AstraZeneca

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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

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Study Statistician IQVIA PPD PPD

AstraZeneca

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PPD

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Global Product Statistician PPD PPD

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AUC	Area under the concentration-time curve
AUCss	Area under the concentration-time curve at steady state
BM	Brain metastases
BMI	Body mass index
BP	Blood pressure
CSR	Clinical Study Report
^{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)
CSF	Cerebrospinal fluid
CSP	Clinical Study Protocol
ctDNA	Circulating tumour DNA
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECHO	Echocardiogram
EGFR	Epidermal growth factor receptor
FSH	Follicle-stimulating hormone
GCV	Geometric coefficient of variation
IP	Investigational Product
$Kp_{u,u}$	Brain/plasma partition coefficient
LM	Leptomeningeal metastases
LVEF	Left ventricular ejection fraction
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
PK	Pharmacokinetics
RECIST	Response Evaluation Criteria in Solid Tumours
ROI	Region of interest
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation or special term	Explanation
SD	Standard deviation
SOC	System organ class
SUV	Standardised uptake value
T_{max}	Time of maximum drug concentration after single dose
Tss_{max}	Time of maximum drug concentration at steady state

AMENDMENT HISTORY

Date	Brief description of change
	N/A

1. STUDY DETAILS

1.1 Study objective

Primary objective

The primary objective of this study and the associated outcome measures are

Primary Objective:	**Outcome Measure:**
To determine the brain exposure of [^{11}C]osimertinib in tumour region of interest (ROI) [brain metastases (BM), including leptomeningeal metastases (LM)] in patients with non-small cell lung cancer (NSCLC) after a single intravenous (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-time curve (K_p=$AUC_{brain\ 0\text{-}90min}$/ $AUC_{blood\ 0\text{-}90min}$). All parameters of exposure will include the tumour region, whole brain and anatomical regions.

AUC: Area under the concentration curve; C_{max}: Maximum concentration after single dose; T_{max}: Time of maximum drug concentration after single dose.

Secondary objective

The secondary objective of this study and the associated outcome measures are

Secondary Objective:	**Outcome Measure:**
To determine the pharmacokinetics (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 measurable time point (AUC_{ss}). Also, the metabolite to parent ratio of the AUC and maximum concertation after a single dose (C_{max}) will be calculated, as appropriate.

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

Safety objective

The safety objective of this study and the associated outcome measures are

Safety Objective:	Outcome Measure:
To examine the safety and tolerability of [^{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.

CCI [redacted]

[redacted]

CCI [redacted]

1.2 Study design

The study design includes 2 phases, the imaging phase and the continued access phase. Using high resolution positron emission tomography (PET), 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 (EGFR) mutated NSCLC 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) and other parameters of brain exposure listed in Section 3.1.

An overall study plan is presented in Figure 1.

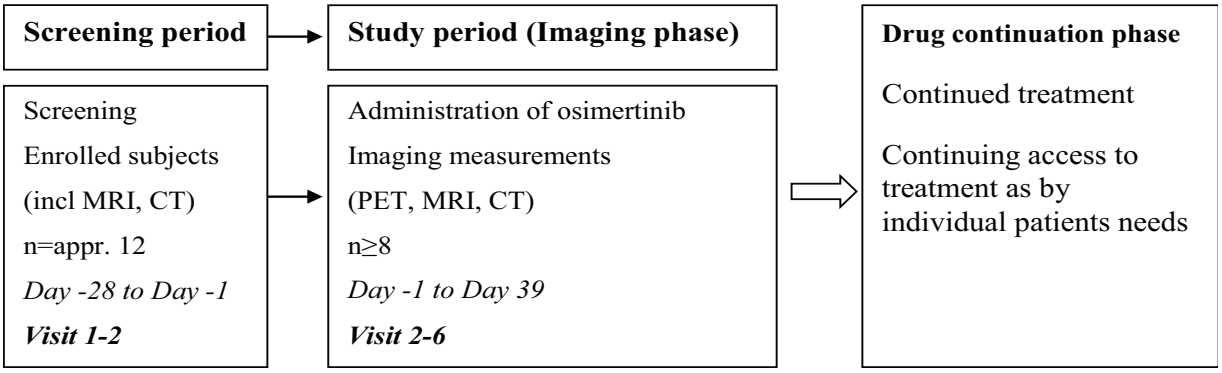
Full details of the assessments conducted at each visit are shown in Table 1 of the protocol.

