale for conducting this study

1.1.1 Non-small cell lung cancer and EGFR

Lung cancer has been the most common cancer in the world for several decades, and by 2012, there were an estimated 1.8 million new cases, representing 12.9% of all new cancers. It was also the most common cause of death from cancer, with 1.59 million deaths (19.4% of the total) (GLOBOCAN 2012). Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis approximately 70% of patients with NSCLC already have locally advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of patients with early stage NSCLC 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).

During the past decade, understanding the critical role of the epidermal growth factor receptor (EGFR) pathway and development of EGFR targeted tyrosine kinase inhibitors (TKI) have led to significant therapeutic advances in NSCLC. Impressive anti-tumour activity was observed in a subset of patients, initially distinguished by their clinical, epidemiologic and histologic characteristics, and subsequently defined by the presence of activating mutations of EGFR (Lynch et al 2004). The benefit of these TKIs in patients with EGFR mutations (EGFRm+) was initially demonstrated in the second-line and maintenance settings and subsequently confirmed in the first-line setting. Such activating mutations are seen in 10% to 15% of NSCLC patients in the Western world and 30% to 40% in Asia. As a result of first-line studies comparing a TKI versus chemotherapy in EGFRm+ patients (IRESSA Pan-Asia Study [IPASS] and EURopean TArceva versus Chemotherapy [EURTAC]), the National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) currently recommend treatment with an EGFR-TKI (erlotinib, gefitinib, or afatinib) in the front-line setting for those patients with documented activating EGFRm+.

In patients with sensitizing mutations of EGFR, response rates of 50% to 80% have been reported with first-line TKI treatment, compared with less than 30% with conventional chemotherapy. Unfortunately, 50% to 60% patients ultimately develop acquired resistance to these agents (via substituition of threonine to methionine at amino acid position 790 mutation [T790M] for first and second generation EGFR-TKIs such as erolotinib, gefitinib and afatanib) with progression of disease after approximately 9 months to 13 months.

Currently T790M that renders first-line TKI agents ineffective, is considered the primary cause of resistance to gefitinib, erlotinib or afatinib (this mutation accounts for approximately 50% to 60% of cases of acquired resistance). Osimertinib is currently approved by the Food and Drug Administration (FDA) and EMA (European Medicines Agency) for the treatment of patients who have progressed on a previous EGFR-TKI with EGFR T790M positive NSCLC and was recently granted Breakthrough Therapy Designation by the FDA as first-line treatment of EGFRm+ treatments for first-line EGFRm+ NSCLC, based on recent data

(AZD9291 versus gefitinib or erlotinib in patients with locally advanced or metastatic NSCLC [FLAURA] data presented at the European Society for Medical Oncology [ESMO] 2017 Congress) (NCCN 2017).

1.1.2 NSCLC and brain metastases

Central nervous system (CNS) metastases are detected in 20% to 30% of patients with advanced NSCLC upon initial diagnosis and are associated with a poor prognosis (Porta et al 2011), with more than 30% of patients experiencing disease progression during treatment with established EGFR-TKIs due to development of brain metastases (BM) (Mujoomdar et al 2007, Heon et al 2010). Non-clinical studies have shown evidence of a superior penetration of the blood brain barrier (BBB) by osimertinib compared to other EGFR-TKIs, as well as its activity in CNS metastases, which was confirmed in a global Phase II study and in a randomised, controlled Phase III study in patients with T790M mutation positive NSCLC after progression on prior treatment with an EGFR-TKI (AURA3). The clinical evidence of osimertinib CNS activity shows a prolonged time to progression by delaying the development of CNS metastases (Goss et al 2017, Mok et al 2017, TAGRISSO US PI 2017). The use of a drug that may more effectively penetrate the CNS has the potential to control and prevent or delay the development of CNS metastases.

1.1.3 [11C]Osimertinib

Positron emission tomography (PET) examinations following microdose administration of ^{11}C-labeled drug has been used to examine distribution of the labelled compound in the brain and/or whole body in human patients (Lapin and Gardner 2003). A PET microdosing study of osimertinib was conducted in non-human primates (NHP) using ^{11}C labelled osimertinib, [^{11}C]osimertinib. Kinetic compartment analysis of PET data showed that the distribution of [^{11}C]osimertinib to the brain was fast (within 10 minutes) and reached a plateau of 1.29% ± 0.42% (n=3) of injected radioactivity, indicating that [^{11}C]osimertinib can penetrate the intact BBB of the NHP brain (Ballard et al 2016). A PET dosimetry study in NHP showed that the effective dose (ED) was 3.85 µSv/MBq (for a detailed radiation exposure description see [^{11}C]Osimertinib Investigator's Brochure 201, AstraZeneca PET study SP-PET-0052on file and ^{11C} IMPD 2017). .

Examination of [^{11}C]osimertinib distribution in the brain in healthy volunteers after a single [^{11}C]osimertinib microdose has been performed (study completed, EudraCT CCI). Preliminary study results suggest that [^{11}C]osimertinib has a fast distribution to the brain regions (5 to 30 minutes after intravenous [IV] injection) and has high exposure with approximately 2% of injected radioactivity crossing the BBB. This exposure is similar to those of established and clinically effective CNS drugs (Schou et al 2015).

This first patient study will extend the examination of [^{11}C]osimertinib brain distribution in patients with NSCLC and BM. There have been anecdotal evidence of BM patients having their tumors considerably reduced within 2 weeks of treatment with osimertinib (Koba et al 2017). Hence, this study will also examine the potential for changes in size and number of BM after 3 weeks of treatment with osimertinib in NSCLC BM patients.

1.1.4 Osimertinib

Osimertinib (TAGRISSO™) 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. Osimertinib has been shown to provide clinical benefit to patients with advanced NSCLC and both the single sensitizing mutations and the resistance mutation following prior therapy with an EGFR-TKI. TAGRISSO™ (osimertinib) is currently approved in more than 65 countries including the US, EU, Japan and Korea for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation positive NSCLC.

1.2 Rationale for study design, doses and control groups

Osimertinib has been shown to be active in treating patients with EGFRm+ NSCLC having pre-existing BM and/or has potential to slow down or prevent development of new BM. Preclinical studies in mice, rats and monkeys show that osimertinib crosses the intact BBB of animals and has good exposure in the brain regions of interest (ROIs). It is hypothesized that the efficacy of osimertinib in the BM is because of its high BBB penetration in both normal and metastatic regions in the brain.

The study will determine the distribution of [^{11}C]osimertinib in the brain of patients with EGFRm+ NSCLC with BM. It is hypothesized that the brain distribution of osimertinib is at least similar compared to the distribution in healthy subjects with an intact BBB (see Section 1.1.3) and it is at least similar at steady state compared to that observed after a single dose. This evaluation of osimertinib BBB penetration in patients with NSCLC will support further use of osimertinib in other CNS mediated oncology indications. The study design includes 2 phases for patients, the first (imaging) phase consisting of single IV microdose administrations of [^{11}C]osimertinib and PET examinations on 3 occasions (baseline, post single dose and post repeat dose) and the second phase consists of continued oral administrations of osimertinib.

The study will test the following hypotheses:

1. Osimertinib penetrates the BBB in patients with NSCLC and BM (including leptomeningeal metastases [LM]); whole brain exposure >1% injected dose.

2. Whole brain and BM exposure of osimertinib at steady state is similar or higher compared to single dose.

3. There may be changes in the size and number of BM at 3 weeks of treatment with osimertinib.

4. Changes in the size and number of BM at 3 weeks correlate to the regional [^{11}C]osimertinib exposure.

5. Higher [^{11}C]osimertinib levels in BM or LM reflect higher [^{11}C]osimertinib exposure and/or binding to EGFR.

6. Exposure of osimertinib to BM region will be at least similar to that of the non-metastatic brain regions.

Using high resolution PET examination, this open-label study will examine brain distribution and retention of a microdose of [^{11}C]osimertinib in approximately 12 patients with EGFRm NSCLC and BM. The imaging data analysis will include quantification of the maximum radioactivity concentration of [^{11}C]osimertinib in the brain after injection (percent of injected dose entering the brain), but not limited to.

After the imaging phase of the study patients will be allowed to continue to take osimertinib tablets (80 mg once daily) as a single agent in the continued access phase (CAP), depending on the agreement between the patient and Investigator. Administration of osimertinib will continue until, in the opinion of the Investigator, the patients are no longer deriving clinical benefit, or the patients 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 IP dispensing/accountability.

Patients not participating in the CAP will return to the clinic for follow-up assessments 30 days (±7 days) after their last dose of osimertinib in the imaging phase. If the patient's last dose of osimertinib is during the CAP, 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).

1.3 Benefit/risk and ethical assessment

The patients with EGFRm (for definition of EGFR see Section 3.1) NSCLC enrolled in this study are likely to receive clinical benefit as osimertinib has shown clinical benefit in these patients across various studies. Osimertinib demonstrates an acceptable benefit-risk profile in patients with NSCLC as evidenced by its approval from the regulatory agencies in more than 65 countries including 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 see to Section 1.3 of the AZD9291 Investigator's Brochure 2019, Edition for details).

Inclusion and exclusion criteria as well as study restrictions are chosen to ensure the selected patients are exposed to minimal risk in this study.

The current benefit/risk analysis is based on the available safety and tolerability data from studies in patients with NSCLC after multiple therapeutic doses of osimertinib.

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 the IP is provided for all osimertinib studies (see Section 6.8). 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. The full clinical experience with osimertinib as monotherapy is described in the current version of the osimertinib Investigator's Brochure.

Although patients may not benefit from a microdose [^{11}C]osimertinib, there may be benefit from the oral 80 mg osimertinib. There is anecdotal evidence of efficacy observed with osimertinib even with 2 weeks of treatment (Koba et al 2017) and hence, some benefit can be seen within the imaging phase. Further benefit may be gained during the CAP. The patient may continue treatment with osimertinib until, in the opinion of the Investigator, the patients are no longer deriving clinical benefit, or stop taking osimertinib for any other reason.

