Clinical Study Protocol	
Drug Substance	AZD9291, Osimertinib
Study Code	D5161C00003
Version	7.0
Date	14 April 2023

A multicentre, open-label, single-arm, molecular profiling study of patients with EGFR mutation-positive locally advanced or metastatic NSCLC treated with osimertinib

Sponsor: *AstraZeneca AB, 151 85 Södertälje, Sweden*

VERSION HISTORY

Version 1.0, 16 June 2017
Initial creation
Version 2.0, 5 September 2017
Changes to the protocol are summarised below
Synopsis, Study Design: and in Section 1.2. text has been amended for consistency purpose; patients are only required to consent to 2 biopsies: 'Patients with EGFR mutation-positive non-small cell lung cancer will be required to consent to ~~at least~~ 2 mandatory tumour biopsies in order to be considered for enrolment in this study.' -Text has been amended for consistency with Section 4.3.1: 'Patients will be followed for ~~a period of 28 days following discontinuation of osimertinib after last dose of study treatment and to~~ the earlier of first subsequent anticancer treatment (including surgical) after discontinuing osimertinib or death.' **Synopsis, secondary objectives and Section 2.3**: Left ventricular ejection fraction and Ophthalmologic assessment have been removed as outcome measures because they will be performed at baseline, and only repeated during the study if clinically indicated. **Section 3.6:** phrase corrected 'Objective disease progression ~~or~~ **and** patient is no longer receiving clinical benefit' **Section 3.6.1:** removal of patient-reported outcomes text as they are not collected. 'Study procedures related to ~~patient-reported outcomes,~~ serious adverse events (SAEs) and anticancer treatment must be captured until the patient no longer has RECIST 1.1 assessments (disease progression or permanent withdrawal from the study).' **Section 3.7.1:** this paragraph was added to clarify in which circumstances the Screening Period may be extended: 'Patients who initially fail screening due to out of range laboratory values will be allowed to repeat the laboratory assessment within the Screening Period, and if the repeat laboratory values are compliant with the inclusion/exclusion criteria, the patient may be enrolled into the study and receive study treatment. For patients who experience a temporary acute medical event that would prohibit enrolment of the patient within the normal duration of the Screening Period, discussion of an extension of the Screening Period with the medical

monitor may occur. Otherwise, patients will not be rescreened and the patient identification number for screen failures will not be re-used.'

Section 4.1: removal of re-screening as patient cannot be re-screened; they can only have their screening period extended in the circumstances mentioned above.

'The following assessments need to be repeated for patients ~~who are re-screened and~~ where > 28 days will have lapsed since their last screening period to the date of proposed enrolment.'

Section 5.2.1: phrase was reworded and simplified to show the approximate amount of blood taken per visit for local safety assessments:

'At each visit, approximately 6 mL of blood for clinical chemistry and 9 mL for haematology will be taken.'

~~Total mandatory blood volume until Cycle 6 is 135 mL. For Cycle 7 onward, assume 6 mL for clinical chemistry and 9 mL for haematology per visit.~~

Section 5.3.2: reference to the volume of blood for ctDNA and blood-borne biomarkers is removed as it is referenced in the Central Laboratory Manual as per Section 5.3.1. and detailed in the Patient Informed Consent Form.
The below phrase in bold was added to clarify that test results cannot be provided because samples will be analysed at a later date:
'The samples will be collected and stored in a central laboratory/repository and analysed at a later date. **Individual patients' test results will not be available in real time, and will be not provided to the Investigators for use in clinical management of patients.'**

Section 5.4.4: the following phrase was removed because the patient may still benefit from treatment even though he/she may withdraw consent to the use of donated samples.

~~As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.~~

Section 6.8 Table 4 and 6.8.2: removed to be consistent with Exclusion criteria #18:

'Withhold osimertinib until QTc interval is less than 481 msec ~~or recovery to baseline if baseline QTc is greater than or equal to 481 msec~~, then restart at a reduced dose (40 mg)'

Version 3.0, 24 January 2018

Main Changes to the Protocol are summarised below:

Synopsis- Primary Objectives and Section 2.1: clarification that only **tumour** genetic profiling is examined.

Synopsis- Statistical methods and sections 8.1, 9.3: Statistical Considerations and End of Study Timelines were revised based on the results of the FLAURA study.

Sections 1.1, 1.2, 1.3 were updated to include the results of the FLAURA study and the latest results from the safety data cut-off. The reference to Soria et al 2018 was added.

Figure 1 was amended to include the whole blood sample taken at progression.

Sections 3.1 and 3.2:

Inclusion #2: was modified to reflect the specificity of country regulation for legal age.

Inclusion #5: was modified following AstraZeneca commitment to FDA request to clarify the tests to be used to select patients for enrolment in the study.

Inclusion #6 and Exclusion criteria #19: were modified to align with the FLAURA protocol. The part about the CNS metastasis was revised and moved to Exclusion criteria #19.

Section 3.6: removed 'Corneal ulceration' to reflect the TAGRISSO Core Data Sheet (CDS). Added 'Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks' to be consistent with Section 6.8.

Table 1, Table 2, Sections 5.2.4, 5.2.6.1, 6.8.4:

An extensive ophthalmological assessment prior to the start of treatment with osimertinib is no longer required according to the CDS. The effect of osimertinib on eyes is no longer under review and therefore the requirement to collect photographs of any eye effects has been removed. A general eye examination is performed as part of the Physical Examination.

Assessment of left ventricular function by Echocardiogram or MUGA is no longer required in all patients prior to the start of treatment with Osimertinib. Left ventricular function assessment is now only required in patients with pre-existing cardiac disease that does not meet the criteria for the study exclusion but may worsen on treatment with osimertinib.

Table 2 and Sections 5.3.2, 5.4: the study design has been changed to allow real time analysis of the tissue and blood sample taken at the time of progression on osimertinib. An additional whole blood sample is required. The analysis will use a Next Generation Sequencing (NGS) panel to identify the mechanism of resistance to first-line osimertinib. The results of these tests will be provided to the sites to inform the choice of treatment after osimertinib.

Section 4.3.1: following phrase "Patients will be followed for the earlier of first subsequent anticancer treatment (including surgical) after discontinuing osimertinib or death" removed as it is more appropriate in Section 4.3.2 where it is already mentioned.

Section 5.2.3.1: only one ECG recording is now taken at each visit instead of 3.

Section 6.8.1: removal of the use of a paper questionnaire as all data should be reported directly in the eCRF instead.

Sections 6.8.5 and 6.8.6: deleted as provision of guidelines for management of toxicity is no longer recommended. Toxicity should be managed according to local guidelines.

Section 9.4: paragraph on Data management of genotype data was removed as no constitutional DNA testing is performed in this study.

Version 4.0, 25 September 2018

Main Changes to the Protocol are summarised below:

Synopsis- Study sites and number of patients planned and Study design, and Sections 1.4 and 8.2: amended to plan for the enrolment of approximately 150 patients instead of 100 patients in order to fulfil the study objectives

Synopsis- Statistical methods and Section 8.1: amended to account for 150 patients and to clarify an analysis will be performed on evaluable paired biopsies. Analysis calculations were revised as follows:

The primary analysis will be performed when at least 50 patients have **evaluable** paired biopsies upon progression. Assuming a 70% rate of patients having a biopsy at both baseline and progression**, and with an assumed technical failure rate of 30% of the samples (assume an overall failure rate of 51%),** then we should expect approximately 50 evaluable paired biopsies to be available when approximately ~~72 (i.e. 72*0.7=50)~~ 103 of the 150 ~~100~~ patients have progressed, which would be expected to occur approximately 38 ~~44~~ months after the first patient is enrolled.

This calculation assumes patients are recruited over 12 months, exponentially distributed progression times with a 19-month median and a **2-piece** recruitment function, ~~that~~ assum**inges** **an exponentially distributed** ~~25% of patients are recruited after 6 months~~ recruitment **rate**.

The first 100 patients to be enrolled within the first 5 months (i.e. from first patient inclusion to the timing of the global protocol amendment). This will be followed by a pause in recruitment of 3 months to account for the issue and approval of the global protocol amendment. This will further be followed by 4 months of recruitment to enrol the remaining 50 patients, assuming an exponentially distributed recruitment rate to account for the regional differences in approval times and slow uptake of recruitment following the protocol amendment.

Section 3.1: the following inclusion criteria was removed: Adequate coagulation: international normalised ratio (INR) ≤1.5 for patients on anti-coagulation therapy. This

inclusion criterion relating to coagulation (and warfarin, a CYP2C9 substrate) was originally included based on in vitro results in human hepatocytes which showed a potential for increasing the messenger ribonucleic acid (mRNA) of cytochrome P450 (CYP) 3A enzymes via pregnane X receptor (PXR) induction. Therefore, all pathways that depend on PXR (including CYP2C9) were thought to have potential for induction with a resultant impact on warfarin. However, a clinical study with the CYP3A substrate simvastatin (Reference Study 14) showed no potential interaction and induction was also minimal. Similarly, another PXR substrate (Pgp study; Reference Study 36) also showed minimal induction. Other PXR substrates, including CYP2C, are unlikely to have an interaction and therefore this inclusion criterion is not required.

Sections 3.1 and 5.3.1: inclusion criterion 7 and mandatory tissue collection details below were amended to further define the requirements of sufficient tissue samples for this study.

7. Possibility of obtaining sufficient tissue sample, via a biopsy or surgical resection of the primary tumour or metastatic tumour tissue, within the 60 days prior to study entry and at or after RECIST 1.1-defined progression. An archival biopsy is acceptable as long as there has been no intervening anticancer treatment since the time the biopsy was obtained to enrolment in this clinical study and as long as it was within 60 days of study entry. ~~For patients who meet the exception to exclusion criterion #11 (Section 3.2), a fresh tissue biopsy must be obtained after the completion of chemotherapy and before osimertinib treatment.~~ **A sufficient tissue sample would consist of formalin-fixed, paraffin-embedded tumour tissue blocks, or at least 15 re-cut unstained sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides. Each section should be 5 µm thick.**

The Investigator will be asked to provide formalin-fixed, paraffin-embedded tumour tissue blocks, or ~~a minimum of 10, but when available,~~**at least** 15 re-cut unstained sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides. Each section is to be 5 µm thick.

Section 3.2: exclusion criterion 11 was updated as patients who have had prior chemotherapy will no longer be allowed to participate in this study: 11. Patients who have received previous treatment for metastatic or stage IV disease ~~*~~
~~* Prior chemotherapy may affect the resistance profile under study; however, patients who have received prior chemotherapy may be permitted if the patients have not received more than 4 cycles of first-line chemotherapy with a limit of 20% of the total enrolment. The site must get Sponsor approval before consenting patients who have received prior chemotherapy (Section 3.3).~~

Subsequently, references to the exception removed from exclusion criterion 11 above have been removed throughout the protocol (previously included in Sections 3.1, 3.3, 4.1 and 5.3.1).

Section 9.3: approximate end of study time has been revised from Q4 2022 to Q3 2022.

Version 5.0, 28 April 2022

Main changes to the protocol are summarised below:

Synopsis, Sections 1.2, 4.1, 5.3.1, 8.3.1: The timing of the second biopsy has been revised.

Two mandatory tumour biopsies will be taken: the first biopsy before initiating osimertinib treatment and the second biopsy at any time between Investigator-assessed, Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1)-defined progression **and before the start of any new anticancer treatment** ~~and up to 7 days after the discontinuation of osimertinib~~….