The imaging phase of the study will include 3 single IV microdose administrations of [^{11}C]osimertinib and PET examinations on Day 1, Day 2 (or up to Day 8) and Day 29. Oral administration of osimertinib tablets (80 mg once daily) to patients will begin from the day of the second PET examination for at least 21 days before the third PET 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 the sudden death of unknown reason, serious adverse events that may be related to osimertinib, outcomes of pregnancy and investigational product (IP) dispensing/accountability.

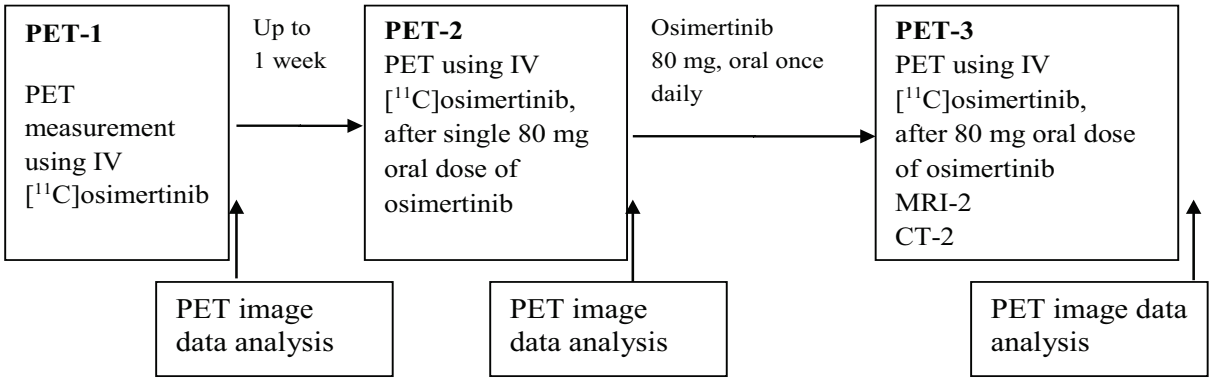
Patients not participating in the continued access phase or who discontinue treatment during the imaging phase will return to the clinic for follow-up assessments 30 days (±7 days) after their last administration of osimertinib in the imaging phase. If the patient's last administration of osimertinib 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.

Figure 1 Overall study plan

A: Study flow

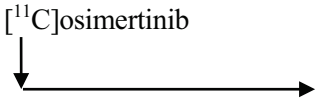


B: Study period (drug administration and imaging measurements)



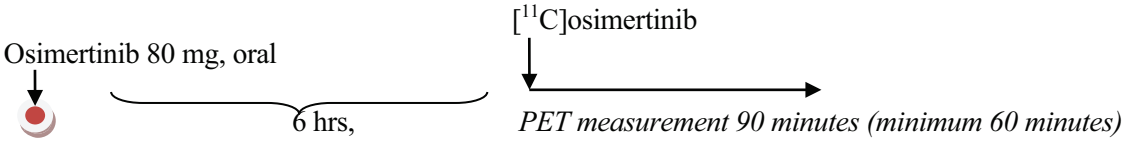
C. PET examination flow

PET1



PET measurement 90 mins (minimum 60 minutes)

PET2 and PET3



= Tablet dosing CT: Computed tomography; IV: Intravenous; MRI: Magnetic resonance imaging; PET: Positron emission tomography

1.3 Number of subjects

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 evaluable 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, and hence, evaluable for analysis.

2. ANALYSIS SETS

2.1 Definition of analysis sets

There will be 4 analysis sets considered in this study:

- The *safety analysis set* will include all patients who receive at least 1 administration of [^{11}C]osimertinib and/or osimertinib
- The *PET analysis set* will include all patients who complete at least 1 PET examination for the evaluation of [^{11}C]osimertinib brain distribution.
- The *complete PET analysis set* will include all patients who complete all three PET examinations. This analysis set is a subset of the PET analysis set and will be used in the assessment of potential treatment effects on brain metastases
- The *PK analysis set* will include all patients who received at least 1 administration of either [^{11}C]osimertinib and/or osimertinib and had post administration PK assessments of osimertinib and/or its metabolite (AZ5104) without any CSP deviations or dosing deviations that might have affected the PK analysis.