Measures have been taken in this Clinical Study Protocol (CSP) to provide appropriate restrictions and/or direction for use of concomitant medications which are substrates for these metabolising enzymes or transporters. The overall risk for the patients who participate in this study to assess the brain distribution of osimertinib in EGFRm NSCLC patients with BM is acceptable.

1.3.1 Risks from study examinations (PET and magnetic resonance imaging)

In the present study each patient will undergo 3 PET and 2 magnetic resonance imaging (MRI) examinations as well as 2 routine clinical thorax/abdomen computed tomography (CT) examinations.

The radioactivity exposure during a single PET examination (300 MBq) renders radiation exposure of 1.15 mSv (ED of 3.85 µSv/MBq; AstraZeneca dosimetry study on line: SP-PET-0052), which is less than half a year background radiation exposure in Sweden. The thorax CT radiation exposure is 0.8mSv. Total radiation exposure of 3 PET examinations (900 MBq, 3.465 mSv) and 2 CT examinations (1.6 mSv) will not exceed 7 mSv. In addition, permission will be obtained from the Radiation Safety Committee at the PPD , on the appropriateness of this radiation dose.

The total amount of mass injected per single PET examination will not exceed 10 µg (total 30 µg during the study period, which is significantly below the maximum dose (100 µg) allowed for a microdose defined by both the EMA (European Medicines Agency 2009) and the FDA (US Department of Health and Human Services 2006).

Other risks associated with PET examinations include pain and/or haematoma from the arterial and venous punctures. Arterial occlusion may occur. Coagulation testing will be performed during screening, and Allen's test will be performed at screening and prior to the PET examination. The arterial catheter will be inserted at the PET centre under local anaesthesia and, if necessary, emergency care can be provided by PPD

Risks from MRI scans are associated with the possible presence of magnetic metallic implants, such as pacemakers or hearing aids that may be dislodged during MRI (see Section 3.2). In case of emerging anxiety during the examination the patient will be able to press an emergency button and immediately will be taken out of MR system. Specific study

exclusion criteria will minimize this risk, and strict safety protocols applied daily in clinical care will be in place to prevent risk occurrence. The contrast injection in gadolinium-enhanced MRI sequences carries a low risk of allergic reactions. The MRI staff are specifically trained and there are specific routines to manage unusual complications. Overall, the MRI investigations involve very low risk and the results of the investigations are crucial for the study, both for ensuring inclusion criteria are met, for use in PET data analysis and to follow early efficacy on tumour growth.

Lumbar puncture will be performed on 2 occasions to obtain cerebrospinal fluid (CSF) samples. The procedure-related risks are few. The procedure may cause temporary headache. The risk for local pain and infection are managed by following routine clinical procedures including local anaesthesia and aseptic techniques.

1.4 Study design

This is an open-label, single centre Phase I study to determine the brain exposure of [^{11}C]osimertinib in patients with NSCLC. This study will be conducted in patients with EGFRm NSCLC with BM. The study will consist of 2 phases, an imaging phase and a CAP (Figure 1A). The patient's participation in the imaging phase of the study will be approximately 32 days. The imaging phase of the study will include 3 single intravenous microdose administrations of [^{11}C]osimertinib and positron emission tomography examinations on: Day 1, Day 2 (or up to Day 8) and Day 29 (see Section 5.3.2). Osimertinib 80 mg once a day will be taken by the patient from the day of the second PET examination for at least 21 days before the PET3 examination will be scheduled.

Positron emission tomography examinations using a microdosing approach (Lee and Farde 2006, Saleem et al 2015) will be used, i.e. osimertinib will be labelled with ^{11}C and administered IV at a microdose (<10 µg).

A sufficient number of eligible patients (approximately 12) will be enrolled in order to obtain at least 8 evaluable patients with BM. . An evaluable patient is defined as a patient who completes at least 2 PET examinations; 1 with a single IV microdose of [^{11}C]osimertinib alone and another with a co-administered oral 80 mg osimertinib and [^{11}C]osimertinib microdose administration.

The identified study population is considered sufficient to examine variability in pharmacokinetic (PK) and PET examinations. The patients will need to have confirmed EGFRm status by either local or central testing. Epidermal growth factor receptor mutation positive status can be confirmed via assessment of tissue or cytological sample from primary or metastatic tumour. All patients will have a baseline brain MRI for eligibility (presence of BM) and for anatomical and manual delineation of brain regions to be applied in PET image analysis (and for detection of BBB disruption). CCI [redacted] Brain MRI will include (but is not limited to) T1 (gadolinium enhanced), T2/FLAIR and diffusion-weighted imaging (DWI).

Thorax/abdomen CT will be performed as routine clinical examination and will serve for the diagnosis and evaluation of primary lung tumour and other metastatic sites. It will be repeated at the end of study treatment (on Day 25 ±4 days), to follow potential early effects on tumours.

Positron emission tomography examination of the brain using [^{11}C]osimertinib (administered before the start of PET) will be carried out 3 times: the first time at baseline (PET1; Visit 2 [Day 1]), the second time after the first oral dose of osimertinib of 80 mg (PET2; Visit 3 [Day 2], or within 1 week after baseline) and the third time after 3 weeks treatment with 80 mg oral dose osimertinib daily (PET3; Visit 5 [Day 29]) (Figure 1B).

At each PET examination [^{11}C]osimertinib will be given IV as a microdose (<10 μg), at a radioactivity of 300 MBq/70 kg of body weight. The minimum injected radioactivity will be 200 MBq/70 kg of body weight and the maximum injected radioactivity will be 330 MBq/70 kg of body weight. Brain radioactivity will be measured for 90 minutes (minimum 60 minutes) in the PET examination system (high resolution research tomograph [HRRT]).

The PET2 examination and the PET3 examination will be performed on Visit 3 and Visit 5 after IV [^{11}C]osimertinib administration. The IV dose will be given ~6 hours after the oral osimertinib 80 mg to coincide with the median time of maximum drug concentration (T_{max}) of the oral dose. All participants will receive at least 3 weeks (21 days) treatment with 80 mg oral dose of osimertinib once daily between the PET2 examination and PET3 examination visits.

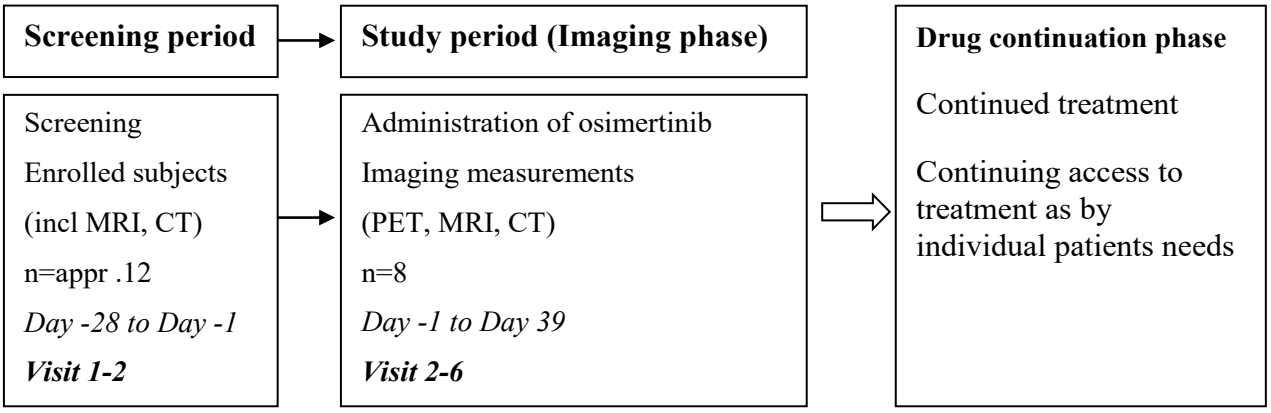
On completion of the imaging phase (ie, at the PET3 examination), patients may continue to take osimertinib tablets (80 mg once daily) as a single agent in the CAP depending on agreement between the patient and the Investigator. This will continue until, in the opinion of the Investigator, the patients are no longer deriving clinical benefit, or the patients stop taking osimertinib for any other reason. No clinical data will be collected during this phase other than sudden death of unknown reason, SAEs that may or may not be related to osimertinib, outcomes of pregnancy and IP dispensing/accountability (Figure 1).

Dose reduction of osimertinib (to 40 mg once daily) according to clinical practise will be allowed in the CAP if deemed necessary by the Investigator due to AEs.

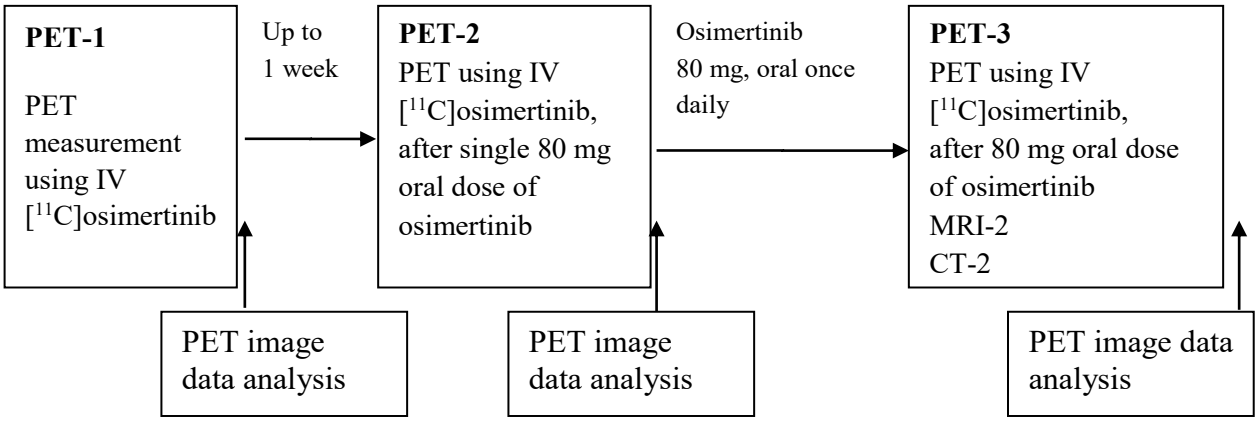
Patients not participating in the CAP or who discontinue treatment during the imaging phase will return to the clinic for follow-up assessments 30 days (±7 days) after their last dose of osimertinib in the imaging phase. If the patient's last dose of osimertinib is in the CAP, the patient should be contacted 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 IP, and record any sudden deaths of unknown cause.