Synopsis, Section 1.4, Figure 1, Table 2, Sections 4.2.2, 4.3.2, 5.1.1, Appendix E: Cycle 7 ~~and subsequent cycles~~ **to 3.5 years (Day 1277)** will be 8 weeks ~~(56~~ **(± 7** days) each. **After that, cycles will be every 10 weeks (± 14 days) …** Patients will be followed for the earlier of first subsequent **systemic** anticancer treatment (including surgical) after discontinuing osimertinib or death.

Synopsis, Section 2.2: The secondary objective "Positive pre-treatment T790M mutation" has been removed.

Synopsis, Section 1.4, Figure 1: Cycle definition adjusted.

From Cycle 7 **to 3.5 years (Day 1277),** a cycle is defined as a 56-day treatment period. **From 3.5 years to disease progression, a cycle is defined as a 70-day treatment period.**

Synopsis, Section 8.1:

The ~~primary~~ **final** analysis will be performed ~~when~~ at ~~least 50 patients have evaluable paired biopsies upon progression~~. **study end (see Section 9.3 for definition of "end of study").** …

This is an exploratory study which may inform other studies in the osimertinib development programme and therefore earlier interim analyses may be performed~~. Furthermore, a later analysis~~, **such interim analyses** may **not** be ~~performed when more than 50 patients have evaluable paired biopsies to understand the profile of patients who have longer times to progression~~ **reported in a formal CSR**.

…**If a patient progresses in the ELIOS study and then enrols in a subsequent AZ study, and if appropriate consent is provided, the biomarker results from a progression biopsy (generated in either the other study or ELIOS), may be shared between both studies and the data may be analysed as part of the ELIOS study.**

Synopsis, Section 8.2:

Recruitment of 150 patients is appropriate to characterise the frequency of tumour genetic and proteomic markers at disease progression regardless of their prevalence. The following table displays the precision of the estimated proportion, **for example,** when 50 evaluable paired biopsies are available ~~at the time of the primary analysis~~.

Section 1.1:

~~Over the past decade,~~ Multiple clinical trials in patients with an activating mutation of the EGFR gene have compared different first- or second-generation oral EGFR TKIs. ... RRs and median PFS intervals for gefitinib, erlotinib, and afatinib are 55**% to** 74% and 9 to 10 months, 58**% to** 83% and 9 **to** 13 months, and 58**% to** 61% and 9 **to** 11 months, respectively...

Osimertinib is approved for:

- the **adjuvant treatment after complete tumour resection in patients with NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.**
- **the first-line** treatment of patients with **locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.**
- **the treatment of patients with locally advanced or** metastatic EGFR T790M mutation-positive NSCLC~~, as detected by an FDA-approved test,~~ whose disease has progressed on or after EGFR-TKI therapy.

…

First-line EGFRm NSCLC: Clinical experience updated to align with the latest safety data and standards.

Adjuvant EGFRm NSCLC: Clinical experience updated to align with the latest safety data and standards.

Second line or greater, T790M mutation-positive, advanced NSCLC: Clinical experience updated to align with the latest safety data and standards.

Adverse Drug Reactions for Osimertinib Monotherapy: Clinical experience updated to align with the latest safety data and standards. New ADR of aplastic anaemia.

Section 1.4, Figure 1: The follow-up column in the study design figure was split into 2 columns, the 28-day Follow-up visit and the period to first subsequent anticancer treatment or death.

Section 1.4.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis – (new section added)

Section 3.2: Text updated to align with the latest safety data and standards. and to add COVID-19 exclusion.

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

    - **Screening for chronic conditions is not required.**

    Should patients with HBV infection be included, patients are only eligible if they meet all the following criteria:

    - **Demonstrated absence of HCV co-infection or history of HCV co-infection.**
    - **Demonstrated absence of HIV infection.**
    - **Patients with active HBV infection are eligible if they are:**
        - **Receiving anti-viral treatment for at least 6 weeks prior to study treatment, HBV DNA is suppressed to < 100 IU/mL and transaminase levels are below ULN.**
    - **Patients with a resolved or chronic infection HBV are eligible if they are:**
        - **Negative for HBsAg and positive for hepatitis B core antibody [anti-HBc IgG]. In addition, patients must be receiving anti-viral prophylaxis for 2 to 4 weeks prior to study treatment and 6 to 12 months (TBD by hepatologist) post treatment.**

or

    - **Positive for HBsAg, but for > 6 months have had transaminases levels below ULN and HBV DNA levels below < 100 IU/mL (ie, are in an inactive carrier state). In addition, patients must be receiving anti-viral prophylaxis for 2 to 4 weeks prior to study treatment and 6 to 12 months (TBD by hepatologist) post treatment. Refer to Section 3.5.**

18. … Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, **hypomagnesaemia, hypocalcaemia,** 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.

Section 3.5: The following restrictions were edited/added to align with the latest safety data and standards.

…

2. Male patients should be asked to use barrier contraceptives (ie, by use of condoms) during sex with all partners of childbearing potential during the trial and for a washout period of 4 months. **Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period**. Male patients should avoid procreation for 4 months after completion of study 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~~ **strong** inducers of CYP3A4 whenever feasible, but patients may receive any medication that is clinically indicated for treatment of AEs. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 **weeks** after the last dose of osimertinib. …

4. … Patients taking concomitant medications whose disposition is dependent upon Breast Cancer Resistance Protein (BCRP) and**/or P-glycoprotein (P-gp), and** which have a narrow therapeutic index should be closely monitored for signs of changed tolerability.

…Patients who have received prior treatment with immune-oncology (IO) therapies should be closely monitored for an appropriate period of time after the last dose of the IO treatment, in accordance with the respective IO label, as immune-mediated adverse reactions with the IO therapy may occur at any time during or after discontinuation of therapy. The stop date of the prior IO drug therapy should be captured in the eCRF.

5. In patients with resolved or chronic hepatitis B infection (inactive carrier state) or active controlled HBV infection on treatment with osimertinib:

- **Recommend monthly monitoring of ALT/AST, HBV DNA levels and HBsAg (if negative at baseline)**
- **Where liver signs and symptoms of viral reactivation appear (HBV DNA levels exceeding 10-fold from baseline or ≥100 IU/ml (if baseline HBV DNA levels are undetectable) or conversion of HBsAg negative to positive):**
    - Expert hepatologist/specialist oversight of the patient is required

- **Consider interruption or discontinuation of study treatment, based on risk-benefit assessment**

Section 3.6: … Text updated to align with the latest safety data and standards.

Patients experiencing any of the following AEs will not be permitted to restart study treatment:

- ILD/**pneumonitis**

…

Section 3.8: The following text was deleted as survival analysis will not be conducted.

~~The status of ongoing, withdrawn (from the study), and 'lost to follow-up' patients at the time of the data cut-off date for the study analyses should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws. In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.~~

Section 4.1, Table 1: footnote updated:

…

[d] **To be performed 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 echocardiogram should also be used for subsequent scans.** ~~To be performed **only** in patients with pre-existing cardiac disease that does not meet the criteria for study exclusion but may worsen on treatment with osimertinib.~~

Section 4.1, Table 2: Table was updated to align with the changes in this protocol amendment, and footnotes updated as follows:

…

[b] Six 4-week cycles followed by 8-week cycles from Cycle 7 ~~onwards~~ **to 3.5 years (Day 1277), and 10-week cycles from 3.5 years to disease progression.** Patients who continue to receive osimertinib beyond RECIST 1.1-defined progression, if continuing to show clinical benefit to treatment as judged by the Investigator, will continue to follow the treatment visit schedule and assessments excluding study specific RECIST assessments and plasma samples for ctDNA and blood-borne biomarkers ~~will only be obtained at treatment discontinuation~~.

[c] As a minimum, telephone contact should be made with the patient 28 days (window + 7 days) following the discontinuation of study drug **(last dose of IP).**

…

[f] The second mandatory tumour tissue biopsy may be performed any time between Investigator-assessed, RECIST 1.1-defined progression and ~~up to 7 days after~~ **the** ~~discontinuation~~ **start** of ~~osimertinib.~~ **before any new systemic anticancer treatment.** If a patient discontinues osimertinib before RECIST 1.1-defined progression, the second biopsy will not be performed.

[g] **Plasma samples for ctDNA and blood-borne biomarkers will only be obtained at the treatment discontinuation visit.**

[h] If screening assessments have been performed within 14 days prior to starting study treatment, they do not have to be repeated on Visit 2 if the patient's condition has not changed. The assessments are to be completed pre-dose on visit day. **Laboratory tests may be performed the day prior to study visits.**

[i] ECG is also to be performed in event of any cardiac AE.

[j] To be performed ~~**only** in patients with pre-existing cardiac disease that does not meet the criteria for study exclusion but may worsen on treatment with osimertinib~~ **at least every 16 weeks throughout the treatment period.** ...

[k] The screening assessment should be performed within 28 days prior to study drug initiation. Subsequent assessments are to be performed every 8 weeks **(± 7 days)** from study enrolment **until 3.5 years (Day 1277), and then every 10 weeks (± 14 days)** until RECIST 1.1-defined progression, even if a patient discontinues treatment prior to progression or receives other anticancer treatment...

…

[n] At progression, a whole blood sample will be obtained ~~at the same time~~ **within 7 days of when** the tissue biopsy is performed.

[o] **The progression biopsy should be done prior to the start of subsequent systemic anticancer treatment**…

Section 4.3: Follow-up clarified:

1. **All patients will be followed up for safety at approximately 28 days.**
2. **All patients will be followed up for RECIST 1.1-defined progression.**
3. **All patients will be followed up for subsequent anticancer treatment/death.**

Section 4.3.1:

As a minimum, telephone contact should be made with the patient 28 days **(± 7 days)** following the discontinuation of osimertinib **(last dose of IP)** to collect new AEs and follow-up on any ongoing AEs and concomitant medications (including any subsequent ~~cancer therapy).~~ **anticancer treatment).** Refer to Section 6.3.1 for full details on AE recordings during follow-up.

Section 4.3.2: ~~**Progression**~~ Follow-up **for RECIST 1.1-defined progression**

Section 5.2.1:

Magnesium was added to the list of chemistry tests in Table 3, Laboratory Safety Tests.

Section 5.2.4:

An echocardiogram or multigated acquisition scan (MUGA) to assess LVEF will be performed at screening (prior to first dose of osimertinib) ~~only in patients with pre-existing~~

~~cardiac disease that does not meet~~ **and at least every 16 weeks throughout** the ~~criteria for study exclusion but may worsen on~~ treatment ~~with osimertinib. Subsequent assessment~~ **period. Additional assessments** of LVEF should be performed as clinically indicated…

Section 5.3.2: A 7-day window was added between progression biopsy sampling and collection of a whole blood sample.

At progression, a whole blood sample will be taken **within 7 days of** the time the tissue biopsy is obtained.

Section 6.5:

A maximum tolerated dose has not been established for osimertinib. ~~In the context of a clinical study,~~ **A**n overdose is any dose which exceeds the daily dose that is defined in the clinical study protocol.

Section 6.8, Table 4: To align with the latest safety data and standards:

Table 4 Osimertinib Dose Adjustment Information for Adverse Reactions

Target organ	Adverse reaction	Dose modification
Pulmonary	Interstitial lung disease/pneumonitis	Permanently discontinue osimertinib
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc interv is less than 481 msec **or recovery to baseline if baseline QTc is more than 481 msec within 3 weeks of interruption,** then restart at a reduced dose (40 mg) **or at 80 mg (at the discretion of the Investigator, to allo for situations where causality in relation to osimertinib may be difficult to determine.)**

…

If a toxicity resolves or reverts to ≤ CTCAE Grade 2 within 3 weeks of ~~onset~~ **withholding osimertinib**, treatment with osimertinib may be restarted at the same dose or a lower dose 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 **of withholding osimertinib**, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

Section 6.8.2: to align with the latest safety data and standards:

QTc Prolongations

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

Patients with ~~QTc~~ **QT interval** corrected using Fridericia's correction (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 40 mg**, or 80mg at the discretion of the Investigator.** If the toxicity does not resolve to ≤ **CTCAE** Grade 1 within 21 days, the patient will be permanently withdrawn from study treatment.