2.2 Protocol deviations

Important protocol deviations (or events) include changes to the procedures that may impact the quality of data. The following will be considered an important protocol deviation. These deviations will be listed and discussed in the CSR as appropriate:

- Patients entered but who did not receive study treatment (Deviation 1).

Deviation 1 will lead to exclusion from the safety, PK and PET analysis set. Patients who receive the wrong treatment at any time (provided they receive at least 1 administration of [^{11}C]osimertinib and/or oral osimertinib) will still be included in the safety analysis set as

described in section 2.

During the study, decisions on how to handle errors in treatment dispensing (with regard to continuation/discontinuation of study treatment or, if applicable, analytically) and any other important protocol deviation will be made on an individual basis with written instruction from the study team leader, appropriate study personnel and/or statistician.

The important protocol deviations will be listed and summarised across all patients.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Parameters of brain exposure of [^{11}C]osimertinib

The primary outcome variables describe the distribution of [^{11}C]osimertinib in the whole brain using a set of exposure parameters including:

- $C_{max,\%ID\ brain}$ Maximum radioactivity concentration in brain (%), expressed as the percentage of injected radioactivity (calculated as the radioactivity concentration in the region of interest multiplied with the volume of the region of interest), divided by the radioactivity injected, and multiplied by 100
- $C_{max,SUV\ brain}$ Maximum radioactivity concentration in brain, expressed as the standardized uptake value corresponding to the regional radioactivity concentration normalized for injected radioactivity and body weight
- $T_{max\ brain}$ Time of maximum radioactivity concentration in the brain (min), obtained directly from the observed concentration versus time data
- $AUC_{brain\ 0\text{-}90}$ Area under the brain radioactivity concentration-time curve between 0 and 90 minutes (SUV*min) after injection calculated by the linear trapezoidal rule
- $AUC_{blood\ 0\text{-}90}$ Area under the plasma radioactivity concentration-time curve between 0 and 90 minutes (SUV*min) after injection calculated by the linear trapezoidal rule
- K_p Brain plasma partition coefficient – ratio of radiolabelled drug in brain to that in plasma calculated as $AUC_{brain\ 0\text{-}90}/AUC_{blood\ 0\text{-}90}$
- V_T Total distribution volume (ml/cc) quantified using kinetic compartment model

Radioactivity concentrations (as %ID) for the whole brain, tumour regions and anatomical regions will be plotted as time activity curves for individual subjects as well as an overlain plot for all subjects with arithmetic mean curve. These figures along with PET images after administration of [^{11}C]osimertinib will be prepared by the AZ PET Centre at Karolinska Institutet.

Exposure parameters will be summarised for all subjects in the PET analysis set using descriptive statistics. Geometric mean and geometric CV% will not be calculated for $T_{max\ brain}$. A by-subject appendix of individual exposure parameters will be provided.

Note: Some PET data variables may need to be amended after evaluation of first few patients, depending on the emerging data and selection of analysis method (kinetic modelling approach). Additionally, the PET team at KI may calculate exposure and/or efficacy parameters, other than those listed above. Subsequently, additional listings, summary tables, and figures may be added to the planned presentation of data. These modifications will be covered in a future SAP amendment when data from first few subjects are available.

3.2 PK Variables

All PK concentrations will be listed. Average of the concentrations between the PET measurement will also be summarised. Summary data for patients in the PK analysis set will be presented in the table. The following PK parameters will be summarized for patients in the PK analysis set. There will be no PK parameters presented for patients after the first dose (PET2 day) and only steady state PK parameters (PET3) will be calculated.

Pharmacokinetic parameters for an individual patient were not included in the summaries if the patient missed a single dose within 3 days of the planned PK sampling, received a different dose on the PK sampling day or ≥7 days of dosing were missed with <10 days back on daily administration before the PK sampling day. This list of patients was provided by the pharmacokineticist. The pre-dose time point on PET3 was also used as the 24 hr time point to calculate the AUCss since at the time of PET3, if the patient met the above criteria, osimertinib and AZ5104 are expected to be at steady state.