Figure 1 Study flow chart

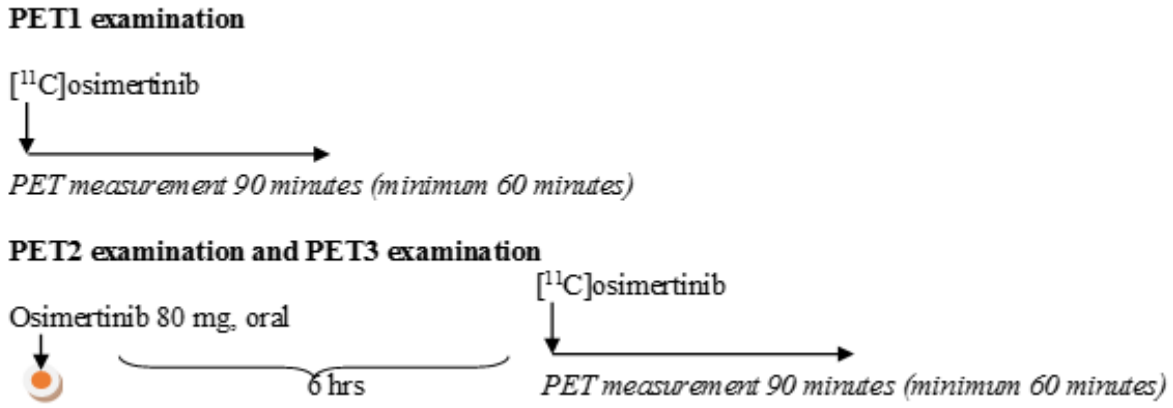
A: Study flow



B: Study period (drug administration and imaging measurements)



C: PET examination flow



= Tablet dosing

CT: Computed tomography; IV: Intravenous; MRI: Magnetic resonance imaging; PET: Positron emission tomography.

1.5 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 in a similar NSCLC patient population is well established and predictable. Therefore, there is 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.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
To determine the brain exposure of [^{11}C]osimertinib in tumour ROI (BM, including LM) in patients with NSCLC after a single IV microdose and after single and multiple therapeutic doses of osimertinib.	The percent of injected dose in the whole brain (%ID) and brain standard uptake value (SUV), to describe maximal radioactivity concentration in the brain, ($C_{max,\ \%ID\ brain;}\ C_{max,\ SUVbrain}$). The time of the maximum radioactivity concentration in the brain ($T_{max\ brain}$). The brain to plasma partition coefficient (concentration brain/plasma ratio) as area under the concentration curve $(AUC)_{brain\ 0\text{-}90min}/AUC_{blood\ 0\text{-}90min}$. All parameters of exposure will include the tumour region, whole brain and anatomical regions.

AUC: Area under the concentration curve; BM: Brain metastases; C_{max}: Maximum concentration after single dose; IV: Intravenous; LM: Leptomeningeal metastases; NSCLC: Non-small cell lung cancer; ROI: Region of interest; T_{max}: Time of maximum drug concentration after single dose.

2.2 Secondary objectives

Secondary Objective:	**Outcome Measure:**
To determine the PK of osimertinib and its metabolite (AZ5104) after multiple administrations of osimertinib.	The following variables will be calculated where the data allow: maximum plasma concentration (C_{ssmax}), time to reach maximum plasma concentration (t_{ssmax}), area under the plasma concentration-time curve from zero to the last measureable time point (AUCss). Also, the metabolite to parent ratio of the AUC and maximum concentration after single dose (C_{max}) will be calculated, as appropriate.

AUC: Area under the concentration curve; C_{max}: Maximum concentration after single dose; PK: Pharmacokinetics

2.3 Safety objectives

Safety Objective:	Outcome Measure:
To examine the safety and tolerability [^{11}C]osimertinib IV doses and multiple oral doses of osimertinib in NSCLC patients with BM.	Assessment of AEs graded by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, standard 12-lead ECGs, physical examination, vital signs (including blood pressure [BP], pulse), and evaluation of laboratory parameters (clinical chemistry, haematology, and urine analysis).

AE: Adverse event; BM: Brain metastases; IV: Intravenous; NSCLC: Non-small cell lung cancer.

3. PATIENT 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 must 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.

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

2. Male or female aged at least 18 years.

3. Histological or cytological confirmation of diagnosis of NSCLC.

4. Confirmation that the tumour harbours an EGFR mutation known to be associated with EGFR-TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q) or T790M EGFR resistance mutation as assessed by local laboratory/or central laboratory via tissue/cytology or in plasma.

5. Mandatory provision (if available) of formalin fixed, paraffin embedded tissue and blood for central confirmation of EGFR mutation status. Please refer to the Laboratory Manual for details.

6. In all patients enrolled, confirmed BM as having at least one non-measurable and/or measurable brain lesion at baseline as per CNS RECIST 1.1 via MRI imaging.

7. World Health Organisation (WHO) performance status 0 to 2 and a minimum life expectancy of 4 weeks.

8. Females should be using adequate contraceptive measures (up to 6 months after the last administration; see restriction section), should not be breastfeeding and must have a negative serum pregnancy test prior to start of dosing if of childbearing potential or must have evidence of non-childbearing potential by fulfilling 1 of the following criteria at screening:

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

- Women under 50 years old would be consider postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with luteinising 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 subjects should be willing to use barrier contraception (see Restrictions, Section 3.8).

10. Have a body mass index (BMI) between 18.0 kg/m^2 and 30.0 kg/m^2 inclusive and weigh at least 40.0 kg and no more than 100.0 kg, inclusive

11. Able and willing to participate in all scheduled evaluations, abide by all study restrictions, and complete all required tests and procedures.

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 centre).

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

3. Treatment with any of the following:

- Treatment with an EGFR-TKI (erlotinib, gefitinib or afatinib) within 10 days or at least 5x the half-life, whichever is the longer, of the first administration of IP. If sufficient washout time has not occurred due to schedule or PK properties, an alternative appropriate washout time based on known duration and time to reversibility of IP related AEs could be agreed upon by AstraZeneca and the Investigator.
- Any cytotoxic chemotherapy, investigational agents or other anticancer drugs from a previous treatment regimen or clinical study within 14 days of the first administration of the IP.
- Osimertinib in the present study (ie, administration with osimertinib previously initiated in this study) or other studies. 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.
- Major surgery (excluding placement of vascular access) within 4 weeks of the first administration of the IP.
- Radiotherapy (including brain) with a limited field of radiation within 1 week of the first administration of the IP, 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 administration of the IP.

- Patients currently receiving (or unable to stop use at least 3 weeks before receiving the first administration of osimertinib) medications or herbal supplements known to be potent inducers of CYP3A4 (see Appendix B).

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

5. History of brain surgery or major brain trauma in the last year (if the surgery is in the same hemisphere as the brain metastasis).

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 CSP, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required (hepatic impairment is excluded from this criterion).

7. Any of the following cardiac criteria:

   – Mean resting corrected QT interval (QTc) >470 msec obtained from 3 ECGs, using the screening clinic ECG machine derived QTc value.

   – 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).

   – Patient with any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as electrolyte abnormalities including:

   – **-** Serum/plasma potassium <lower limit of normal (LLN)

   – **-** Serum/plasma magnesium <lower limit normal (LLN)

   – **-** Serum/plasma calcium <lower limit normal (LLN)

   heart failure, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval and cause Torsades de Pointes.

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

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

- Absolute neutrophil count $<1.5 \times 10^9$/L
- Platelet count $<100 \times 10^9$/L
- Haemoglobin <90 g/L
- Alanine aminotransferase (ALT) >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 (AST) >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 or Gilbert's Syndrome.
- 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. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of osimertinib.

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

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

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

- Previous allogenic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection

14. Patients on anticoagulant treatment.

15. Absence of collateral flow between ulnar and radial artery as assessed by the Allen´s test" to avoid misunderstandings.

16. Suffering from claustrophobia and/or having implanted metal devices or implants such as pacemaker, vascular or heart valves, stents, clips, also metal deposits such as bullets, shells, metal grains in the eyes.

17. Previous participation in a research PET or PET/CT study.

18. The following are exclusion criteria for contrast enhanced MRIs:

- Glomerular filtration rate <30 ml/min
- History of renal insufficiency
- Pregnancy

19. Women who are breast-feeding.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment

The Investigator should keep a record, the patient screening log, of patient's who entered pre-study screening.

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 patients 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's eligibility. See Section 3.1 and 3.2.

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

Patients who were enrolled, screened but not administered the IP (ie, withdrew from the study prior to administration) may be re-enrolled and re-screened if, in the opinion of the Investigator, the reason(s) for earlier withdrawal no longer applies. A new enrolment code will be assigned to these patients. Patients cannot re-enter the study if the IP was administered and subsequently withdrawn from the study. Patients who discontinue their participation in the imaging phase prematurely may still be eligible to continue to take osimertinib in the CAP, if the Investigator believes it is in the patient's interest, ie, discontinuation from the imaging 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 be enrolled or receive IP under any circumstances. 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 that 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 the IP and for the specified times before and after:

1. Females of child-bearing potential should use reliable methods of contraception from the time of screening until 6 weeks after discontinuing study treatment. Acceptable methods are provided in Appendix C (Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods).

2. Male patients should be asked to use barrier contraceptives (ie, by use of condoms) during sex with all partners during the trial and for a washout period of 4 months. Male patients should avoid procreation for 4 months after completion of trial treatment. Patients should refrain from donating sperm from the start of dosing until 4 months after discontinuing study treatment.