Permanent discontinuation due to toxicity

Patients experiencing interstitial lung disease, QTc prolongation with signs/symptoms of serious arrhythmia or Grade 3 or higher adverse reaction that does not improve to Grade 0 to 2 **after withholding for up to 3 weeks will not be permitted to restart study treatment.**

Section 6.8.3: to align with the latest safety data and standards:

Keratitis

~~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.

Section 6.8.4: Erythema multiforme and Stevens-Johnson syndrome (new section) to align with the latest safety data and standards:

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

Section 6.8.5 Aplastic anaemia (new section) to align with the latest safety data and standards:

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

Section 6.8.6: to align with the latest safety data and standards:

Changes in cardiac contractility

~~Across clinical trials, 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 one follow-up LVEF assessment.~~ Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established. ~~Echocardiogram/MUGA to assess LVEF should be performed at screening~~ In patients with ~~pre-existing~~ cardiac ~~disease~~ **risk factors and those with conditions** that ~~does not meet the criteria for study exclusion but may worsen on treatment with osimertinib. Subsequent~~ **can affect LVEF, cardiac monitoring, including an** assessment of LVEF **at baseline and during treatment,** should be ~~performed as clinically indicated.~~ **considered.** In patients who develop **relevant** cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

Section 7.8: Patients receiving study treatment at the time of study completion (ie, after final DCO date) **will be switched to commercial supply and/or another study to ensure continuation of treatment,** ~~may continue to receive osimertinib~~, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment.

Synopsis, Section 8.1: …The ~~primary~~ **final** analysis will be performed **at study end (see Section 9.3 for definition of "end of study").** ~~when~~ **approximately** ~~50 patients have evaluable paired biopsies upon progression.~~

…The first 100 patients to be enrolled within the first 5 months (ie, from first patient inclusion to the timing of the global protocol amendment). This will be followed by a pause in recruitment of ~~3~~ **6** months to account for the issue and approval of the global protocol amendment. This will further be followed by ~~4 months~~ **1 month** of recruitment to enrol the remaining 50 patients, assuming an exponentially distributed recruitment rate to account for the regional differences in approval times and slow uptake of recruitment following the protocol amendment.

This is an exploratory study which may inform other studies in the osimertinib development programme and therefore earlier interim analyses may **not** be **reported in a formal CSR.** ~~performed. Furthermore, a later analysis may be performed when more than 50 patients have evaluable paired biopsies to understand the profile of patients who have longer times to progression.~~

If a patient progresses in the ELIOS study and then enrols in a subsequent AZ study, and if appropriate consent is provided, the biomarker results from a progression biopsy (generated in either the other study or ELIOS), may be shared between both studies and the data may be analysed as part of the ELIOS study.

Section 8.3.1: Primary analysis set~~ – Intention to Treat (PAS-ITT)~~

~~An extension of~~ The PAS will include all patients with evaluable paired biopsies (~~i.e. valid sequencing results from Foundation Medicine Inc. for both the baseline and progression biopsies),~~, which are defined as follows: the first biopsy taken prior to osimertinib treatment and the second biopsy taken at any time between Investigator-assessed, RECIST 1.1-defined progression and **before** the start of any ~~new anti-cancer therapy. Any patients that discontinue osimertinib prior to disease progression e.g. patient decision, adverse event etc. will not be considered part of the primary analysis set~~ **systemic anticancer treatment**. Any patients that discontinue osimertinib prior to disease progression eg, patient decision, adverse event etc. will not be considered part of the primary analysis set **systemic anticancer treatment**. If the Investigator judges the patient to have progressed but the programmatically defined RECIST progression does not occur, the patient will still be considered evaluable, as long as an adequate tissue sample is provided at the time of progression. This analysis set will be used ~~as a sensitivity~~ **for the** analysis of the primary endpoint.

Section 8.5.4 (deleted): ~~Interim analysis~~

~~This is an exploratory study which may inform other studies in the osimertinib development program and therefore earlier interim analyses may be performed.~~

Section 8.5.4:

The analyses associated with the exploratory objective will be reported separately and will not form part of the CSR. **Any HER2/tissue/plasma analysis may be published outside of the CSR.**

Section 9.3:

~~The estimated date of the first patient enrolled is Q2 2018.~~

A patient is considered to have completed the study when he/she has progressed or died.

The end of the study is defined as **when the earliest of these scenarios is met**:

- **All enrolled patients complete their participation in the study either through disease progression or withdrawal for other reasons.**
- **The study will end in October 2024, as it is estimated that by then there will be sufficient data to support study endpoints. If, at this time (October 2024 or at another time if AstraZeneca or Regulatory Authorities decide to stop study due to any concerns, eg, patient safety), there are ongoing patients who are drawing benefit from study treatment, they will be switched to commercial supply and/or another study to ensure continuation of treatment, and the study will close using the available data for the final analysis. A CSR will be written at this time, including all data collected during the study. For any patients who continue in progression follow-up, any additional safety data will be collected and summarised in the CSR.**

…

The study **may** be terminated at individual centres ~~after the primary analysis has concluded,~~ if there are no ongoing patients.

Section 9.4:

ILD-like events (new)

ILD/pneumonitis are to be reported as AEs in the CRF, with additional details captured in the "ILDIS" eCRF.

Appendix D: Guidance Regarding Potential Interactions with Concomitant Medications

Table D1: Drugs inducing CYP3A4

Contraindicated drugs	**Withdrawal period prior to osimertinib start**
Carbamazepine, phenobarbital **(phenobarbitone),** phenytoin, rifampicin, rifabutin, rifapentine, St John's Wort	3 weeks
~~Phenobarbitone~~	~~5 weeks~~

Osimertinib may increase the concentration of sensitive ~~breast cancer resistance protein (~~BCRP~~)~~ **and P-gp** substrates (concentration of the sensitive BCRP substrate, rosuvastatin~~, is~~ **and sensitive P-gp substrate, fexofenadine, are** increased).

Table D2: 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 co-administration with osimertinib.
Sulfasalazine	
Doxorubicin	
Daunorubicin	
Topotecan	
Dabigatran	
Aliskiren	
Digoxin	

D 2 Drugs that ~~May~~ prolong QT interval

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics ~~and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland. Ref: http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm.~~ **on the CredibleMeds® website https://www.crediblemeds.org/. The website categorises drugs based on the risk of inducing Torsades de Pointes (TdP).**

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

D 2.1 Drugs with a known risk of Torsades de Pointes

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

D 2.1.1 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 D4.

D 2.1.2During study treatment

It is recommended that drugs in the category of known risk of TdP are not ~~be combined~~ **co-administered** with study treatment (osimertinib~~. Recommended withdrawal periods following cessation of treatment with~~ **) and for a period of two weeks after discontinuing study treatment, however, if it is considered essential for patient management to co-administer** these ~~agents are provided in the table~~ **drugs with study treatment (osimertinib), close monitoring of 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 D3 Drugs ~~Prolonging QT Interval~~with a known risk of TdP

~~Contraindicated drug~~ **Drug name**	**Withdrawal period prior to ~~osimertinib~~ study treatment start** [b]
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 [c] **, 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.**

[b] **Values determined from comprehensive review (internal to AZ) of each compound's PK half-life and determination of the washout period.**

[c] Estimated value as PK of arsenic trioxide has not been studied.

AZ = AstraZeneca; PK = pharmacokinetics; TdP = Torsades de Pointes.

D 3 Other TdP risk categories

Patients receiving drugs that ~~may possibly~~ prolong QT interval ~~The use of the following drugs is permitted (~~**or may increase the risk of TdP from other TdP risk categories can be enrolled,** notwithstanding other exclusions and restrictions~~) provided~~**, if these drugs are considered essential for patient management and** the patient has been stable on therapy ~~for the periods indicated~~**. Close monitoring of ECGs and electrolytes is recommended**.

[Table D 4 deleted]

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

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 of ECGs and electrolytes is recommended.

Appendix G: Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis (new)

Appendix added.

Throughout the document: "subsequent therapy", "subsequent treatment", etc., aligned to "subsequent **systemic** anticancer treatment" for consistency.

Version 6.0, 02 November 2022

Main changes to the protocol are summarised below:

Section 4.1 (Table 1 and Table 2): The frequency of the echocardiogram and MUGA assessments was changed from "at least every 16 weeks throughout the treatment period" to "at least every 16 weeks throughout the treatment period up to 3.5 years and then at least every 20 weeks for the remainder of the treatment period".

Section 5.2.4: An echocardiogram or multigated acquisition scan (MUGA) to assess LVEF will be performed at screening (prior to first dose of osimertinib) and at least every 16 weeks throughout the treatment period **until patients have reached 3.5 years on the study. Thereafter, echocardiogram or MUGA will be performed at least every 20 weeks for the remainder of the treatment period**.

Section 4.3.1: The window period for the 28-day follow-up was corrected to "+7 days".

As a minimum, telephone contact should be made with the patient 28 days (~~±~~+ 7 days) following the discontinuation of osimertinib (last dose of IP) to collect new AEs and

follow-up on any ongoing AEs and concomitant medications (including any subsequent anticancer treatment).

Synopsis (study design), Section 4.1 (Table 2), and Section 8.3.1: The text "new systemic anticancer treatment" and "subsequent systemic anticancer treatment" were changed to "new ~~systemic~~ anticancer treatment" and "subsequent ~~systemic~~ anticancer treatment".

Throughout the document: Minor typographical errors were corrected.

Version 7.0, 14 April 2023

Main changes to the protocol are summarised below:

Synopsis, Section 8.1: The details related to final analysis are updated.

The final analysis will be performed at study end (see Section 9.3 for definition of "end of study"), **and when approximately 50 patients have evaluable paired biopsies upon progression**. Assuming a 70% rate of patients having a biopsy at both baseline and progression, and with an assumed technical failure rate of 30% of the samples (assume an overall failure rate of 51%), then we should expect approximately 50 evaluable paired biopsies to be available when approximately 103 of the 150 patients have progressed, which would be expected to occur approximately 38 months after the first patient is enrolled.

Section 1.1: Per Investigator Brochure's annual update, study details were updated.

…
Adjuvant EGFRm NSCLC

…
At the DCO of the DFS analysis (11 April 2022), the DFS HR for HR for patients with stage II-IIIA disease was 0.23 (95% CI: 0.18, 0.30), demonstrating a clinically meaningful 77% reduction in the risk of disease recurrence or death for patients randomised to osimertinib compared with patients randomised to placebo.

Adverse Drug Reactions for Osimertinib Monotherapy

As of 12 November 202**2**~~1~~, a total of **5273**~~4939~~ **patient**~~subject~~s (**5155**~~4821~~ NSCLC patients and 118 healthy volunteers) have been included in the osimertinib clinical development programme (not including those patients enrolled in Named Patient Supply [NPS], Early Access Programmes or Real-World Evidence studies). Of these **5273**~~4939~~ **patient**~~subject~~s, **3075**~~2983~~ **patient**~~subject~~s received osimertinib monotherapy (2**957**~~865~~ patients and 118 healthy volunteers), **1151**~~989~~ patients received osimertinib in combination with another treatment, and **1047**~~967~~ patients were exposed to comparator treatment (including placebo). Of the **1047**~~967~~ patients exposed to comparator treatment, 1**69**~~90~~ patients subsequently

crossed over from comparator treatment to osimertinib monotherapy during their respective studies. A total of **11295**~~11041~~ patients have been dosed with osimertinib.