Osimertinib: Area under the concentration time curve from 0-24 hrs at steady state (AUCss), maximum plasma concentration at steady state (Cssmax), time of maximum plasma concertation at steady state (Tssmax), apparent clearance at steady state (CLss/F).

AZ5104: AUCss, Cssmax, Tssmax, AZ5104 AUCss/osimertinib AUCss, AZ5104 Cssmax/osimertinib Cssmax.

For PET2, ie, after single dose of osimertinib, no PK parameters will be presented due to planned limited sampling and only the concentration data will be listed and summarized.

Events or changes to procedures that may impact the evaluation of PK data including, but not limited to, vomiting following oral dosing occurring within the timeframe of 2 times the median tmax, wrong dose administered, patient received a prohibited concomitant medication,

sample processing errors that lead to inaccurate bioanalytical results, and incomplete PK profile. The final decision on the inclusion of the patient in the PK analysis set will be determined by the PK scientist and documented in the CSR. The affected PK data collected (as deemed by the study pharmacokineticist) will be excluded from the summaries and statistical analyses, but will still be reported in the study result listings. Pharmacokinetic parameters for an individual patient may not be included in the summaries if the patient missed a single dose within 3 days of the planned PK sampling, received a different dose on the PK sampling day or ≥7 days of dosing were missed with <10 days back on daily administration before the PK sampling day. This list of patients will be provided by the pharmacokineticist. The pre-dose time point on PET3 may also be used as the 24 hour time point to calculate the AUCss as at the time of PET3, if the patient met the above criteria, and osimertinib and AZ5104 are expected to be at steady state.

CSF analysis:

The CSF concentration will be listed for all patients and summarized for patients in the PK analysis set. The CSF to plasma and CSF to free plasma ratio will be listed for all patients and summarized for patients in the PK analysis set. The free fraction value to 5.27% free for osimertinib and 7.92% for AZ5104 will be used for the free plasma calculation based on the in vitro plasma protein binding assessments.

3.3 Safety and tolerability variables

Safety and tolerability will be assessed by:

- Assessment of adverse events (AEs), graded by Common Terminology Criteria for Adverse Events (CTCAE) (v4.03)
- Physical examination
- Vital signs (including blood pressure [BP], pulse rate, body temperature, and weight)
- Standard 12 lead electrocardiograms (ECGs)
- Evaluation of laboratory parameters (clinical chemistry, coagulation, haematology and urine analysis)
- Echocardiogram/multiple gated acquisition scan (MUGA)
- Concomitant medications

Adverse events will be classified according to the terminology of Medical Dictionary for Regulatory Activities (MedDRA), Version 21.0 or higher (preferred term and system organ class [SOC]).

Adverse events reported before any administration of osimertinib will be listed only and be referred to as "pre-treatment". Similarly, AEs reported before any administration of osimertinib that continue after the first administration without worsening will also be classified as "pre-treatment".

A treatment emergent AE (TEAE) will be defined as any AE with start date and time on or after the first IV dosing of osimertinib in imaging phase up to 30 days after their last study treatment administration or immediately before initiation of any other cancer therapy, whichever occurs first.

For laboratory data, vital signs and ECG data, baseline is defined as the latest result obtained prior to the first IV dose of osimertinib in the imaging phase.

For all safety data, an on-treatment period is from after the first IV dose of osimertinib in the imaging phase, up to and including the follow-up visit.

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 will 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. This follow-up assessment will serve as the end-of study assessment for a patient.

Concomitant medications are those which were taken at any time between first dose of osimertinib in the imaging phase and completion of or withdrawal from the study. This includes medications which were started before first IV dose of osimertinib in the imaging phase, but stopped during the course of study (after first IV dosing date/time) or were ongoing at completion of or withdrawal from the study.

Exposure to [^{11}C]osimertinib will be summarized by number of patients receiving 1, 2 or all 3 doses.