3. Once enrolled all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods that are known to be potent inducers of CYP3A4 whenever feasible, but patients may receive any medication that is clinically indicated for treatment of AE. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 months after the last administration of osimertinib. All concomitant medications should be captured on the paper case report form (pCRF). Guidance on medicines to avoid, medications that require close monitoring and on washout periods is provided (see Appendix B “Guidance regarding Potential Interactions with Concomitant Medications”).

4. If medically feasible, patients taking regular medication, with the exception of strong inducers of CYP3A4 (see Appendix B), should be maintained on their regular medication throughout the study period. Patients taking concomitant

medications whose disposition is dependent upon the Breast Cancer Resistance Protein (BCRP) and/or P-glycoprotein (P-gp) with a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving Osimertinib. Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (see Appendix B "Guidance regarding Potential Interactions with Concomitant Medications").

5. 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.

6. Refrain from hard physical training (such as heavy lifting) for a period of 7 days following arterial catheterisation.

3.9 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations:

- Patient decision. At any time the patient is free to discontinue treatment, without prejudice to further treatment
- AE
- Severe non-compliance with the CSP
- Disease progression and/or the Investigator believes they are no longer deriving clinical benefit
- Incorrectly enrolled patients
- Corneal ulceration
- ILD/pneumonitis
- QTc interval prolongation with signs/symptoms of serious arrhythmia

3.9.1 Procedures for discontinuation of a patient from investigational product

A patient who decides to discontinue the 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. Adverse events will be followed up (See Section 6.3.2); and all IP should be returned by the patients.

In the imaging phase, any patient discontinuing the IP should be seen at 30 days (±7 days) after their last administration for the evaluations outlined in the Study Plan (see Table 1). After discontinuation of the 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.

After discontinuation of the IP in the imaging 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). All new AEs and SAEs occurring during the 30 calendar days after the last administration 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 complete AE information and/or collect IP. Any untoward event occurring subsequent to the 30 day AE reporting follow-up period that the Investigator assesses as possibly related to the IP should also be reported as an AE.

At the end of the imaging phase, patients may continue to receive the 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 the 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 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 the CSP 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
- Patient becomes pregnant
- Patient lost to follow-up

3.10.1 Screen failures

Screen 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 Section 3.1 and Section 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. The Investigator will follow up AEs outside the clinical study.

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 judgement 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 the IP
- 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 pCRF. 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 imaging phase.

Table 1 Study Plan and timing of procedures

Activity	Screening period	Study period					Follow up
		PET1	PET2	Clinical Visit 2	Clinical Visit 3 and PET3	MRI2	
Visit[a]	**1[a,b]**	**2**	**3[c]**	**4[d]**	**5[e]**	**6**	**7[w,x]**
Day (window)	-28 to -1 day before dosing	1	2 (within 6 days)	14 (±2 days)	+25 (±4 days)		
Obtain informed consent and/or consent for pharmacogenetics	X						
Confirm eligibility	X						
Demographics & baseline characteristics	X[b]						
Inclusion/exclusion criteria	X	X					
Relevant medical and surgical history (including smoking status)	X						
Ophthalmic examination[f]	X						
WHO performance status	X						
Physical examination	X			X	X		X
Brain MRI	X[g, h]				X[h]	X[h]	
Allen's test[i]	X	X	X		X		
Thorax/abdomen CT	X					X[e]	
Resting standard 12-lead ECG	X[b]	X	X	X	X		
Echcardiography (ECHO/MUGA[j])	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]
HBV, HCV and HIV serology	X						
Weight and height	X[k]				X		
Vital signs	X	X	X	X	X		X
Laboratory tests (haematology, clinical chemistry, coagulation)[l]	X	X	X	X	X		X
Urine analysis[l]	X	X	X	X	X		
Serum or urine pregnancy test[m] (LH, FSH)	X	X	X	X	X		X
Review current medications	X[n]	X[n]	X[n]	X[n]	X[n]		X
Blood sampling for osimertinib PK			X[o]		X[o]		
CSF[p]	X				X		

Table 1 Study Plan and timing of procedures

Activity	Screening period	Study period					Follow up
		PET1	PET2	Clinical Visit 2	Clinical Visit 3 and PET3	MRI2	
Visit[a]	**1[a,b]**	**2**	**3[c]**	**4[d]**	**5[e]**	**6**	**7[w,x]**
Day (window)	-28 to -1 day before dosing	1	2 (within 6 days)	14 (±2 days)	+25 (±4 days)		
Tissue and blood sampling for EGFR mutations/resistance mechanisms[q]	X[q]						X[q]
Blood sampling for ctDNA/exosomal DNA/RNA/protein	X	X	X		X		X
Arterial catheter placement[r], and arterial blood sampling for [11C]osimertinib[s]		X	X		X		
Venous blood sampling for [11C]osimertinib radioactivity and metabolites[r,t]		X	X		X		
[11C]osimertinib administration		X	X		X		
PET examination		X[e,t]	X[e,t]		X[e,t]		
Osimertinib oral administration 80mg once daily[u]			X (continuous daily administration)				
Adverse event review (AEs and SAEs)	X[v]	X[v]	X[v]	X[v]	X[v]		X[v,w,x]

AE: Adverse event; BM:Brain metastases; CSF: Cerebrospinal fluid; CT: Computed tomography; ctDNA: Circulating tumour DNA; ECHO: Echocardiogram DNA: Deoxyribonucleic acid; ECG: Electriocardiogram; EGFR: Epidermal growth factor receptor; FSH: Follicle-stimulating hormone; HBV: Hepatitis B virus, HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; IP: Investigational product; IV; Intravenous; MRI: Magnetic resonance imaging; MUGA: Multigated radionuclide angiogram; LH: Luteinising hormone; PET: Positron emission tomography; PK: Pharmakonitetics; RNA: Ribonucleic acid; SAE: Serious adverse event; WHO: World Heatlh Organisation.

a Study procedures designated for a specific visit should be performed in 1 day whenever possible and in the best interest of the patient. If this is not possible and/or not in the best interest of the patient, study procedures may be performed across more than 1 day, but within the visit window.

b Day -1 is the day before dosing. All Day 1 procedures must be performed on Day -1 or pre-administration 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 urine analysis) do not need to be repeated.

c PET2 can be conducted on Day 2 (1 day after the PET1 or within the 1 week of PET1 ie, 1 to 6 days of [11C]osimertinib washout is allowed).

d A clinical visit will be scheduled for when the patient has been on the continuous IP administration for 10 days (window of ±2 days).

e The clinical visit for the PET3 examination and CT-2, MRI-2 can be conducted on the same day or on a different day. If the assessmnets cannot be conducted on the same day, the CT-2, MRI-2 can be conducted within a window of 7 days.

f Full ophthalmic assessment, including slit lamp examination, will be performed at screening and if a patient experiences any visual symptoms (including blurring of vision), with additional tests, if clinically indicated. Photographs will be taken to record any clinically significant findings.

g Brain MRI should confirm presence of BM.

h CCI
RECIST will aslo be applied for the evaluation of thorax/abdomen CT images (see Section 5.1 and Section 8.5.4).

i The PI will perform Allen's test at screening and anaesthesiologist will repeat the Allen´s test on PET examination day to make sure there is normal flow in the wrist between radial and ulnar arteries.

j Required at baseline. Repeated during the imaging phase only if clinically indicated at any time point or subsequently at follow-up 30 (±7) days after last administration of study medication (for example to follow up on a cardiac AE).

k Patient must weigh at least 40.0 kg and no more than 100.0 kg (see Section 3.1).

l Blood and urine samples will be collected for routine laboratory tesing (haematology, clinical chemistry), and urine analysis (see Section 5.4).

m Serum pregnancy test at screening and follow-up. FSH and LH to be tested at screening. All other visits, urine pregnancy test.

n Current medications will be reviewed and recorded.

o PK sampling: at pre-administration, 2, 4 and 7.5 hour(s) (can be modified if necessary). During PET examinations, PK sampling schedule maybe limited to the PET examination time (see Section 5.3.2.2).

p CSF samples will be collected at pre-administration prior to start of treatment and at the PET3 examination day.

q A re-biopsy from tissue may be collected as part of clinical routine upon disease progression during continued access treatment. A blood sample (2 x 10 mL) will be collected at screening only for additional option for central confirmation of EGFR status if tissue confirmation is not possible).

r An arterial line will be inserted on the day the patient arrives for the administration of the IP and PET examination. The arterial line will be placed in the opposite arm than the 1 being used to administer the single IV microdose of [11C]osimertinib bolus injection. A venous access line will also be inserted to collect blood samples. The arterial line will be removed at the conclusion of the PET examinations, after the last sample has been collected. The placement of the arterial line, venous access line, administration of the IV microdose [11C]osimertinib bolus injection, PET examinations (see Section 5.3.2.2), and removal of the arterial line (and venous access line) will take place on the same day. Standard institutional procedures will be followed for arterial line removal. In case of failure with arterial sampling during the PET examination, because of spasm or blood clots, the PET examination will continue and venous samples will be taken according to the planned schedule of arterial samples.

s Arterial blood sampling for [11C]osimertinib will occur at approximately 2, 4, 6, 8, 10, 15, 20, 30, 40, 50, 60, 75, and 90 minutes post-[11C]osimertinib injection. Venous blood samples will be collected at 30, 60 and 90 minutes. In case of failure to sample arterial blood (eg, spasm, occlusion) the arterial blood sampling may be substituted by venous blood smaples throughout the PET examination. The blood sampling schedule may be adjusted at the Investigator's discretion, but will not exceed 120 mL per patient per measurement (see point i, in case of failure of arterial sampling).

t If a patient cannot undergo the PET examination at the scheduled time or if technical failure occurs, eg, camera breakdown or radioligand synthesis failure, the patient will be discharged and the visit rescheduled to a later time point. PET examinations will continue over 90 minutes (minimum 60 minutes). If examination duration becomes shorter due to the technical or patient-related reasons, the data will be inspected and if quantitative analysis will not be possible, the measurement maybe rescheduled. In case of radiosynthesis failure and if radioactivity available for injection will be below 200 MBq (per 70 kg body weight), the PET examination will be rescheduled and the patient will be invited to participate on an additional visit. In case of technical failure on examination days, please contact AstraZeneca for alternate examination days.

u Osimertinib 80 mg once a day will be taken by the patient from the day of the second PET examination for at least 21 days before the PET3 examination will be scheduled. On Day 14 (±2 days), a clinical visit to evaluate the safety of the patient will be performed.

v AEs will be assessed. SAEs will be collected from the time of signature of informed consent throughout the treatment period and including the follow up period. AEs will be collected throughout the study, from informed consent until the end of the follow up period. The follow-up period is defined as 30 working days after the IP is discontinued.

w A post study assessment will be performed within 30 working days after the IP has been infused and last PET examination completed. In the event of a holiday or weather delay, the follow-up visit may be postponed 1 to 2 working days (see Section 4.4).

x The patient is to be instructed to contact the Investigator or designee at the PET centre if within a 30 day period following participation in the study if he feels ill effects related to the study.