…
Other ADRs associated with administration of osimertinib included interstitial lung disease (ILD) or ILD-like adverse reactions (eg, pneumonitis), QTc interval prolongation, keratitis, haematological effects, erythema multiforme (EM), Stevens-Johnson syndrome (SJS), **toxic epidermal necrolysis (TEN)**, and aplastic anaemia.

Section 3.2: Text updated to align with the latest safety data and standards.

…

- Demonstrated absence of HIV infection.

….

- Patients with a resolved or chronic infection HBV are eligible if they are:

  - Negative for HBsAg and positive for hepatitis B core antibody [anti-HBc IgG]. In addition, patients must be receiving anti-viral prophylaxis for 2 to 4 weeks prior to study treatment ~~and 6 to 12 months (TBD by hepatologist post treatment.~~

or

  - Positive for HBsAg, but for > 6 months have had transaminases levels below ULN and HBV DNA levels below < 100 IU/mL (ie, are in an inactive carrier state). In addition, patients must be receiving anti-viral prophylaxis for 2 to 4 weeks prior to study treatment ~~and 6 to 12 months (TBD by hepatologist post treatment~~. Refer to Section 3.5.

Should patients with HIV infection be included, patients are only eligible if they meet ALL of the following criteria:

- **Undetectable viral RNA load for 6 months**
- **CD4+ count of > 350 cells/µL**
- **No history of AIDS-defining opportunistic infection within the past 12 months**
- **Stable for at least 4 weeks on the same anti-HIV medications**.

Section 3.5: to align with the latest safety data and standards, following restrictions were added.

6. **Patients should receive HBV anti-viral prophylaxis post treatment as determined by their hepatologist**.

7. In patients with resolved or chronic hepatitis B infection (inactive carrier state) or active controlled HBV infection on treatment with osimertinib:

   - Recommend monthly monitoring of ALT/AST, HBV DNA levels and HBsAg (if negative at baseline)
   - Where liver signs and symptoms of viral reactivation appear (HBV DNA levels exceeding 10-fold from baseline or ≥100 IU/mL (if baseline HBV DNA levels are undetectable) or conversion of HBsAg negative to positive):
     - Expert hepatologist/specialist oversight of the patient is required
     - Consider interruption or discontinuation of study treatment, based on risk-benefit assessment.

8. In patients with HIV, viral RNA load and CD4 + cell count should be monitored per local SoC (eg, every 3 months).

Section 4.1: Table 1, footnote a and Table 2, footnote p: to align with the latest safety data and standards, following was added as a footnote:

"**Monthly pregnancy testing and monitoring of WOCBP is recommended, however this schedule may be modified to comply with local legislation**".

Section 5.2.1 Laboratory safety assessments, Table 3: to align with the latest safety data and standards, addition of laboratory parameter (creatine phosphokinase).

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
..	…
	S/P-Magnesium
	Creatine phosphokinase

Section 6.8: Table 4: to align with the latest safety data and standards, following details were updated:

Table 4 Osimertinib Dose Adjustment Information for Adverse Reactions

Target organ	Adverse reaction	Dose modification
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 more than 481 msec within 3 weeks of interruption, then restart at a reduced dose (40 mg) or at 80 mg (at the discretion of the Investigator, to allow for situations where causality in relation to osimertinib may be difficult to determine.)
Cutaneous	**Stevens-Johnson Syndrome and toxic epidermal necrolysis (TEN)**	**Permanently discontinue osimertinib**
Blood and lymphatic system	**Aplastic anaemia**	**Permanently discontinue osimertinib**

Section 6.8.4: to align with the latest safety data and standards, following details were updated:

6.8.4 Erythema multiforme, ~~and~~ Stevens-Johnson syndrome **and toxic epidermal necrolysis**

Case reports of EM **and TEN have been uncommonly reported, and** SJS have been ~~uncommonly and~~ rarely reported, ~~respectively,~~ in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of EM, ~~and~~ SJS **and TEN**. If signs and symptoms suggestive of EM develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. If signs and symptoms suggestive of SJS appear, osimertinib should be interrupted. **Osimertinib should be** ~~or~~ discontinued immediately **if diagnosis of SJS or TEN is confirmed**.

Section 9.3: End of study detail was updated.

…

- The study will end **by Q2**~~in October~~202**3**4, as it is estimated that by then there will be sufficient data to support study endpoints. If, at this time **(Q2**~~October~~ 202**3**4 or at another time if AstraZeneca or Regulatory Authorities decide to stop study due to any concerns, eg, patient safety), there are ongoing patients who are drawing benefit from study treatment, they will be switched to commercial supply and/or another study to ensure continuation of treatment, and the study will close using the available data for the

final analysis. A CSR will be written at this time, including all data collected during the study.

Section 6.7, Section 7.8, Section 9.3.1, Section 10, Appendix A, Appendix B1: According to Late Phase oncology template release note, CSP amendment was updated.

Throughout the document: Minor typographical errors were corrected.

CLINICAL STUDY PROTOCOL SYNOPSIS

A multicentre, open-label, single-arm, molecular profiling study of patients with EGFR mutation-positive locally advanced or metastatic NSCLC treated with osimertinib

International Coordinating Investigator

Zofia Piotrowska, MD

Thoracic Oncology

55 Fruit Street

Boston, MA 02114-2696

USA

Study sites and number of patients planned

Approximately 150 patients with epidermal growth factor receptor (EGFR) mutation-positive locally advanced or metastatic non-small cell lung cancer will be recruited from multiple centres globally.

Phase of development II

Study design

This is a phase II, open-label, single-arm tissue and plasma acquisition study assessing the efficacy, safety and underlying resistance mechanisms of osimertinib (80 mg orally, once daily) as first-line treatment in patients with locally advanced or metastatic EGFR mutation-positive non-small cell lung cancer who are EGFR tyrosine kinase inhibitor treatment-naïve and eligible for first-line treatment.

It has been determined that approximately 150 patients need to be recruited to fulfil the objectives of the study. EGFR mutation status should be determined based on a tumour biopsy or plasma sample by a local laboratory certified by Clinical Laboratory Improvement Amendments (United States of America [USA] sites) or an accredited local laboratory (sites outside of the USA).

Patients with EGFR mutation-positive non-small cell lung cancer will be required to consent to 2 mandatory tumour biopsies in order to be considered for enrolment in this study. The first biopsy will be done prior to initiating treatment with osimertinib and the second biopsy will be obtained any time between Investigator-assessed, Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1)-defined progression and before the start of any new anticancer treatment. A third optional biopsy may be taken during the course of treatment at the Investigator's discretion if the patient consents and if clinically feasible.

Tumour tissue and plasma samples will be collected and examined for tumour genetic and non-genetic aberrations that may be important in determining response and resistance to the treatment that patients will receive as a part of their cancer care.

The primary objective of this study is to examine and compare the molecular profile at or after the point of disease progression with that prior to treatment initiation in patients receiving osimertinib as first-line EGFR tyrosine kinase inhibitor therapy. Secondary efficacy endpoints are those that are appropriate to this patient population and include progression-free survival, objective response rate, duration of response, and disease control rate (complete response + partial response + stable disease). Characterisation of the safety and tolerability of osimertinib will also be assessed as secondary endpoints. CCI [redacted]

Patients should continue on osimertinib until Investigator assessed, RECIST 1.1-defined progression or until other treatment discontinuation criteria are met. However, if patients continue to show clinical benefit to treatment as judged by the Investigator, patients may continue to receive osimertinib beyond RECIST 1.1-defined progression. Therefore, there is no maximum duration of treatment. Tumour assessments according to RECIST 1.1 are to be performed at baseline and then every 8 weeks (± 7 days) from study enrolment until 3.5 years (Day 1277), and then every 10 weeks (± 14 days) until RECIST 1.1-defined progression. Patients will be followed for the earlier of first subsequent anticancer treatment (including surgical) after discontinuing osimertinib or death.

Objectives

Primary Objective:	**Outcome Measure:**
To examine the tumour genetic and proteomic profile at the point of disease progression in patients receiving osimertinib as first-line EGFR tyrosine kinase inhibitor therapy for EGFR mutation-positive locally advanced or metastatic non-small cell lung cancer compared to the profile prior to initiation of treatment	Proportion of patients with a given tumour genetic and proteomic marker (including, but not limited to, EGFR mutations, human epidermal growth factor receptor 2, and proto-oncogene encoding hepatocyte growth factor receptor expression and/or amplification) at the point of disease progression as defined by the Investigator; the choice of markers is dependent on the profile comparison at the point of disease progression and prior to treatment initiation

Secondary Objectives:	**Outcome Measures:**
To assess the efficacy of osimertinib as first-line EGFR tyrosine kinase inhibitor therapy for patients with EGFR mutation-positive locally advanced or metastatic non-small cell lung cancer	Progression-free survival, according to RECIST 1.1 by Investigator assessment, and other selected clinical efficacy endpoints including: • Objective response rate • Duration of response • Disease control rate
To assess the efficacy of osimertinib in patient subgroups defined by molecular profile, including but not limited to: • EGFR Ex19del or L858R mutation • EGFR Ex19del or L858R detectable in plasma-derived circulating tumour deoxyribonucleic acid	Progression-free survival, according to RECIST 1.1 by Investigator assessment, and other selected clinical efficacy endpoints including: • Objective response rate • Tumour shrinkage/depth of response, defined as best change from baseline in target lesion tumour size • Time to treatment discontinuation or death • Important patient and disease characteristics
To further assess the efficacy of osimertinib post-progression	• Time to treatment discontinuation or death • Time to first subsequent therapy or death (TFST)
Safety Objective:	**Outcome Measures:**
To summarise the safety and tolerability profile of osimertinib as first-line EGFR tyrosine kinase inhibitor therapy for patients with EGFR mutation-positive locally advanced or metastatic non-small cell lung cancer	• Adverse events graded by Common Terminology Criteria for Adverse Events version 4.0 • Clinical chemistry, haematology and urinalysis • Vital signs, physical examination, body weight • Electrocardiogram • World Health Organization performance status

Target patient population

Male and female patients aged 18 years and over with locally advanced or metastatic pathologically confirmed adenocarcinoma of the lung, not amenable to curative surgery or radiotherapy. Patients will have a tumour that harbours one of the EGFR mutations known to be associated with EGFR tyrosine kinase inhibitor sensitivity, either alone or in combination with other EGFR mutations (EGFR mutation status determined by a local laboratory). Patients must be EGFR tyrosine kinase inhibitor treatment-naïve and eligible to receive first-line treatment with osimertinib.

Duration of treatment

Treatment with osimertinib 80 mg once daily will commence following enrolment. A cycle of treatment is defined as 28 days of once daily treatment with osimertinib (Cycle 1 to Cycle 6 inclusive). From Cycle 7 to 3.5 years (Day 1277), a cycle is defined as a 56-day treatment period. From 3.5 years to disease progression, a cycle is defined as a 70-day treatment period. Patients may continue to receive osimertinib as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria.

Investigational product, dosage and mode of administration

Osimertinib is an oral, potent, selective, irreversible inhibitor of both EGFR tyrosine kinase inhibitor sensitising and resistance mutations in non-small cell lung cancer with a significant selectivity margin over wild type EGFR. Osimertinib (80 mg orally, once daily) will be administered. Doses may be reduced to 40 mg if needed for the management of toxicity.

Statistical methods

The final analysis will be performed at study end (see Section 9.3 for definition of "end of study"), and when approximately 50 patients have evaluable paired biopsies upon progression. Assuming a 70% rate of patients having a biopsy at both baseline and progression, and with an assumed technical failure rate of 30% of the samples (assume an overall failure rate of 51%), then we should expect approximately 50 evaluable paired biopsies to be available when approximately 103 of the 150 patients have progressed, which would be expected to occur approximately 38 months after the first patient is enrolled. This calculation assumes patients are recruited over 12 months, exponentially distributed progression times with a 19-month median and a 2-piece recruitment function that assumes an exponentially distributed recruitment rate.