Exposure to oral osimertinib, during imaging phase, will be assessed using total exposure time and actual exposure time

- Total exposure time (months) will be calculated from the first dose to the last dose

$$Total\ exposure = \frac{(\ last\ dose\ date\ where\ dose\ > 0\ mg\ -\ first\ dose\ date) + 1}{30.4375}$$

- Actual exposure time (months) will be calculated from first dose to the last dose, taking account of dose interruptions.

$$Actual\ exposure = \frac{[(last\ dose\ date\ where\ dose\ > 0\ mg\ -\ first\ dose\ date) + 1 - \text{total duration of dose interruption (i. e. number of days with dose} = 0\text{mg})]}{30.4375}$$

3.4 Other imaging variables

Result of MRI assessments and thorax/abdomen CT scan will be presented in listings. Overall response from the BM assessment according to CNS RECIST v1.1, as captured on the pCRF, from the brain MRI after 3 weeks of multiple administrations will be summarised. Overall response from the extra-cranial tumour assessment according to RECIST v1.1, as captured on the pCRF, from thorax/abdomen CT after 3 weeks of multiple administrations will also be summarised.

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3.5 Compliance to study treatment (imaging phase)

The administration of study treatment will be recorded in the appropriate sections of the paper case report form (pCRF). For the imaging phase, when the patients are not resident in the clinic, patients will report any self-administered medications along with date and time of each administration in the Patient Diary Card. 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 and recorded in the pCRF.

Study centre pharmacy staff will make tablet counts at regular intervals during treatment. For the imaging phase, diaries will be reviewed and tablet counts 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 sections of the pCRF. After the tablet count has been performed, the remaining capsules will not be returned to the patient but will be retained by the study centre until reconciliation is completed by the study monitor.

Estimated overall compliance will be derived using the following formula:

$$Overall\ Compliance = \frac{Total\ number\ of\ tablets\ dispensed - Total\ number\ of\ tablets\ returned}{Last\ date\ of\ tablets\ returned - First\ date\ of\ tablets\ dispensed} \times 100$$

where, ‘total number of tablets dispensed’ refers to all dispensed tablets over multiple time periods and ‘total number of tablets returned’ refers to all returned tablets over multiple time periods.

4. ANALYSIS METHODS

4.1 General principles

Derivation of the quantitative PET imaging parameters for [^{11}C]osimertinib will be the responsibility of Karolinska Institute, Department of Clinical Neuroscience, PPD , Solna, Sweden. Pharmacokinetic analysis and derivation of PK parameters will be the responsibility of AstraZeneca. Statistical summaries and analyses of data will be performed by IQVIA under the direction of the Biostatistics Group, AstraZeneca using SAS® Version 9.4 or higher and, where appropriate, additional validated software.

The clinical database will close and the data will be reported in a CSR when the last patient either completes the 30-day (±7 days) follow-up visit after their last administration in the imaging phase, or discontinues from the study, whichever comes first.

All individual data as recorded in the final study database will be provided by IQVIA Data Management for analysis.

The treatments will be labelled in relevant summaries and listings as:

- "Osimertinib 80 mg"
- "[^{11}C]osimertinib"

and defined as follows:

- "Osimertinib 80 mg": 80 mg osimertinib film-coated oral tablets, manufactured by AstraZeneca
- "[^{11}C]osimertinib": radiolabelled [^{11}C]osimertinib, manufactured *ex tempore* by the positron emission tomography centre, Radiochemistry Laboratory at the Karolinska Institutet, PPD , Solna, Sweden

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented.

Quantitative variables will be summarised using descriptive statistics, including n, arithmetic mean, standard deviation (SD; calculated using untransformed data), median, minimum (min), and maximum (max) values. Geometric mean and coefficient of variation will be included for exposure parameters, as applicable.

Where appropriate, safety data will be summarised by scheduled visit.

4.2 General variables

4.2.1 Study day definitions

For data summaries, Study Day 1 is defined as the date of first IV microdose administration of [^{11}C]osimertinib. For visits (or events) that occur on or after Study Day 1, study day is defined as (date of visit [event] – date of first IV microdose administration of [^{11}C]osimertinib + 1). For visits (or events) that occur prior to Study Day 1, study day is defined as (date of visit [event] – date of first IV microdose administration of [^{11}C]osimertinib). There is no Study Day 0.

For listings (such as for AEs) that include the derivation of "days since last dose", this is defined as (event date – date of last dose). Events that occur on the same day as the last dose of study drug will therefore be described as occurring zero days from the last dose of study drug.