4.1 Screening/Enrolment period

Screening procedures will be performed according to the Study Plan for the imaging phase (Table 1). At screening, consenting patients are assessed to ensure that they meet eligibility criteria (Sections 3.1 and Section 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 PET examination with [11C]osimertinib.

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

- Signed informed consent for the study and pharmacogenetics informed consent (optional).
- Review inclusion/exclusion criteria; ensure that patient has documented an EGFRm (local testing conducted at an accredited laboratory) known to be associated with EGFR-TKI sensitivity (eg, G719X, exon 19 deletion, L858R, L861Q) and a T790M mutation in EGFR if previously treated with EGFR-TKI.
- 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 (see Section 7.7) and Appendix B.
- Physical examination, WHO performance status, vital signs (supine BP and pulse, body temperature), ECG, echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) for left ventricular ejection fraction (LVEF), body weight and height
- Haematology, clinical chemistry and coagulation, serology (hepatitis B and hepatitis C status) and urine analysis.
- Serum or urine pregnancy test (pre-menopausal women of childbearing potential).
- Ophthalmology: Full ophthalmic assessment, including slit lamp examination, should be performed at screening and if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Ophthalmology examination results should be collected in the pCRF. 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 the IP.
- AEs

4.2 Treatment period

Descriptions of the procedures for this period are included in the Study Plan with exceptions of the following specific requirements for the treatment period.

4.2.1 Sequence of assessments

It is important that arterial and venous 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-administration time point is:

1. ECGs

2. Vital signs

3. Blood sample (at scheduled time)

4. Any other measurements

Before the first administration of [^{11}C]osimertinib, pre-administration ECGs and vital signs should be collected within 60 minutes prior to administration. All Day -1 procedures in the imaging phase must be performed in the clinic on Day -1 or pre-administration 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 urine analysis) do not need to be repeated.

4.3 Continued access phase (CAP)

During the CAP osimertinib can be taken with or without food. Following completion of the imaging 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 clinical data will be collected during this phase other than sudden death of unknown reason, SAEs that may be related to osimertinib, outcomes of pregnancy and IP dispensing/accountability.

4.4 Follow-up period

Descriptions of the procedures for this period are included in the Study Plan with exceptions of the following specific requirements for the follow-up period:

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

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

A post-study assessment will be performed 7 working days after the last [^{11}C]osimertinib has been infused and the PET examination is completed. In the event of a holiday or weather delay the follow-up call may be postponed 1 to 2 working days. If the patient can not be contacted within 14 days as scheduled, the Investigator designee/centre staff must try again.

The patient will be asked about any symptoms or ill-effects since the time of the procedure. The patient will also be reminded to:

- Contact the Investigator or designee at the PET centre, if within the follow-up period following participation in the study, they feel ill effects related to the study.

The post study follow-up call and outcome will be recorded in the patient's medical record.

5. STUDY ASSESSMENTS

The In Form 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 pCRF as specified in the CSP 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 pCRFs. A copy of the completed pCRFs will be archived at the study centre.

5.1 Imaging assessments

The following study assessments will be obtained. The timings of these assessments are detailed in the Study Plan (Table 1).

- MRI assessment

Patients will undergo a pre-scan check prior to an MRI scan of the brain. Patients will be asked to lie on their back in the MRI scanner where a head coil will be placed over the head and shoulders. During the scan, the patients will undergo an IV injection of gadolinium contrast agent. The scans will be used for BM assessments by CNS RECISTv1.1 (Eisenhauer et al 2009) delineation of brain lesions regions for corresponding PET analysis and to examine BBB breakdown.

- Thorax/Abdomen CT

Patients will undergo a thorax/abdomen CT scan, including chest and abdomen and pelvis if there is disease present. The scans will be used for extra-cranial tumour assessments according to RECSIT v1.1. Additional CT scans, including neck region, may be included depending on metastasis location.

- PET examinations

Brain PET examination procedures will include IV administration of [^{11}C]osimertinib followed by brain radioactivity measurements using the HRRT PET system and radioactivity measurements in blood (arterial and venous) (for detailed description see Section 5.3.2.2).

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urine analysis will be taken during Visit 1 as indicated in the Study Plan.

The date and time of each collection will be recorded in the appropriate pCRF.

Following a review of data from a group of patients, the timing of blood samples may be adjusted for subsequent groups of patient.

The following laboratory variables will be measured:

Table 2 Laboratory safety variables

Clinical chemistry (2.7 mL sample)	**Haematology (2.7 mL sample)**
S/P-Albumin	B-Hb
S/P-ALT	B-Leukocyte
S/P-AST	B-Absolute leukocyte differential count: neutrophils, lymphocytes, monocytes, basophils, eosinophils
S/P-Alkaline phosphatase	B-Platelet count
S/P-Bilirubin, total	B-Red cell count
S/P-Calcium, total	B-Hematocrit (PCV)
S/P-Creatinine	**Coagulation (1.8 mL sample)**
S/P-Glucose	PT/INR
S/P-Magnesium	aPTT/TT
S/P-Phosphate	**Urine analysis (dipstick):**
S/P-Potassium	U-Hb/Erythrocytes/Blood
S/P-Sodium	U-Protein/Albumin
Serology screen (1.8 mL sample)	U-Glucose
HBC, HCV, HIV	U-Leucocytes
	U-Nitrites
Pregnancy test	
Blood or urine	

aPTT: Activated partial thromboplastin time; ALT: Alanine aminotransferase; AST: Alkaline phosphatase; B: Blood; Hb: Haemoglobin; HBC: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; INR: International normalised time; P: Plasma; PCV: Packed cell volume; PT: Prothrombin time; S: Serum; TT: Thrombin time; U: Urine.

Please Note. In case a patient shows an AST **or** ALT ≥3×ULN **or** total bilirubin ≥2×ULN please see Appendix D 'Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law (HL), for further instructions.

5.2.2 Physical examination

A complete physical examination will be performed during Visit 1 as indicated in the Study Plan (Table 1) and include an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems. The anaesthesiologist will perform the Allen´s test to make sure there is normal flow in the wrist between radial and ulnar arteries.

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.

5.2.3 ECG

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes. All ECGs should be recorded with the patient in the same physical position. For each time point 3 ECG recordings should be taken at about 5 minute intervals. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study if possible.

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

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

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

If there is a clinically significant abnormal ECG finding during the treatment period, this should be recorded on the AE pCRF, according to standard AE collection and reporting processes (see Section 6.3.6). A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of the IP or study, to confirm reversibility of the abnormality. Information on osimertinib dose reduction for QTc interval prologation is detailed in Section 6.8.4.

5.2.4 Echocardiogram/ MUGA scan

An ECHO or MUGA scan to assess LVEF will be performed at screening (prior to first dose of TAGRISSO) and at least every 16 weeks throughout the treatment period. The modality of the cardiac function assessments must be consistent within a patient ie, if echocardiogram is used for the screening assessment then ECHO should also be used for subsequent scans. The patients should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken. A 28-day follow-up assessment will be required if an on treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality

5.2.5 Vital signs

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

5.2.5.1 Pulse and blood pressure

Supine BP and pulse/heart rate will be measured using a semi-automatic BP recording device with an appropriate cuff size after the patient has rested for approximately 10 minutes.

As as guide, any readings outside the following should be considered in the evaluation:

- Systolic BP >140 mmHg
- Diastolic BP >90 mmHg
- Heart rate <35 bpm or >100 bpm

5.2.5.2 Body temperature

Body temperature will be measured using a semi-automatic body temperature recording device in accordance with local practice.

5.2.5.3 Height and weight

Height (cm) and weight (kg) will be evaluated at screening and BMI (kg/m^2) will be calculated. Patients will be required to remove their shoes and wear light indoor clothing for these measurements.

5.3 Other assessments

5.3.1 Ophthalmologic exam

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

Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs should be performed to record any clinically significant

findings. These photographs should be available for central review by AstraZeneca and AstraZeneca representatives if necessary.

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

5.3.2 Imaging assessments

5.3.2.1 MRI assessment

As part of the inclusion process, all patients will undergo an MRI scan to exclude macroscopic pathology (stroke, diffuse white matter, vascular changes) and confirm the presence of BM. Magnetic resonance images will also be used as anatomical reference for PET examinations.

The examinations will be done at the MRI centre, PPD using the 3.0T system using the clinical routine MRI protocol as defined at PPD . This includes a high resolution T1 sequence, T2 sequences and a gadolinium enhanced T1 sequence and DWI (but not limited to these).

5.3.2.2 PET examination procedures

The PET examinations will be performed at the PET centre, Karolinska Institutet, Department of Clinical Neuroscience, PPD , Solna, Sweden.

PET examinations will include radioactivity measurements in blood and in the brain. Prior to brain PET examinations, a plastic helmet will be made for each patient individually for use during the PET examinations in order to minimize head movement. Brain PET examinations will be performed using a HRRT PET system (Siemens Molecular Imaging, Knoxville, TN, US). The patient will be placed recumbent with his/her head in the PET system. After the IV injection of [^{11}C]osimertinib emission data will be acquired in list mode over 90 minutes.