This is an exploratory study which may inform other studies in the osimertinib development programme and therefore earlier interim analyses may be performed, such interim analyses may not be reported in a formal clinical study report (CSR).

Recruitment of 150 patients is appropriate to characterise the frequency of tumour genetic and proteomic markers at disease progression regardless of their prevalence. The following table displays the precision of the estimated proportion, for example, when 50 evaluable paired biopsies are available.

Precision of Estimates of Marker Frequency with 50 Available and Evaluable Paired Biopsies

Marker Frequency	95% confidence interval [a]
10%	(3%, 22%)
30%	(18%, 45%)
50%	(36%, 64%)

[a] Exact binomial confidence intervals.

If a patient progresses in the ELIOS study and then enrols in a subsequent AZ study, and if appropriate consent is provided, the biomarker results from a progression biopsy (generated in either the other study or ELIOS), may be shared between both studies and the data may be analysed as part of the ELIOS study.

The primary data analysis set will include all patients with evaluable paired biopsies. This analysis set will be used for the analysis of the primary endpoint. The full analysis set will include all patients who receive at least one dose of osimertinib and will be used for all other efficacy and safety analyses.

The number of patients with a given tumour genetic and proteomic marker will be divided by the number of patients who have evaluable biopsies and have progressed according to the Investigator to calculate the proportion with a given marker at progression. Exact binomial 95% confidence intervals will be calculated.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

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
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCRP	Breast Cancer Resistance Protein
BICR	Blinded Independent Central Review
CDS	Core Data Sheet
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
cMET	Proto-oncogene encoding hepatocyte growth factor receptor
CNS	Central nervous system
CRO	Contract Research Organisation
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumour deoxyribonucleic acid
CYP	Cytochrome P
DCO	Data cut-off
DCR	Disease control rate
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EGFRm+	Epidermal growth factor receptor mutation-positive

Abbreviation or special term	Explanation
EM	Erythema multiforme
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HBV	Hepatitis B virus
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HL	Hy's Law
HR	Hazard ratio
HRCT	High-resolution computed tomography
IATA	International Airline Transportation Association
IB	Investigator brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
IMP	Investigational medicinal product
INR	International normalised ratio
International Coordinating Investigator	If a study is conducted in several countries the International Coordinating Investigator is the Investigator coordinating the Investigators and/or activities internationally
IO	Immune-oncology
IP	Investigational product, also referred to as 'study drug' and 'study treatment' in this protocol
IRB	Institutional Review Board, synonymous to Ethics Committee
ITT	Intent to Treat
IUD	Intrauterine Device
IUS	Intrauterine System
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition scan
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PAS	Primary analysis set
PFS	Progression-free survival
P-gp	P-glycoprotein
PHL	Potential Hy's Law
PK	Pharmacokinetics
PR	Partial response
PXR	Pregnane X receptor
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected using Fridericia's correction
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Response rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SJS	Stevens-Johnson syndrome
SoC	Standard of Care
T790M	Amino acid substitution at position 790 in EGFR, from a threonine to a methionine
TBL	Total bilirubin
TdP	Torsades de Pointes
TFST	Time to first subsequent therapy or death
TKI	Tyrosine kinase inhibitor
TL	Target lesions

Abbreviation or special term	Explanation
TNM	Tumour, Node, and Metastasis Classification of Malignant Tumours
TTD	Time to treatment discontinuation or death
ULN	Upper limit of normal
USA	United States of America
WBDC	Web based data capture
WHO	World Health Organization
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background and Rationale for Conducting This Study

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

Epidermal growth factor receptor (EGFR) inhibition is the standard of care (SoC) for locally advanced or metastatic non-small cell lung cancer (NSCLC) in patients with EGFR-activating mutations. In approximately 50 to 60% of patients, resistance to EGFR tyrosine kinase inhibitor (TKI) agents develops by acquiring a T790M mutation (amino acid substitution at position 790 in EGFR, from a threonine to a methionine) (Cross et al 2014, Kuiper et al 2014, Li et al 2014, Oxnard et al 2011, Yu et al 2013).

Multiple clinical trials in patients with an activating mutation of the EGFR gene have compared different first- or second-generation oral EGFR TKIs. Several studies have consistently demonstrated that EGFR TKIs (gefitinib, erlotinib, and afatinib) produce higher response rates (RRs), longer progression-free survival (PFS), and improve quality of life compared with standard platinum-based doublet chemotherapy in patients with good performance status (Grade 0-2) whose tumour harbours an activating (sensitising) EGFR mutation. RRs and median PFS intervals for gefitinib, erlotinib, and afatinib are 55% to 74% and 9 to 10 months, 58% to 83% and 9 to 13 months, and 58% to 61% and 9 to 11 months, respectively (Asami and Atagi 2016). Based on the results of previous prospective studies, these EGFR TKIs seem to demonstrate comparable efficacy with regard to RR and PFS in patients with locally advanced or metastatic EGFR-mutated NSCLC.

Osimertinib Mechanism of Action

Investigators should be familiar with the current Investigator Brochure (IB).

Osimertinib (AZD9291, TAGRISSO) is an oral, potent, irreversible EGFR-TKI selective for EGFR-TKI-sensitising and T790M resistance mutations with a significant selectivity margin over wild type EGFR. As a result, osimertinib can effectively block EGFR signalling both in EGFR single mutant cells with activating EGFR mutations and in double mutant cells bearing both the primary EGFR-activating and secondary resistance T790M mutation. Osimertinib is currently under investigation as a treatment option in 1) patients with advanced T790M mutation-positive NSCLC who have previously failed an EGFR TKI; 2) patients with advanced EGFR-mutated NSCLC who are treatment-naïve; and 3) in combination with novel agents for patients with EGFR TKI-resistant NSCLC.

Osimertinib is approved for:

- the adjuvant treatment after complete tumour resection in patients with NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.
- the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.
- the treatment of patients with locally -advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR TKI therapy.

Experience with osimertinib in NSCLC

Clinical experience with osimertinib is described in the current version of the IB. Please refer to the IB for details of the clinical programme.

In the phase I/II AURA study (D5160C00001), osimertinib was administered to patients with locally advanced or metastatic EGFR mutation-positive (EGFRm+) NSCLC (Gil-Bazo and Rolfo 2016). Promising efficacy results were observed in 127 patients evaluable for response among the 138 patients with T790M mutation-positive disease confirmed by central testing who were previously treated with an EGFR TKI: objective response rate (ORR) was 61% (95% confidence interval [CI], 52%-70%), and disease control rate (DCR; complete response + partial response + stable disease) was 95% (95% CI, 90%-98%). In the 138 patients with detectable T790M mutation-positive disease, the median PFS based on 30% maturity of data was 9.6 months (95% CI, 8.3-not reached), and 88% of these patients had an estimated duration of response (DoR) of 6 months or longer (Jänne et al 2015).

Promising evidence of efficacy has also been observed in patients with treatment-naïve NSCLC treated with osimertinib as the first-line EGFR TKI. Results are available from 2 phase I expansion cohorts in which patients received osimertinib as first-line treatment in the AURA study (n = 60; 30 patients on 80 mg per day and 30 patients on 160 mg per day). The median follow-up at the data cut-off (DCO) date of 04 Jan 2016 was 16.6 months. The overall RR was 77% (95% CI, 64%-87%), which was amongst the best reported for first-line therapy of EGFR-mutated locally advanced or metastatic NSCLC. The overall DCR was 98% (95% CI: 89%-100%). The maximum DoR was 22.1 months (patient ongoing in response at 04 Jan 2016). The median PFS was 19.3 months; data were immature with respect to DoR and PFS, but the lower 95% CIs for the median were 12.5 months for DoR and 13.7 months for PFS. The percentage of patients remaining progression-free at 12 months was 72% (95% CI: 59%-82%) and 55% (95% CI: 41%-67%) at 18 months. The drug was well tolerated with few adverse events (AEs), particularly at the approved 80 mg dose, where just 10% of patients required dose reduction to manage toxicities. Initial data suggest that patients who had disease progression did not have a T790M mutation as the mechanism of resistance, suggesting that first-line treatment with osimertinib may be beneficially changing the biology of the disease.

First-line EGFRm NSCLC

In a phase III study (FLAURA study; D5160C00007), a total of 673 patients with locally-advanced or metastatic EGFRm NSCLC have been dosed with first-line treatment in the FLAURA study (in both the Global cohort and the China cohort) (Soria et al 2018).

Of the 556 patients randomised in the Global cohort, 279 received osimertinib 80 mg once daily and 277 received the SoC (gefitinib or erlotinib). At data cut-off 1 (DCO1) (12 June 2017), the data provided strong evidence for the clinical benefit of osimertinib for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR with Ex19Del or L858R activating mutations, with a median Investigator-

assessed PFS of 18.9 months with osimertinib and 10.2 months with SoC, representing an 8.7-month improvement for osimertinib compared with SoC ($p < 0.0001$; hazard ratio [HR] 0.46; 95% CI 0.37, 0.57).

Data from the FLAURA study also confirmed the superior CNS efficacy results in first-line setting that have been reported in later lines of therapy with osimertinib. There was a statistically significant ($p = 0.014$) and clinically meaningful improvement in CNS PFS in the osimertinib arm compared with the SoC arm based on CNS Blinded Independent Central Review (BICR; HR: 0.48 [95% CI: 0.26, 0.86]), indicating a 52% reduction in the risk of CNS disease progression or death in the osimertinib arm compared to the SoC arm.

At DCO2 (25 June 2019), final overall survival (OS) analysis in the global study, 321/556 patients had died (CCI [redacted]). The HR for OS was 0.799 (adjusted 95.05% CI: 0.6406, 0.9968), signifying a 20% lower risk of death in the osimertinib arm compared with the SoC arm. The difference between treatment arms in favour of osimertinib was statistically significant, as the p-value of 0.0462 was below the pre-defined level of 0.0495 required at this analysis. Median OS was 38.6 (95% CI: 34.5, 41.8) months in the osimertinib arm, and 31.8 (95% CI: 26.6, 36.0) months in the SoC arm, a difference of 6.8 months. Post-progression outcomes showed a clinically relevant longer time from randomisation to TFST or death for patients on osimertinib compared to patients on SoC (HR: 0.478 [95% CI: 0.3927, 0.5810]; 2-sided $p < 0.0001$). There was also a clinically relevant longer time to second subsequent therapy for patients on osimertinib compared to patients on SoC (HR: 0.687 [95% CI: 0.5610, 0.8424]; 2-sided $p = 0.0003$).

Adjuvant EGFRm NSCLC

The effectiveness of osimertinib in the adjuvant setting was investigated in the Phase III ADAURA study, which investigated the use of osimertinib versus placebo in patients with stage IB-IIIA NSCLC with a centrally confirmed common EGFRm mutation (Ex19del and/or L858R, either alone or in combination with other EGFR mutations), who had undergone complete tumour resection, with or without postoperative adjuvant platinum-based chemotherapy. A total of 682 patients were randomised to treatment, of whom 337 osimertinib arm patients and 343 placebo arm patients received at least 1 dose of study treatment. -At the DCO of the primary analysis (17 January 2020), in patients with stage II-IIIA disease, a statistically significant and clinically meaningful improvement in DFS for patients randomised to receive osimertinib versus placebo was observed (HR: 0.17; 99.06% CI: 0.11, 0.26; $p < 0.0001$). A greater proportion of osimertinib arm patients was alive and disease-free at all assessed timepoints compared with those in the placebo arm. At the DCO of the DFS analysis (11 April 2022), the DFS HR for HR for patients with stage II-IIIA disease was 0.23 (95% CI: 0.18, 0.30), demonstrating a clinically meaningful 77% reduction in the risk of disease recurrence or death for patients randomised to osimertinib compared with patients randomised to placebo.