4.2.2 Visit windows

For summaries of vital signs, laboratory data, ECG, etc., assessments will be assigned to calculated visit windows (using study day).

The time windows should be exhaustive so that data recorded at any time point has the potential to be summarised. Inclusion within the visit window should be based on the actual date and not the intended date of the visit. For summaries at a subject level, all values should be included, regardless of whether they appear in a corresponding visit based summary, when deriving a subject level statistic such as a maximum.

The windows for the visits following baseline (including scheduled visits) will be constructed in such a way that the upper limit of the interval falls half way between the two visits.

For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval). Values from scheduled and unscheduled visits will be included. Listings should display all values contributing to a time point for a subject; they should also highlight the value for that subject that was used in the summary table, wherever feasible.

For visit-based summaries, if there is more than one value per subject within a visit window then the closest to the planned study day value should be summarised, or the earlier in the event the values are equidistant from the planned study day. The visit will be missing if no assessment was reported within the specified visit window around the planned study day.

4.2.3 Handling missing data

In general, other than for partial dates, missing data will not be imputed and will be treated as missing.

4.2.3.1 Imputation of partial dates

Concomitant medication and adverse events start dates

- If year is missing (or completely missing), do not impute
- If (year is present and month and day are missing) or (year and day are present and month is missing), impute as January 1st
- If year and month are present and day is missing, impute days as first day of the month

Concomitant medication and adverse events end dates

- If year is missing (or completely missing), do not impute
- If (year is present and month and day are missing) or (year and day are present and month is missing), impute as December 31st, unless this is after the date of death in which case date of death will be used instead
- If year and month are present and day is missing, impute day as last day of the month, unless this is after the date of death in which case date of death will be used instead

In addition, for AEs and CMs if, for a partial start date, the start date could (when also considering the end date) potentially be on the first study medication date, the start date will be imputed with the first study medication date to assume a "worst case" scenario; e.g. AE from UNK-Feb-2014 to 23-Mar-2014 with first study medication date 21-Feb-2014, then the AE start date will be imputed to 21-Feb-2014.

4.2.4 Imputation rules for lab values outside of quantification range

Lab values below the lower limit of quantification (LLoQ) that are reported as "<LLoQ" or "≤LLoQ" in the database will be imputed by LLoQ × 0.99 for analysis purposes. The original value will be listed.

Lab values above the upper level of quantification (ULoQ) that are reported as ">LLOQ" or "≥ULoQ" in the database will be imputed by ULoQ × 1.01 for analysis purposes. The original value will be listed.

4.3 Analysis methods

4.3.1 Screening and demographic measurements

Disposition of patients

A summary table will be presented specifying the number of patients enrolled, who received treatment, who completed the study, and who terminated prematurely. Data will be summarised across all patients.

In addition, the number of patients included in safety analysis set as well as important protocol deviations will also be summarised within separate tables. These data will be summarised across all patients.

Demographic data

Descriptive statistics will be presented for age, height, weight and BMI, In addition, frequencies and percentage of patients will be tabulated for the categorical variables age group (< 40, >=40 up to 50, >=50 up to 65, and >=65 years), smoking status (never, former, and current), sex and ethnic group. Data will be summarised across all patients.

Concomitant medication

Prior medications, concomitant and post-treatment medications are defined based on imputed start and stop dates as follow:

- Prior medications are those taken prior to study treatment with a stop date prior to the date of first IV microdose administration of [^{11}C]osimertinib
- Concomitant medications are those with a stop date on or after the date of first IV microdose administration of [^{11}C]osimertinib (and could have started prior to or during treatment)
- Post-treatment medications are those with a start date after the date of last IV microdose administration of [^{11}C]osimertinib or oral osimertinib, whichever is later

Concomitant medications will be summarised by the coded terms in separate tables per whether the medication is allowed or disallowed based on Appendix C of the clinical study protocol. For inclusion in concomitant medication summaries, incomplete medication start and stop dates will be imputed as detailed in Section 4.2.3.1.The number of patients receiving a medication will be summarised across all patients. A patient is only counted once even if they receive the medication more than once. For detailed information regarding concomitant treatments see Section 7.7 of the protocol.