During the PET examination time, a series of arterial blood samplings will be taken to measure radioactivity and radiometabolites of [^{11}C]osimertinib. The purpose of blood measurements is to obtain a metabolite-corrected arterial input function which is used for the kinetic compartment analysis of [^{11}C]osimertinib brain exposure. The anaesthesiologist will perform the Allen´s test to make sure there is normal flow in the wrist between radial and ulnar arteries. An arterial cannula will be inserted in the radial or brachial artery of 1 of the arms (the non-dominant arm if possible) under local anaesthesia. A venous cannula will be inserted in another arm for the administration of [^{11}C]osimertinib .

An arterial cannula will be used for arterial blood sampling during the PET examination time (first 10 minutes automatic blood sampling system [ABSS], followed by manual blood samples according to predefined KI PET centre protocol; at approximately 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, 60, 75 and 90 minutes post-[^{11}C]osimertinib injection). A venous cannula will be used for the bolus injection of [^{11}C]osimertinib, after it is dissolved in a sterile physiological phosphate buffer (pH 7,4). The mass of the tracer injected per single measurement will be less than 10 µg, the radioactivity per single injection will not exceed 330 MBq/70 kg of body weight. The cannula will be immediately flushed with 10 mL saline.

The collection of arterial and venous samples is required at PET1 and PET2 examinations for analysis. However, based on the preliminary data analysis in the first microdosing study in healthy patients, arterial assessments may be removed for PET3 examination.

5.4 Pharmacokinetics

5.4.1 Collection of PK samples

Venous blood sampling for osimertinib PK: venous samples will be collected at selected time points to determine the PK of osimertinib and its metabolite, AZ5104 after single administration and at steady state.

Although every attempt should be made to collect all samples as per the CSP-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 CSP or not) is recorded in the pCRF. See Section 5.8 for volume of samples to be collected.

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

5.4.2 Determination of drug concentration

Samples for determination of the osimertinib and AZ5104 concentration in plasma and CSF will be analysed by Covance Laboratories on behalf of AstraZeneca, using appropriate bioanalytical methods. Full details of the analytical methods used will be described in a separate bioanalytical Report.

5.4.3 Storage and destruction of PK samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

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

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

Any residual back-up PK samples may be used for future CCI (in this case, residual back-up PK samples will be shipped to PPD (see details in the Laboratory Manual).

5.5 Pharmacodynamics (Not applicable)

5.6 Genetics (Not Applicable)

CCI [redacted]

5.7.1 Collection of plasma and CSF samples

The following tissue/cytology samples will be taken:

- Formalin-fixed paraffin embedded tissue sample for biomarkers will collected during screening (mandatory) and at progression (optional) for determination of the EGFRm status.

The following plasma samples will be taken:

- Venous blood sampling for biomarkers: blood samples will be collected at pre-administration of selected days from all patients for the determination of changes in ctDNA/exosomal DNA/RNA/protein at different days of treatment.

- Venous blood sampling for EGFR mutation detection in plasma: at baseline for confirmation for the presence of EGFRm status.

CSF sampling for ctDNA and exosomal DNA/RNA/protein:

- CSF samples (20 mL to be taken 2 to 3 times) will be collected at pre-administration prior to start of treatment and at the PET3 examination day for the analysis of ctDNA and exosomal DNA/RNA/protein. CSF samples may be collected during continued access treatment if disease progression in CNS.

5.7.2 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the IP to generate hypotheses to be tested in future research. Only the PI at the clinic has access to the code list kept locked under the current rules/regulations for each clinic. The samples are kept in an approved biobank at the study centre. CCI [redacted] The samples will be used only in the way that patients have approved for in their consents.

5.7.3 Labelling and shipment of biological samples

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

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

5.7.4 Chain of custody of biological samples

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

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

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

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

Samples retained for further use are registered in the PPD during the entire life cycle.

5.7.5 Withdrawal of Informed Consent for donated biological samples

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

As collection of the biological samples is an optional part of the study, then the patient may continue in the study.

The Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study centre, are immediately identified, disposed of/destroyed and the action documented
- Ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study centre
- Ensures that the patient and AstraZeneca are informed about the sample disposal

AstraZeneca ensures the organisations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study centre.

5.8 Volume of blood

The number of blood samples that will be drawn from each patient is shown in Table 3. Additional details will be described in a separate Laboratory Manual.

Table 3 Volume of blood to be drawn from each patient

Assessment	Sample volume (mL)	No of samples	Total volume (mL)
Blood chemistry	2.7	5	13.5
Coagulation	1.8	3	5.2
Haematology	2.7	5	13.5
Serology	1.8	1	1.8
Osimertinib PK	2	10 (5×2)	20
Biomarkers	20	5	100
EGFR mutation	20	2	40
Arterial blood radioactivity measurements	25	2 (or 3)	75 (or 100)
Arterial blood radioactivity and metabolite measurements (manual blood samples)	2	20 (or 30)	40 (or 60)
Arterial blood radioactivity and metabolite measurements (manual blood samples)	4	8 (or 12)	32 (or 48)
Venous blood radioactivity and metabolite measurements	4	18 (or 24)	72 (or 108)
Total	86	79 (100)	413 (or 510)

ABSS: Automatic blood sampling system; PET: Positron emission tomography; PK: Pharmacokinetics.
Note: arterial blood sampling includes ABSS used for the first 5 minutes, 5 mL/min. Manual blood samples will be in the range of 2 to 4 mL, not exceeding 40 mL. The study will include 2 PET examinations with arterial blood sampling and the third PET examination may omit arterial blood sampling.
Additional 50 mL blood may be drawn if repeated laboratory tests are needed or if PET examination protocol needs adjustment. The maximum volume to be drawn from each patient will not exceed 550 mL.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An AE is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no IP has been administered.

6.2 Definitions of serious adverse event

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 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 or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent 1 of the outcomes listed above.

For further guidance on the definition of a SAE, see **Error! Reference source not found.** to t he CSP.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected throughout the study, from informed consent until the end of the follow up period. Serious AEs will be collected from the time of signature of informed consent throughout the treatment period and including the follow up period. The follow-up period is defined as 30 working days after the IP is discontinued. SAEs occurring in the follow-up period should be reported to AstraZeneca in the usual manner (see Section 6.4).

6.3.2 Follow-up of unresolved adverse events

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

If an Investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to osimertinib, the Investigator should notify AstraZeneca.

If patients who are gaining clinical benefit are allowed to continue the 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.

6.3.3 Variables

The following variables will be collect for each AE;

- AE diagnosis/description
- The date and time when the AE started and stopped
- Intensity grading according to revised National Cancer Insititute CTCAE version 4.03
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE causedd patients' withdrawal from study (yes or no)
- Outcome

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, 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 4.03 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

6.3.4 Causality collection

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

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

A guide to the interpretation of the causality question is found in Appendix A to the CSP.

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 centre staff: "*Have you/the child had any health problems since the previous visit/you were last asked?*" or revealed by observation will be collected and recorded in the pCRF. 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 laboratory tests, vital signs, ECGs and other safety assessments will be summarised. 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.

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 nonmandated 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 HL 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 1 of the serious criteria. New cancers are those that are not the primary reason for the administration of the IP 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 administration of IP, should be reported as follows:

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

6.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other centre staff inform the appropriate AstraZeneca representatives within1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other centre staff inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other centre staff indicate an AE is serious in the web based data capture system, an automated email alert is sent to the designated AstraZeneca representative.

If the web based data capture system is not available, then the Investigator or other study centre staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study centre staff how to proceed.

6.5 Overdose

A maximum tolerated dose has not been established for Osimertinib, therefore an overdose is any dose which exceeds the daily dose that is defined in the clinical study protocol. Investigators should be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

Such overdoses should be recorded as follows:

- An overdose with associated AEs/SAEs is recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the pCRF and on the overdose pCRF module.
- An overdose with no associated symptoms is only reported on the overdose pCRF module.

If an overdose occurs in the course of the study, then Investigators or other centre staff inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

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

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca during the course of the study and within 6 weeks of the last administration of osimertinib.

6.6.1 Maternal exposure

If a patient 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 IP 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) 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 or within 6 weeks of the final administration of the IP, then the Investigator or other centre staff informs the appropriate AstraZeneca representatives within 1 day ie, immediately but no later than 24 hours of when he or she becomes aware of it and enters this into the pregnancy report pCRF.

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 pCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

Pregnancy of the subject's partners is not considered to be an adverse event. However, the outcome of all pregnancies (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. A consent form specific to this situation must be used. The outcome of any conception occurring from the

date of the first administration until 4 months after the last administration should be followed up and documented.

However, the Investigator should report pregnancies according to the procedures and timelines described for reporting of SAEs. The pregnancy report form should be used instead of the SAE form.

6.7 Medication error

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

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

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the patient received the IP
- Did not occur, but circumstances were recognized that could have led to an error

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

- Investigational product name confusion.
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the patient.
- Investigation product not administered as indicated, for example, wrong route or wrong site of administration.
- Investigational product not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet .
- Investigational product not stored as instructed eg, kept in the fridge when it should be at room temperature.
- Wrong patient received the medication.
- Wrong IP administered to patient.

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

- Errors related to or resulting to those which lead to 1 of the above listed events that would otherwise have been a medication error.
- Patient accidentally missed IP administration(s) eg, forgot to take medication.
- Accidental overdose (will be captured as an overdose).
- Patient failed to return unused medication or empty packaging.
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product.

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

If an medication error occurs in the course of the study, then the Investigator or other centre staff informs the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

6.8 Management of IP related toxicities

Patients who have IP-related toxicities requiring dose interruption or dose reduction may be discontinued from the imaging phase and entered into the CAP following discussion with an AstraZeneca representative. Dose reduction is not allowed in the imaging 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 imaging phase and may be entered into the CAP.

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), including a dose-limiting toxicity not attributable to the disease or disease-related processes under investigation, 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 4.