Second line or greater, T790M mutation-positive, advanced NSCLC

The AURA3 study demonstrated superior efficacy of osimertinib compared to chemotherapy in patients with advanced EGFR T790M mutation-positive NSCLC, whose disease had progressed on or after EGFR TKI therapy.

At the time of the primary efficacy analysis (DCO1: 15 April 2016), there was a statistically significant and clinically meaningful improvement in Investigator-assessed PFS for patients on osimertinib versus those on chemotherapy (HR: 0.30, 95% CI: 0.23, 0.41; $p < 0.001$), indicating a 70% reduction in risk of disease progression or death (in the absence of a Response Evaluation Criteria In Solid Tumors [RECIST] progression) in the osimertinib arm. Treatment with osimertinib resulted in a 5.7-month improvement in median PFS (10.1 months [95% CI: 8.3, 12.3]) compared with chemotherapy (4.4 months [95% CI: 4.2, 5.6]). Similar results were seen with the BICR assessment of PFS. A BICR assessment of CNS efficacy in patients with CNS metastases at baseline showed a clinically meaningful improvement for patients randomised to receive osimertinib versus chemotherapy. The improvements in CNS efficacy outcomes were consistent across multiple analyses (ORR of 70% vs 31.3%, OR of 5.13, $p = 0.015$; DoR 8.9 months vs 5.7 months; PFS 11.7 months vs 5.6 months, for osimertinib vs chemotherapy, respectively). At the final OS analysis in AURA3 (DCO4 of 15 March 2019), osimertinib demonstrated a numerical advantage in OS compared to chemotherapy, which did not reach statistical significance (HR = 0.87 [95.564% CI: 0.67, 1.13]; $p = 0.277$). The median OS was 26.8 months (95% CI: 23.49, 31.54) in the osimertinib arm and 22.5 months (95% CI: 20.17, 28.81) in the chemotherapy arm.

Efficacy findings in the osimertinib arm of the AURA3 study were consistent with those in the pooled phase II studies (AURA extension and AURA2).

Adverse Drug Reactions for Osimertinib Monotherapy

As of 12 November 2022, a total of CCI patients CCI NSCLC patients and CCI healthy volunteers) have been included in the osimertinib clinical development programme (not including those patients enrolled in Named Patient Supply [NPS], Early Access Programmes or Real-World Evidence studies). Of these CCI patients, CCI patients received osimertinib monotherapy (CCI patients and CCI healthy volunteers), CCI patients received osimertinib in combination with another treatment, and CCI patients were exposed to comparator treatment (including placebo). Of the CCI patients exposed to comparator treatment, CCI patients subsequently crossed over from comparator treatment to osimertinib monotherapy during their respective studies. A total of CCI patients have been dosed with osimertinib.

In addition to the clinical development programme, an additional CCI NSCLC patients have participated in the osimertinib Early Access Programme and Named Patient Supply, and CCI patients have participated in the ASTRIS real-world-evidence study (D5160C00022).

The current list of expected adverse drug reactions is in the IB Section 5.4, 'Emerging safety profile.' Section 5.2.4.3 of the IB provides a summary of safety in treatment-naïve patients.

Osimertinib 80 mg, oral, once daily has an acceptable safety profile in patients receiving treatment for NSCLC, in both the adjuvant and advanced NSCLC treatment settings. In the pivotal osimertinib clinical development programme to date (n = CCI patients), the majority of adverse drug reactions (ADRs) were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2 in severity. The most commonly reported ADRs were diarrhoea (47%) and rash (45%), paronychia (33%), dry skin (32%), and stomatitis (24%). Other ADRs associated with administration of osimertinib included interstitial lung disease (ILD) or ILD-like adverse reactions (eg, pneumonitis), QTc interval prolongation, keratitis, haematological effects, erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and aplastic anaemia.

Based on the available clinical trial data, cardiac failure is considered to be an important potential risk; however, a causal relationship between changes in cardiac contractility and osimertinib has not been established. In the placebo-controlled ADAURA study, 1.6% (5/312) of patients treated with osimertinib and 1.5% (5/331) of patients treated with placebo experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50%.

1.2 Rationale for Study Design, Doses and Control Groups

Study D5160C00007 A Phase III, Double-Blind Randomised Study to Assess the efficacy and safety of osimertinib versus SoC EGFR TKI as first-line treatment in patients with EGFRm+ locally advanced or metastatic NSCLC (FLAURA) has demonstrated a significant benefit for osimertinib vs SoC EGFR TKIs with respect to efficacy endpoints. It is hypothesised that osimertinib may deliver this clinical benefit in the first-line setting by preventing the most common type of EGFR TKI resistance observed in NSCLC patients with acquired EGFR TKI resistance (T790M-mediated resistance).

This study is an uncontrolled, single-arm study in patients with locally advanced or metastatic EGFRm+ NSCLC. The study will investigate whether the use of osimertinib as first-line therapy will result in favourable efficacy due to delayed T790M-mediated resistance. Additionally, while it is known that 50% to 60% of patients receiving first- and second-generation EGFR TKIs first-line will progress on treatment due T790M-mediated resistance, the mechanisms of resistance to osimertinib first-line are not well characterised, and this study aims to investigate these further.

The primary objective of this study is to examine and compare the tumour molecular profile at or after the point of disease progression with that prior to treatment initiation in patients receiving osimertinib as first-line EGFR TKI therapy. To gain a better understanding of resistance mechanisms in patients receiving osimertinib treatment, tumour tissue and plasma samples will be examined for tumour genetic and non-genetic aberrations that may be important in determining response and resistance to treatment. Two mandatory tumour biopsies will be taken: the first biopsy before initiating osimertinib treatment and the second biopsy at any time between Investigator-assessed, Response Evaluation Criteria in Solid

Tumours version 1.1 (RECIST 1.1)-defined progression and before the start of any new anticancer treatment, as indicated in the Schedule of Assessments (see Table 2).

The secondary endpoints are those that are appropriate to determine efficacy in this patient population and include PFS, ORR, DoR, and DCR.

Once-daily doses of 20, 40, 80, 160 and 240 mg of osimertinib were evaluated in the dose escalation phase of the AURA study (D5160C00001). Based on the totality of the safety, pharmacokinetic, and preliminary efficacy data, 80 mg once daily was selected as the recommended phase II dose. Efficacy of osimertinib 80 mg as first-line treatment in patients with EGFRm+ locally advanced or metastatic NSCLC with respect to mPFS has been demonstrated in the first analysis of data from the FLAURA study. Please refer to the IB for additional details. No dosage adjustment is required due to patient age, body weight, gender, ethnicity, or smoking status. All patients will receive 80 mg once daily in this study. If patients continue to show clinical benefit to treatment as judged by the Investigator, patients may continue to receive osimertinib beyond RECIST 1.1-defined progression. Therefore, there is no maximum duration of treatment.

1.3 Benefit/Risk and Ethical Assessment

Please see the current edition of the IB (Sections 5.2 and 5.4) for the most recent summary of the risks of osimertinib.

Preclinical data and clinical efficacy and safety data from the FLAURA study (D5160C00007) support the hypothesis that osimertinib monotherapy is an effective first-line treatment of NSCLC tumours driven via the EGFR pathway.

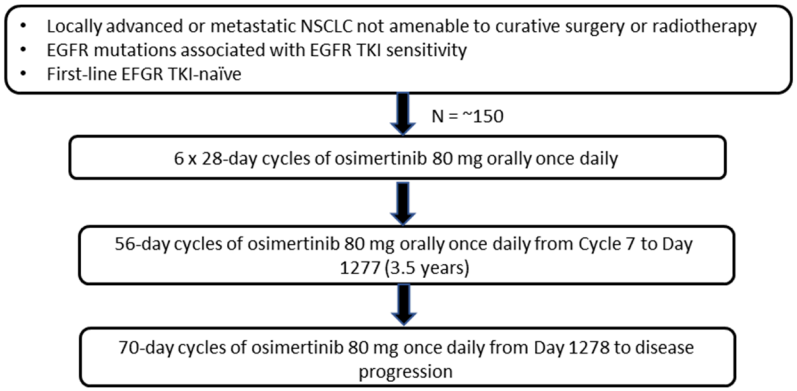
The safety profile of osimertinib in the first-line setting in the FLAURA study was favourable with the majority of toxicities being Grade 1 or 2 EGFR-related AEs, ie, diarrhoea, dry skin and paronychia (Soria et al 2018). The safety profile of osimertinib in the first-line setting was consistent with the existing safety profile for osimertinib in the second line and later setting. All trials of osimertinib, including the present study, exclude patients with clinically significant toxicities related to prior treatments and they exclude patients with a history of ILD or clinically active ILD as this is an uncommon but well documented EGFR-related toxicity.

It is therefore, reasonable and appropriate to evaluate osimertinib monotherapy as first-line treatment in EGFRm+ NSCLC patients, according to the proposed study design.

1.4 Study Design

This is a phase II, open-label, single-arm tissue and plasma acquisition study assessing the efficacy and safety of osimertinib (80 mg orally, once daily) as first-line treatment in EGFR TKI treatment-naïve patients with locally advanced or metastatic EGFRm + NSCLC, and the underlying resistance mechanisms to treatment (Figure 1).

Figure 1 Study Flow Chart



	Treatment	Biospecimen Acquisition	Tumour Assessment		Follow -up	
					28-day FU	To first subsequent therapy or death
Pre-treatment		• Tumour tissue [a] • Plasma [a]	At screening		–	–
Before disease progression	As in flow chart above	• Tumour tissue (optional) [a] • Plasma [a, b]	Every 8 weeks up to 3.5 years or disease progression	Every 10 weeks from 3.5 years until disease progression	–	–
At disease progression	May be continued per investigator's judgement	• Tumour tissue [c] • Whole blood [c,d]	–		After last dose of study treatment	–
After disease progression		• Plasma [a, e]	–		–	–

EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; TKI = tyrosine kinase inhibitor.

[a] Analysed at a later date
[b] As per visit schedule until discontinuation of study treatment
[c] Prospective analysis (real time)
[d] A whole blood sample should be taken at the same time (±7 days) as the tumour biopsy at the time of disease progression
[e] If osimertinib is continued beyond investigator-assessed RECIST progression, an additional plasma sample should be taken when osimertinib is stopped

1.4.1 Study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the patient's ability to conduct the study. The Investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study patients, maintain compliance with Good Clinical Practice, and minimise risks to study integrity.

Where allowable by local health authorities, Ethics Committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the ICF should be signed at the patient's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened patients. The Investigator should confirm this with the designated Study Physician.
- Home or Remote visit: Performed by a site qualified HCP or HCP provided by a third-party vendor.
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home investigational product (IP) administration: Performed by a site qualified HCP, HCP provided by a third-party vendor, or by the patients or the patient's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, see Appendix H.