Other baseline data

Other demographic and baseline data will be listed and/or summarised (as appropriate) across all patients. These data will include nicotine usage, medical and surgical history, past cancer treatments and radiotherapy, performance status, serology, and results from pregnancy test, follicle-stimulating hormone assessment, luteinising hormone assessment, and physical examination.

4.3.2 Important protocol deviations

Important protocol deviations are described in Section 2.2. A listing detailing the important protocol deviations for each enrolled patients will be presented. Minor protocol deviations, not expected to affect the treatment outcome, will not be included in this listing.

A table summarizing the important protocol deviations, along with the number and percentage of patients overall will be presented (based on the safety analysis set).

4.3.3 Safety parameters

Safety variables

All safety analyses will be performed on the safety analysis set.

Treatment Exposure

Treatment exposure data will be listed and summarised. Total exposure time and actual exposure time will be summarized using descriptive statistics for oral osimertinib exposure while frequency count of subjects taking number of doses (1, 2 or 3) will be presented for [^{11}C]osimertinib exposure.

Adverse Events

All AEs will be listed for each patient, and TEAEs will be summarised.

The following summary tables will be presented across all patients.

- Summary of number (%) of patients who had at least one AE in any category (Any AE, any causally related AE, any AE of CTCAE grade 3 or higher, any causally related AE of CTCAE grade 3 or higher, any AE with outcome = death, any causally related AE with outcome=death, any SAE (including events with outcome = death), any causally related SAE (including events with outcome = death), any SAE leading to discontinuation of investigational product (IP ie, osimertinib), any causally related SAE leading to discontinuation of IP, any AE leading to discontinuation of IP, any causally related AE leading to discontinuation of IP, any other significant AE, any other causally related significant AE (OAE).

- Summary of number (%) of patients who had at least 1 AE by system organ class and preferred term presented by maximum reported CTCAE grade.

- Summary of number (%) of patients who had at least 1 AE with CTCAE grade 3 or higher by system organ class and preferred term.

- Summary of number (%) of patients who died and a listing of deaths.

- A listing of key information for SAEs, and a listing of key information for SAEs with outcome other than death will be presented.

- A listing of key information for AEs leading to discontinuation of IP will be presented.

- Summary of number (%) of patients who had an AE which started prior to study treatment or more than 30 days after last dose of study treatment, by system organ class and preferred term.

Clinical laboratory variables (haematology, clinical chemistry, coagulation and urine analysis)

All laboratory safety data, incorporating haematology, clinical chemistry, coagulation and urine analysis will be listed for each patient with values outside the standard reference ranges indicated in the listings.

Observed and change from baseline values will be summarised by scheduled time point.

Vital signs (pulse and BP), body temperature and weight

Pulse rate, systolic and diastolic BP, body temperature and weight will be listed by patient and summarised for observed and change from baseline by scheduled time point.

Electrocardiogram, physical examination and echocardiogram/MUGA

Electrocardiogram variables (heart rate, RR, PR, QRS, QT, and QTcF intervals) will be listed individually by patient and summarized for observed and change from baseline by scheduled time points. QTc outliers are defined as QTcF values following dosing that are greater than 450 ms or are increases from baseline greater than 30 ms. QTcF outliers will be highlighted in the data listings and summarised using the following categories:

- Values >450 ms, >480 ms, >500 ms
- Increase from baseline of >30 ms, increase from baseline of >60 ms, increase from baseline of >90 ms
- Values >450 ms and increases of >30 ms, values >500 ms and increases of >60 ms.

The number and percentage of patients who meet the ECG outlier criteria at any assessment post-date of first administration of microdose of [^{11}C]osimertinib will be summarised.

Overall ECG evaluation will be summarised using shift tables summarising the change from baseline to last on-treatment observation across all patients.

The results of physical examination and echocardiogram conducted during the study will be presented in listings. Left Ventricular Ejection Fraction (LVEF) data from echocardiogram will be summarised.

5. INTERIM ANALYSES (NOT APPLICABLE)

No interim analyses are planned.

6. CHANGES OF ANALYSIS FROM PROTOCOL

There are no changes in analyses.

7. REFERENCES

CTCAE v4.03 2010
Common Terminology Criteria for Adverse Events Version 4.03 2010.

8. APPENDIX (NOT APPLICABLE)