Table 4 Osimertinib dose adjustment information for adverse reactions

Target Organ	Adverse Reaction	Dose Modification
Pulmonary	ILD/Pneumonitis	Permanently discontinue osimertinib
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than 481 msec within 3 weeks of onset, then restart at a reduced dose (40 mg) or at 80mg (at the discretion of the investigator).
	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 of 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 for up to 3 weeks	Permanently discontinue osimertinib

ECG: Electrocardiogram; ILD: Interstitial lung disease; msec: Millisecond; QTc:QT interval corrected.

If a toxicity resolves or reverts to ≤CTCAE grade 2 within 3 weeks of onset, treatment with osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg) using the rules below for dose modifications (Table 5) and with discussion and agreement with the AstraZeneca study team physician as needed. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption.

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

Table 5 Dose interventions

Intervention	Osimertinib Dose
Starting dose procedure for discontinuation	80 mg
Reduced Dose –1	40 mg

On resolution of toxicity within 3 weeks:

If an AE subsequently requires dose interruption, osimertinib may be restarted at the same dose or at the reduced dose, on resolution/improvement of the AE at the discretion of the Investigator.

6.8.1 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 is provided in osimertinib IB.

The following is not applicable to the patients in continued access:

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

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

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.

6.8.2 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 IB. During the imaging phase, changes in CTCAE grade of diarrhoea will be captured in the AE pCRF.

6.8.3 ILD/Pneumonitis-like toxicity

If new or worsening pulmonary symptoms (eg, dyspnoea) or a radiological abnormality suggestive of ILD/pneumonitis is observed, an interruption in IP administration 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 pCRF during the imaging phase. During the CAP, a questionnaire regarding the results of the full diagnostic workup may be sent to the 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 ILD/pneumonitis should be considered and the IP permanently discontinued (per Table 4 above).

Patients experiencing ILD/pneumonitis will not be permitted to restart the IP. In the absence of a diagnosis of ILD/pneumonitis, the IP may be restarted.

An AstraZeneca or representative study team physician must be contacted.

6.8.4 QTc prolongation

In light of the potential for QT changes associated with osimertinib, electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia) must be corrected to be within normal ranges prior to first dose and electrolyte levels monitored during study treatment

Refer to Table 4 above. Patients with QTcF prolongation to >500 msec should have study treatment interrupted and regular ECGs performed until resolution to <481 msec, or recovery to baseline if baseline QTcF is ≥ 481 msec and then restarted at a reduced dose of 40mg, or 80mg at the discretion of the investigator. If the toxicity does not resolve to ≤ grade 1 within 21 days the patient will be permanently withdrawn from study treatment. 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.

6.8.5 Keratitis and corneal ulceration

Keratitis was reported in 0.7% (n=6) of the 833 patients treated with osimertinib in the AURA studies. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. Any patient developing corneal ulceration will be permanently discontinued from the IP (see Table 4) and should be followed regularly until resolution of the event. Corneal ulceration should be treated according to local guidance.

6.8.6 Changes in cardiac contractility

Across clinical studies, LVEF decreases greater than or equal to 10% and a drop to less than 50% occurred in 4.0% (26/655) of patients treated with osimertinib who had baseline and at least 1 follow-up LVEF assessment. Based on the available clinical study data, a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply osimertinib. [11C]osimertinib will be synthesized at Karolinska Institute and immediately administered to patients.

7.1.1 Osimertinib

Osimertinib 40 mg and 80 mg film-coated oral tablets, manufactured by AstraZeneca will be provided for the study. Osimertinib 40 mg film-coated tablets will only be provided if dose reduction is required.

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 the IP to a patient. Osimertinib should be swallowed whole with approximately 240 mL of water, and not chewed, crushed, dissolved or divided.

Additional information about may be found in the AZD9291 Investigator's Brochure 201.

7.1.2 [11C]osimertinib

The radiolabelled [11C]osimertinib will be manufactured ex tempore by the PET centre Radiochemistry Laboratory at Karolinska Institutet, PPD, Solna, from a precursor "AZ13774738" supplied by PharmaSynth AS (Tartu, Estonia) and close in time to each PET examination. After synthesis, the [11C]osimertinib will be dissolved in a sterile buffer solution and sterile filtered and the final product will undergo quality control prior to release for human administration. The identity of the IPs are shown in Table 6.

Table 6 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer
[11C]osimertinib ([11C]osimertinib / *N*-[2-[2-(dimethylamino)ethyl-methyl-amino]-4-[11C]methoxy-5-[[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino]phenyl]prop-2-enamide)	Solution for intravenous injection	PET Centre, PPD
Osimertinib film-coated tablets	40 mg and 80 mg tablets	AstraZeneca Sodertalje

PET: Positron emission tomography.

Investigational product manufacturing, labelling, packaging and release will be conducted following Good Manufacturing Practice (GMP).

7.2 Dose and treatment regimens

Radioligand [^{11}C]osimertinib will be administered IV, synchronized with the start of the PET system examination. Each patient will undergo a single administration of [^{11}C]osimertinib repeated 3 times over the study (Day 1, Day 2 [or up to Day 8] and Day 29). Mass injected will not exceed 10 µg per injection. Radioactivity injected will be 300 MBq/70 kg of body weight. The minimum injected radioactivity will be 200 MBq/70 kg body weight and the maximum radioactivity injected will be 330 MBq/70 kg body weight.

The first administration of [^{11}C]osimertinib will be administered on Day 1 in the clinic via an IV route. After 90 minutes of the PET examination, the patient may be discharged from the clinic.

The second administration of [^{11}C]osimertinib will be approximately 6 hours after the single oral 80 mg administration of osimertinib to coincide with the oral T_{max}. The oral administration can be with or without food. Pharmacokinetic samples will be collected (up to 6 hours) and the PET examination will be conducted for 90 minutes (minimum 60 minutes) after the IV administration is given. This visit can happen on Day 2 (1 day after the first IV administration) and up to Day 8.

Osimertinib 80 mg once a day will be taken by the patient from the day of the second PET examination for at least 21 days before the PET3 examination will be scheduled. On Day 14 (±2 days), a clinical visit to evaluate the safety of the patient will be performed.

Patients will come to the clinic on Day 29 (±3 days), prior to taking their daily dose of osimertinib. It is important to record date/time of the last administration taken before the visit and make sure that the trough (pre-administration) sample is collected no less than 18 hours and no more than 30 hours after the last administration before the PK blood sample. On Day 29, in addition to receiving their daily administration of osimertinib, patients will receive [^{11}C]osimertinib via IV route at approximately 6 hours after the oral administration. Safety information will be collected during this visit and the patient will be discharged after the PET examination is finished. Computed tomography/MRI measurement can be conducted on the same day or within 7 days of this visit.

7.3 Labelling

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

The label will include the following information:

For the [^{11}C]osimertinib the vial with the prepared radiolabelled osimertinib will be labelled with the following information: signature of the responsible radiochemist, name of the PET ligand: "[^{11}C]osimertinib", batch number, date and time of injection. In addition the vial will

be marked “För injektion”, “Radioaktiv”, “Karolinska universitetssjukhuset” and with the symbol for radioactivity and the logotype of the PPD. The lead container for the vial will be labelled with an identical label as that described above, but will also contain the following additional information: total radioactivity (in MBq) and total volume (in mL). The batch protocol will contain all the information above, except that weight will be recorded instead of volume (g=mL).

7.4 Storage

The IP should be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage.

7.5 Compliance

The administration of all IP should be recorded in the appropriate sections of the pCRF. For the imaging 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 IP, and the date of their next clinic appointment. Patients will need to complete diaries, which will record the date and time of each administration.

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

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

Study centre pharmacy staff will make tablet counts at regular intervals during treatment. For the imaging phase, diaries should be reviewed and tablet counts be performed at each outpatient visit and at check-in on Day 29.

Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the pCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the study centre 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 centre staff of missed doses. Dates of missed or held doses will be recorded on the pCRF. 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 CSP. 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.
- Investigational products are handled and stored safely and properly as stated on the label.
- Investigational products are only dispensed to study patients in accordance with the CSP.

The study staff 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 pCRF. 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 centre file. Dispensing and accountability records will continue to be collected after the end of the imaging phase for as long as patients continue to receive IP.

7.7 Concomitant and other treatments

Information on any treatment in the 2 weeks prior to starting the IP and all concomitant treatments given during the study, with reasons for the treatment, will be recorded in the pCRF.

Please see Appendix B for medication that may potentially have interactions with osimertinib.

7.7.1 Other concomitant treatment

Medication other than that described in Appendix B, which are considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the pCRF.

7.8 Post study access to study treatment

On completion of the imaging phase (ie, at the PET3 examination), 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, SAEs that may or may not be related to osimertinib, outcomes of pregnancy and IP dispensing/accountability.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

Statistical analyses will be performed by IQVIA (formerly QuintilesIMS) under the direction of Biometrics & Information Sciences, AstraZeneca using SAS® version 9.2 or higher and, where appropriate, additional validated software.

IQVIA (formerly QuintilesIMS) will finalise the SAP according to any required regulatory timelines and description of services.

Calculations for the PET parameters will be performed by the Karolinska Institute, Department of Clinical Neuroscience, PPD , Solna, Sweden.

8.2 Sample size estimate

Given that this a PET study, sample size is based on the generally applied numbers in the exploratory pilot type studies, where 8 subjects is the accepted minimum number. These types of studies have no statistics to give better ground for sample size calculations. Therefore the minimum sample size is accepted both by regulatory and scientific communities. Given the nature, no formal statistical analysis will be performed in this study. The statistical analysis will be descriptive.

The number of patients is based on the desire to obtain evaulable data while exposing as few evaluable patients as possible to the study procedures. Approximately 12 patients with NSCLC will receive osimertinib to obtain at least 8 patients to complete all study assessment procedures.

8.3 Definitions of analysis sets

8.3.1 PET analysis set

All patients who complete at least 2 PET examinations will be included in PET data analysis and evaluation of [11C]osimertinib brain distribution. Patients who have completed all PET examinations; will be included in the assessment of potential treatment effects.

8.3.2 Safety analysis set

All patients who receive at least 1 administration of either [^{11}C]osimertinib and/or osimertinib will be included in the assessment of the safety.