2 STUDY OBJECTIVES

2.1 Primary Objective

Primary Objective:	Outcome Measure:
To examine the tumour genetic and proteomic profile at the point of disease progression in patients receiving osimertinib as first-line EGFR TKI therapy for EGFRm+ locally advanced or metastatic NSCLC compared to the profile prior to initiation of treatment	Proportion of patients with a given tumour genetic and proteomic marker (including, but not limited to, EGFR mutations, human epidermal growth factor receptor 2 [HER2], and proto-oncogene encoding hepatocyte growth factor receptor [cMET] expression and/or amplification) at the point of disease progression as defined by the Investigator; the choice of markers is dependent on the profile comparison at the point of disease progression and prior to treatment initiation

2.2 Secondary Objectives

Secondary Objectives:	Outcome Measures:
To assess the efficacy of osimertinib as first-line EGFR TKI therapy for patients with EGFRm+ locally advanced or metastatic NSCLC	PFS, according to RECIST 1.1 by Investigator assessment, and other selected clinical efficacy endpoints including: • ORR • DoR • DCR
To assess the efficacy of osimertinib in patient subgroups defined by molecular profile, including but not limited to: • EGFR Ex19del or L858R mutation • EGFR Ex19del or L858R detectable in plasma-derived circulating tumour deoxyribonucleic acid (ctDNA)	PFS, according to RECIST 1.1 by Investigator assessment, and other selected clinical efficacy endpoints including: • ORR • Tumour shrinkage/depth of response, defined as best change from baseline in target lesion tumour size • Time to treatment discontinuation or death (TTD) • Important patient and disease characteristics
To further assess the efficacy of osimertinib post-progression	• TTD • Time to first subsequent therapy or death (TFST)

2.3 Safety Objective

Safety Objective:	Outcome Measures:
To summarise the safety and tolerability profile of osimertinib as first-line EGFR TKI therapy for patients with EGFRm+ locally advanced or metastatic NSCLC	• AEs graded by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 • Clinical chemistry, haematology and urinalysis • Vital signs, physical examination, body weight • Electrocardiogram (ECG) • World Health Organization (WHO) performance status

2.4 Exploratory Objective

Exploratory Objective:	Outcome Measures:
CCI [redacted]	CCI [redacted]

3 PATIENT SELECTION, ENROLMENT, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Male and female patients aged 18 years and over with locally advanced or metastatic pathologically confirmed adenocarcinoma of the lung, not amenable to curative surgery or radiotherapy. Patients will have a tumour that harbours one of the EGFR mutations known to be associated with EGFR TKI sensitivity, either alone or in combination with other EGFR mutations (EGFR mutation status determined by a local laboratory). Patients must be EGFR TKI treatment-naïve and eligible to receive first-line treatment with osimertinib.

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

3.1 Inclusion Criteria

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

1. Provision of informed consent prior to any study specific procedures (signed and dated Informed Consent Form).

2. Patients aged 18 years or older (specific age may vary according to country regulations for legal age).

3. Patients with histological confirmation of locally advanced or metastatic, non-squamous NSCLC who are not candidates for local curative treatment.

4. Patients with M1 stage according to the Tumour, Node, and Metastasis Classification of Malignant Tumours (TNM) version 7 including M1a (malignant effusion) or M1b (distant metastasis), or locally advanced disease that is not a candidate for curative treatment (including patients who progress after chemo-radiotherapy in stage III disease).

5. Patients with an EGFR deletion or mutation known (from tumour biopsy or plasma) to be associated with EGFR TKI sensitivity before treatment assessed by a local laboratory certified by Clinical Laboratory Improvement Amendments (USA sites) or an accredited local laboratory (sites outside of the USA).

6. Existence of measurable or evaluable disease (as per RECIST 1.1 criteria).

7. Possibility of obtaining sufficient tissue sample, via a biopsy or surgical resection of the primary tumour or metastatic tumour tissue, within the 60 days prior to study entry and at or after RECIST 1.1-defined progression. An archival biopsy is acceptable as long as there has been no intervening anticancer treatment since the time the biopsy was obtained to enrolment in this clinical study and as long as it was within 60 days of study entry. A sufficient tissue sample would consist of formalin-fixed, paraffin-embedded tumour tissue blocks, or at least 15 re-cut unstained sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides. Each section should be 5 μm thick.

8. WHO performance status 0-1.

9. Life expectancy ≥ 12 weeks.

10. Capacity to swallow.

11. Patients able to complete study and within geographical proximity allowing for adequate follow-up.

12. Resolution of all acute toxic effects of previous anticancer therapy (which can only be adjuvant or neoadjuvant) or surgical interventions to Grade 1 according to the National Cancer Institute (NCI) CTCAE version 4.0 (except for alopecia or other side effects that the Investigator does not consider to be a risk to patient safety).

13. Female patients must be using highly effective contraceptive measures, and must have a negative pregnancy test prior to start of dosing if of childbearing potential or must have evidence of non-childbearing potential by fulfilling one of the following criteria at screening:

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

- Women under 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with luteinising hormone and follicle -stimulating hormone levels in the postmenopausal range for the institution.

- Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

14. Male patients must be willing to use barrier contraception (see Restrictions, Section 3.5).

3.2 Exclusion Criteria

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

1. Locally advanced lung cancer candidate for curative treatment through radical surgery and/or radio(chemo)therapy.

2. Patients diagnosed with another lung cancer subtype, patients with mixed NSCLC with predominantly squamous cell cancer, or with any small cell lung cancer component.

3. Patients with an EGFR exon 20 insertion.

4. Patients with just one measurable or evaluable tumour lesion that has been resected or irradiated prior to their enrolment in the study.

5. Second active neoplasia.

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

7. Participation in another clinical study with an IP during the last 3 weeks before the first day of study treatment.

8. Patients who have received prior immunotherapies.

9. Patients who have received prior EGFR treatments for lung cancer.

10. Patients who have received prior treatment with an EGFR TKI including in the adjuvant setting.

11. Patients who have received previous treatment for metastatic or stage IV disease.

12. Prior treatment with cytotoxic chemotherapy for advanced NSCLC (neoadjuvant/adjuvant chemotherapy is permitted if at least 6 months have elapsed between the end of chemotherapy and the first day of study treatment).

13. Patients with a history of cancer that has been completely treated, with no evidence of malignant disease currently cannot be enrolled in the study if their chemotherapy was completed less than 6 months prior and/or have received a bone marrow transplant less than 2 years before the first day of study treatment.

14. Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy.

15. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol, or active infection (eg, patients receiving treatment for infection) including hepatitis C and human immunodeficiency virus (HIV), or active uncontrolled Hepatitis B virus (HBV) infection.

    — Screening for chronic conditions is not required.

    Should patients with HBV infection be included, patients are only eligible if they meet all the following criteria:

    — Demonstrated absence of HCV co-infection or history of HCV co-infection.

    — Demonstrated absence of HIV infection.

    — Patients with active HBV infection are eligible if they are:

    - Receiving anti-viral treatment for at least 6 weeks prior to study treatment, HBV DNA is suppressed to < 100 IU/mL and transaminase levels are below upper limit of normal (ULN).

    — Patients with a resolved or chronic infection HBV are eligible if they are:

    - Negative for HBsAg and positive for hepatitis B core antibody [anti-HBc IgG]. In addition, patients must be receiving anti-viral prophylaxis for 2 to 4 weeks prior to study treatment.

or

    - Positive for HBsAg, but for > 6 months have had transaminases levels below ULN and HBV DNA levels below < 100 IU/mL (ie, are in an inactive carrier state). In addition, patients must be receiving anti-viral prophylaxis for 2 to 4 weeks prior to study treatment. Refer to Section 3.5.

Should patients with HIV infection be included, patients are only eligible if they meet ALL of the following criteria:

- Undetectable viral RNA load for 6 months
- CD4+ count of > 350 cells/μL
- No history of AIDS-defining opportunistic infection within the past 12 months
- Stable for at least 4 weeks on the same anti-HIV medications.

16. Patients who have had a surgical procedure unrelated to the study within 14 days or major surgery within 1 month prior to the administration of the study drug; patients with a significant traumatic lesion (as judged by the Investigator that would risk patient safety) during the 4 weeks prior to starting the administration of the study drug; patients who have not recovered from the side effects of any major surgery; or patients who might need major surgery during the course of the study.

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

18. Any of the following cardiac criteria:

    - Mean resting QT interval corrected for heart rate (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, and second-degree heart block.
    - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, hypomagnesaemia, hypocalcaemia, 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.

19. Spinal cord compression, symptomatic and unstable brain metastases except for those patients who have completed definitive therapy and have had a stable neurological status for at least 2 weeks after completion of definitive therapy. Patients may be on corticosteroids to control brain metastases if they have been on a stable dose for 2 weeks (14 days) prior to the start of study treatment and are clinically asymptomatic.

20. 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.

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

    - Absolute neutrophil count < 1.5 x 109/L.
    - Platelet count < 100 x 109/L.
    - Haemoglobin (Hb) < 90 g/L.
    - Alanine aminotransferase (ALT) > 2.5 times the 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 (TBL) > 1.5 times ULN if no liver metastases or >3 times ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia) or liver metastases.
    - Creatinine > 1.5 times ULN concurrent with creatinine clearance < 50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is > 1.5 times ULN.

22. Female patients who are breastfeeding.

23. Patients currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be potent inducers of cytochrome (CYP) 3A4 (at least 3 weeks prior; Appendix E). All patients must try to avoid concomitant use of any medications, herbal supplements, and/or ingestion of foods with known inducer effects on CYP3A4.

24. Patient unwilling to undergo a biopsy at the time of disease progression.

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

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

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

28. Previous enrolment in the present study.

For procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient Screening and Enrolment

Investigators should keep a record, the patient screening log, of patients who entered pre-study screening.

The Investigators will:

1. Determine patient eligibility (see Section 3.1 and Section 3.2).

2. Obtain signed informed consent from the potential patient or their guardian/legal representative before any study specific procedures are performed.

3. Assign potential patient a unique enrolment number, beginning with 'E#' (generated in the Interactive Voice Response System/Interactive Web Response System [IVRS/IWRS]).

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

3.4 Procedures for Handling Incorrectly Enrolled Patients

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

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

3.5 Restrictions

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

1. Females of childbearing potential should use highly effective methods of contraception from the time of screening until 6 weeks after discontinuing study treatment. Highly effective methods are provided in Appendix G.

2. Male patients should be asked to use barrier contraceptives (ie, by use of condoms) during sex with all partners of childbearing potential during the trial and for a

washout period of 4 months. Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period. Male patients should avoid procreation for 4 months after completion of study 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 strong inducers of CYP3A4 whenever feasible, but patients may receive any medication that is clinically indicated for treatment of AEs. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 weeks after the last dose of osimertinib. All concomitant medications should be captured on the electronic case report form (eCRF). Guidance on medicines to avoid, medications that require close monitoring, and on washout periods is provided (see Appendix E).

4. If medically feasible, patients taking regular medication, with the exception of potent inducers of CYP3A4 (see above), should be maintained on their regular medication throughout the study period. Patients taking concomitant medications whose disposition is dependent upon Breast Cancer Resistance Protein (BCRP) and/or P-glycoprotein (P-gp), and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication while receiving osimertinib. Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (see Appendix E).

   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.

   Patients who have received prior treatment with immune-oncology (IO) therapies should be closely monitored for an appropriate period of time after the last dose of the IO treatment, in accordance with the respective IO label, as immune-mediated adverse reactions with the IO therapy may occur at any time during or after discontinuation of therapy. The stop date of the prior IO drug therapy should be captured in the eCRF.

5. Patients should receive HBV anti-viral prophylaxis post treatment as determined by their hepatologist.

6. In patients with resolved or chronic hepatitis B infection (inactive carrier state) or active controlled HBV infection on treatment with osimertinib:

- Recommend monthly monitoring of ALT/AST, HBV DNA levels and HBsAg (if negative at baseline)

- Where liver signs and symptoms of viral reactivation appear (HBV DNA levels exceeding 10-fold from baseline or ≥100 IU/mL (if baseline HBV DNA levels are undetectable) or conversion of HBsAg negative to positive):

  - Expert hepatologist/specialist oversight of the patient is required

  - Consider interruption or discontinuation of study treatment, based on risk-benefit assessment.