8.3.3 PK analysis set

Pharmacokinetics parameters will be summarised for all patients who had post administration PK assessments without any CSP deviations or dosing deviations that might have affected the PK analysis.

8.4 Outcome measures for analyses

The primary outcome variables describe the distribution of [^{11}C]osimertinib in the brain using a set of exposure parameters including but not limited to:

- The maximum concentration in the whole brain, expressed as the %ID: $C_{max,\ \%ID\ brain}$ or as SUV $C_{max,\ SUV\ brain}$
- The time to the maximum radioactivity concentration in brain: $T_{max\ brain}$
- Brain plasma partition coefficient (ratio of radiolabelled osimertinib concentration in brain to that in plasma) as $AUC_{brain\ 0\text{-}90min}/AUC_{blood\ 0\text{-}90min}$. The area under the brain as well as the plasma radioactivity concentration-time curve between 0 and 90 minutes after injection ($AUC_{0\text{-}90\ min}$) will be calculated by the linear trapezoidal rule.

8.5 Methods for statistical analyses

The analysis will be descriptive and consist of patient listings, graphs, summary statistics comprising geometric mean, arithmetic mean, standard deviation (SD), median, minimum and maximum values as appropriate.

8.5.1 Patient disposition

Continuous variables will be summarised using descriptive statistics (n, mean, SD, minimum, median and maximum) by phase. Categorical data will be summarised using frequencies and percentages by phase where applicable.

8.5.2 Demographic and baseline data

Demographic and baseline characteristic data recorded at the screening Visit will be listed. Demographic data will include date of birth, age, sex, race and ethinicity. Patient characteristics and baseline data will include smoking details (quatity and duration of smoking history) and physical examination findings.

8.5.3 Exposure

Exposure to IP i.e., total amount of IP received will be described for all patients.

8.5.4 PET imaging and RECIST

Parameters from PET imaging (Section 8.5.7) will be summarised. Overall response from the BM assessment according to CNS RECIST v1.1 from the brain MRI after 3 weeks of multiple administrations will be summarised. Modified RECIST criteria, referred to here as CNS RECIST, will allow the selection of up to 5 lesions in the brain as target lesions, in contrast to RECIST 1.1 which categorises brain metastases as non-measurable lesions. Overall response from the extra-cranial tumour assessment according to RECIST v1.1 from thorax/abdomen CT after 3 weeks of multiple administrations will also be summarised.

8.5.5 Pharmacokinetics

Pharmacokinetic parameters include Css_{max}, tss_{max}, AUCss for osimertinib (parent), and the metabolite to parent ratio of AUCss and Css_{max} for AZ5104, as appropriate.

8.5.6 Safety

Safety data will be summarised as appropriate. These include AEs, ECGs, physical examination, vital signs (including BP, pulse), and laboratory parameters (clinical chemistry, haematology, and urine analysis).

8.5.7 Quantitative PET brain imaging data analysis

PET image data analysis includes sequential steps:

(i) Image pre-processing (re-orientation, re-alignment, co-registration to MR images, etc.)

(ii) Manual or/and automatic delineation of the anatomical and tumour ROIs

(iii) Extraction of regional radioactivity (time activity curves)

(iv) Preparation of arterial input function using conventional PET analysis methods and

(v) Quantification of [^{11}C]osimertinib distribution in the brain

A set of exposure parameters including but not limited to will be quantified:

- C_{max}, %ID brain (%ID)
- C_{max}, SUV brain (SUV)
- $T_{max\ brain}$ (min)
- Brain plasma partition coefficient (concentration brain/plasma ratio) as ($AUC_{brain\ 0\text{-}90min}/AUC_{blood\ 0\text{-}90minu}$)

For detailed description of quantitative analysis methods see Section 5.3.2 and Saleem A, Searle GE, Kenny LM, Huiban M, Coombes RC, et al. Lapatinib access into normal brain and brain metastases in patients with Her-2 overexpressing breast cancer. EJNMMI Res. 2015; April 30;5:20.

Schou et al 2015.

CCI [redacted]

CCI [redacted]

PPD /CCI [redacted]

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study centre staff

Before the first patient is entered into the study, an AstraZeneca representative will visit the study centre to review and discuss the requirements of the CSP and related documents with the investigational staff and also to train them in any study specific procedures including collection of samples. The Investigator will ensure that appropriate training relevant to the study is given to all of the staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

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

9.2 Monitoring of the study

The AstraZeneca and IQVIA (formerly Quintiles IMS) representatives will be available between visits if the Investigator(s) or other staff at the centre that needs information and advice about the study conduct.

During the study, an IQVIA (formerly QuintilesIMS) representative will have regular contacts with the study centres, 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 CSP including the specific requirements, that data are being accurately and timely recorded in the pCRFs, and that IP accountability checks are being performed.
- Perform source data verification (a comparison of the data in the pCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of the informed consent forms (ICFs) of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).
- If applicable, ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The Investigator at 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 CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

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

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as after the last patient has left the CAP.

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

9.3.1 Study and site closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

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

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

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

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

- Discontinuation of further study intervention development.

9.4 Data management by AstraZeneca

Data management will be performed by the CRO on behalf of AstraZeneca, according to the Data Management Plan.

When the completed paper CRFs have been scanned and indexed, the data are entered into the study database and proofread.

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 Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

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

9.4.1 SAE reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the study centre.

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 International Council for Harmonisation (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

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

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 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.

10.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final CSP, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The PI will ensure the distribution of these documents to the applicable EC, and to the study centre 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.

The PI is responsible for providing the EC/Institutional Review Board with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the PI so that he/she can meet these reporting requirements.

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

AstraZeneca will provide Regulatory Authorities, EC and the PI with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions, where relevant.

10.4 Informed consent

The PI at the 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 informed consent 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.

Any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation should be described in the informed consent form that is approved by an Ethics Committee.

The PI at the PET centre will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study Ensure that each patient is notified that they are free to withdraw from the study or the research components at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure each original, signed ICF is stored in the Investigator's Study File
- Ensure a copy of each signed ICF is given to the patient.

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

If there are any substantial changes to the CSP, then these changes will be documented in a new version of the CSP.

The new version of the CSP 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 new versions of CSPs.

AstraZeneca will distribute any new versions of the CSP to the PI. For distribution to the EC see Section 10.3.

If a change to a CSP 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.

Study procedures will not be changed without the mutual agreement of the Investigator, and AstraZeneca.

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

If local regulations require, any administrative change will be communicated to or approved by the 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 CSP, GCP, guidelines of the ICH, and any applicable regulatory requirements. The PI will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

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Appendix A Additional Safety Information

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

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the 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 1 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 recognized feature of overdose of the drug?
- Is there a known mechanism?

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

The causality assessment is performed based on the available data including enough information to make an informed judgement. 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 A 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 patient 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 B Guidance Regarding Potential Interactions with Concomitant Medications

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

1. 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 C1 Drugs Inducing CYP3A4

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

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

2. Medicines Whose Exposures may be Affected by Osimertinib that AstraZeneca Considers may be Allowed with Caution

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

Table C2 Exposure, Pharmacological Action and Toxicity may be Increased by Osimertinib

Warning of possible interaction	Advice
Rosuvastatin	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to coadministration with osimertinib.
Sulfasalazine	
Doxorubicin	
Daunorubicin	
Topotecan	
Dabigatran	
Aliskiren	
Digoxin	

3. Drugs that may Prolong QT Interval

The drugs listed in this section are taken from information provided by the Arizona Center for Education and Research on Therapeutics on the CredibleMeds® website https://www.crediblemeds.org/. The website categorizes drugs based on the risk of inducing Torsade de Pointes (TdP).

During screening the drugs that patients are currently receiving (prescription and nonprescription) should be checked opposite the ArizonaCert website. In addition, drugs intended for use following study treatment initiation should be checked opposite the website.

3.1 Drugs with a known risk of Torsades de Pointes

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

3.1.1 Before commencing study treatment

Drugs in the category of known risk of TdP must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in Table C3.

3.1.2 During study treatment

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

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

Table C3 Drugs with a known risk of TdP[a]

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

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

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

3.2 Other TdP risk Categories

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

Patients with congenital long QT syndrome (CLQTS) are excluded from this study.

3.3 Guidance regardless of TdP risk category

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

Appendix C Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods.

Definition of Women of Childbearing Potential

Women of Childbearing Potential (WoCBP):

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

Women NOT of Childbearing Potential:

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

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

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

Acceptable contraception methods

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

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

Acceptable contraception methods are:

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

Unacceptable contraception methods

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

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

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

1. Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law (HL). 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 HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Product (IP).

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

2. Definitions

Potential Hy's Law

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3×Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥2×ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

A Potential Hy's Law (PHL) case is defined as a study patient with an increase in serum AST or ALT ≥3×ULN together with total bilirubin (TBL) ≥2×ULN irrespective of serum ALP, at any point during the study following the start of study medication.

Hy's Law

AST or ALT ≥3×ULN **together with** TBL ≥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 TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

A HL case is defined as a study patient with an increase in serum AST or ALT ≥3×ULN together with TBL ≥2×ULN, where no other reason can be found to explain the combination of increases, eg, elevated serum ALP indicating cholestasis, viral hepatitis,

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

3. Identification of Potential Hy's Law Cases

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

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

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result.

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2. Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

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

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

4. Follow-up

4.1 Potential Hy's Law Criteria not met

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

- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (see Section 6. 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 etiology of the event and perform diagnostic investigations as discussed with the Study Physician. For studies using a central laboratory add: This includes deciding which the tests available in the HL lab kit should be used.
- Complete the 3 Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

5. Review and Assessment of Potential Hy's Law Cases

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

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

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

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

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

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

- Report an SAE (report term 'HL') 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 'PHL') 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 amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

6. 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 Section 4.2 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.

7. Actions Required for Repeat Episodes of Potential Hy's Law

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

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

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

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, 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 Section 6. Actions Required when Potential Hy's Law Criteria are Met Before and After Starting Study Treatment?

If No: follow the process described in Section 4.2 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'