7. In patients with HIV, viral RNA load and CD4 + cell count should be monitored per local SoC (eg, every 3 months).

3.6 Discontinuation of Investigational Product

Patients may be discontinued from IP in the following situations:

- Patient decision; the patient is at any time free to discontinue treatment, without prejudice to further treatment
- AE
- Severe noncompliance with the Clinical Study Protocol
- Pregnancy
- Patient incorrectly initiated on study treatment
- Objective disease progression and patient is no longer receiving clinical benefit
- Lost to follow-up
- Patient starts receiving additional anticancer therapy

Patients experiencing any of the following AEs will not be permitted to restart study treatment:

- ILD/pneumonitis
- QTc interval prolongation with signs/symptoms of serious arrhythmia (see Table 4)
- Grade 3 or higher adverse reaction that does not improve to Grade 0 to 2 after withholding study treatment for up to 3 weeks

3.6.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue IP or withdraw from the study (ie, IP and assessments; see Section 3.7) without prejudice to further treatment. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). AEs will be followed up (see Section 6); all study drugs should be returned by the patient.

Study procedures related to serious adverse events (SAEs) and anticancer treatment must be captured until the patient no longer has RECIST 1.1 assessments (disease progression or permanent withdrawal from the study).

If a patient is withdrawn from the study, see Section 3.7.

3.7 Criteria for Withdrawal

3.7.1 Screen failures

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

These patients should have the reason for study withdrawal recorded as ‘Screen failure’ (ie, the potential patient who does not meet one or more criteria required for participation in a trial). For those patients, only demography data and reason for discontinuation will be recorded. Supporting safety information can be collected in case of a SAE, if applicable.

Patients who initially fail screening due to out of range laboratory values will be allowed to repeat the laboratory assessment within the Screening Period, and if the repeat laboratory values are compliant with the inclusion/exclusion criteria, the patient may be enrolled into the study and receive study treatment. For patients who experience a temporary acute medical event that would prohibit enrolment of the patient within the normal duration of the Screening Period, discussion of an extension of the Screening Period with the medical monitor may occur. Otherwise, patients will not be rescreened and the patient identification number for screen failures will not be re-used.

3.7.2 Withdrawal of informed consent

Patients are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment. Withdrawal of consent should be clearly documented in the patient notes and in the eCRF.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow-up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be re-used. Withdrawn patients will not be replaced.

3.8 Discontinuation of the Study

The study may be stopped if, in the judgement of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that:

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

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

4 STUDY PLAN AND TIMING OF PROCEDURES

The Schedule of Assessments for the screening visit is shown in Table 1. On study assessments are shown in Table 2.

4.1 Screening/Enrolment Period

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

Procedures will be performed according to Table 1 within 28 days prior to Day 1.

The following assessments need to be repeated for patients where > 28 days will have lapsed since their last Screening Period to the date of proposed enrolment.

Table 1 Screening (Visit 1) Study Schedule

Day	**Day -28 to -1**
Informed consent	X

Day	**Day -28 to -1**
Assignment of unique enrolment number (IVRS/IWRS)	X
Demography and baseline characteristics	X
Medical and surgical history	X
Inclusion/exclusion criteria	X
Physical examination including weight and eyes	X
WHO performance status (0-1)	X
Vital signs (includes blood pressure, pulse and temperature), height	X
Haematology/clinical chemistry	X
ECG	X
Echocardiogram/MUGA [d]	X
Prior cancer therapies including radiotherapy	X
Urinalysis	X
Pregnancy test [a]	X
Tumour assessment (CT or MRI according to RECIST 1.1) [b]	X
AEs (from time of consent)	X
Concomitant medications	X
Tumour tissue [c]	X
Plasma sample for ctDNA and blood-borne biomarkers	X

[a] WOCBP must have a negative urine or serum pregnancy test within 28 days prior to starting treatment and a confirmatory test before treatment on Day 1. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately. Monthly pregnancy testing and monitoring of WOCBP is recommended, however this schedule may be modified to comply with local legislation.

[b] RECIST assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis and should be performed no more than 28 days before the first treatment, and as close as possible to the start of study treatment.

[c] For central collection and baseline resistance profiling; testing will be conducted at a later date. The first mandatory tumour tissue biopsy may be an archival or fresh tissue sample obtained within 60 days of study entry. An archival biopsy is acceptable as long as no intervening anticancer treatment occurred since the time the biopsy was obtained to enrolment in this study, and as long as it is within 60 days of study entry.

[d] To be performed at least every 16 weeks throughout the treatment period up to 3.5 years and then at least every 20 weeks for the remainder of 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 echocardiogram should also be used for subsequent scans.

AE = adverse event; CT = computed tomography; ctDNA = circulating tumour deoxyribonucleic acid; ECG = electrocardiogram; IVRS/IWRS = interactive voice response system/interactive web response system; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; RECIST = Response Evaluation Criteria in Solid Tumours; WHO = World Health Organization; WoCBP = women of childbearing potential.

Table 2 Study Schedule – On Study Treatment and Discontinuation

	Screening/ Enrolment [a]	Treatment Period (further treatment cycles as per C7) [b]									Follow-up Period	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9**	**10+**		**Treatment discontinued**	**28 days [c]**	**Progression follow-up [o]**
		C1			**C2**	**C3**	**C4, 5, 6**	**C7 to 3.5 years**	**3.5 Years to Disease Progression**			
Cycles / Day		**D1**	**D8**	**D15**	**D1**	**D1**	**D1**	**D169-1277**	**D1278+**			
Day	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85, 113, 141**	**Every 8 weeks**	**Every 10 weeks**			**Every 8 weeks prior to Day 1277/ Every 10 weeks thereafter**
Window (Days)		**0**	**± 2**	**± 2**	**± 2**	**± 7**	**± 7**	**± 7**	**± 14**	**± 7**	**+ 7**	**± 7/± 14**
Informed consent	x											
IVRS/IWRS	x											
Demography and baseline characteristics	x											
Medical/surgical history	x											
Inclusion/exclusion criteria	x	x										
Pregnancy test (WOCBP) [p]	x	x										
Tumour tissue sample [d]	x [d]											
Tumour tissue sample on treatment (optional) [e]				x [e]								
Tumour tissue sample upon disease progression [f]										x [f]		
Plasma sample for ctDNA and blood-borne biomarkers	x	x pre-dose	x	x	x	x	x	x	x	x [b, g]		

	Screening/ Enrolment [a]	Treatment Period (further treatment cycles as per C7) [b]									Follow-up Period	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9**	**10+**		**Treatment discontinued**	**28 days [c]**	**Progression follow-up [o]**
		C1			**C2**	**C3**	**C4, 5, 6**	**C7 to 3.5 years**	**3.5 Years to Disease Progression**			
Cycles / Day		**D1**	**D8**	**D15**	**D1**	**D1**	**D1**	**D169-1277**	**D1278+**			
Day	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85, 113, 141**	**Every 8 weeks**	**Every 10 weeks**			**Every 8 weeks prior to Day 1277/ Every 10 weeks thereafter**
Window (Days)		**0**	**± 2**	**± 2**	**± 2**	**± 7**	**± 7**	**± 7**	**± 14**	**± 7**	**+ 7**	**± 7/± 14**
Whole blood sample at progression [n]										x		
Physical examination, including weight and eyes [h]	x	x			x	x	x	x	x	x		
Height	x											
WHO performance status	x	x			x	x	x	x	x	x		once at start of subsequent anticancer treatment
Vital signs	x	x	x	x	x	x	x	x	x	x		
Clinical chemistry/ Haematology/ Urinalysis [h]	x	x	x	x	x	x	x	x	x	x		
ECG [i]	x	x	x	x	x	x	x	x	x	x		
Echocardiogram/ MUGA (for LVEF) [j]	(x)	At least every 16 weeks up to 3.5 years on study drug and then at least every 20 weeks for as long as on study drug								If clinically indicated		

	Screening/ Enrolment [a]	Treatment Period (further treatment cycles as per C7) [b]									Follow-up Period	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9**	**10+**		**Treatment discontinued**	**28 days [c]**	**Progression follow-up [o]**
		C1			**C2**	**C3**	**C4, 5, 6**	**C7 to 3.5 years**	**3.5 Years to Disease Progression**			
Cycles / Day		**D1**	**D8**	**D15**	**D1**	**D1**	**D1**	**D169-1277**	**D1278+**			
Day	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85, 113, 141**	**Every 8 weeks**	**Every 10 weeks**			**Every 8 weeks prior to Day 1277/ Every 10 weeks thereafter**
Window (Days)		**0**	**± 2**	**± 2**	**± 2**	**± 7**	**± 7**	**± 7**	**± 14**	**± 7**	**+ 7**	**± 7/± 14**
Tumour assessments (RECIST) [k]	x					x	C5D1 and every 8 weeks until Day 1277		Every 10 weeks until progression			x
Dispense study medication		x			x	x	x	x	x			
Dose with osimertinib				Daily dosing								
Concomitant medication and procedures	x	x	x	x	x	x	x	x	x	x	x	(once) [l]
AEs	x	x	x	x	x	x	x	x	x	x	x	(once) [l]
First subsequent anticancer therapy [m]											x	x

a Consent must be taken prior to 28-day Screening Period. The Screening Period will start with first study-related assessment.

b Six 4-week cycles followed by 8-week cycles from Cycle 7 to 3.5 years (Day 1277), and 10-week cycles from 3.5 years to disease progression. Patients who continue to receive osimertinib beyond RECIST 1.1-defined progression, if continuing to show clinical benefit to treatment as judged by the Investigator, will continue to follow the treatment visit schedule and assessments excluding study specific RECIST assessments and plasma samples for ctDNA and blood-borne biomarkers.

c As a minimum, telephone contact should be made with the patient 28 days (window + 7 days) following the discontinuation of study drug (last dose of IP).

d For baseline resistance profiling; testing will be conducted at a later date. The first mandatory tumour tissue biopsy may be an archival or fresh tissue sample obtained within 60 days of study entry. An archival biopsy is acceptable as long as no intervening anticancer treatment occurred since the time the biopsy was obtained to enrolment in this study, and as long as it is within 60 days of study entry.
e The optional on-treatment biopsy may be performed between Day 15 and Day 21 of Cycle 1.
f The second mandatory tumour tissue biopsy may be performed any time between Investigator-assessed, RECIST 1.1-defined progression and before the start of any new anticancer treatment. If a patient discontinues osimertinib before RECIST 1.1-defined progression, the second biopsy will not be performed.
g Plasma samples for ctDNA and blood-borne biomarkers will only be obtained at the treatment discontinuation visit.
h If screening assessments have been performed within 14 days prior to starting study treatment, they do not have to be repeated on Visit 2 if the patient's condition has not changed. The assessments are to be completed pre-dose on visit day. Laboratory tests may be performed the day prior to study visits.
i ECG is also to be performed in event of any cardiac AE.
j To be performed at least every 16 weeks throughout the treatment period up to 3.5 years and then at least every 20 weeks for the remainder of 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 echocardiogram 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.
k The screening assessment should be performed within 28 days prior to study drug initiation. Subsequent assessments are to be performed every 8 weeks (± 7 days) from study enrolment until 3.5 years (Day 1277), and then every 10 weeks (± 14 days) until RECIST 1.1-defined progression, even if a patient discontinues treatment prior to progression or receives other anticancer treatment. Tumour assessment will be performed using CT or MRI of the chest, abdomen (including liver and adrenal glands) and pelvis. Any other sites where disease is suspected or known at screening must also be imaged.
l If the first scheduled progression follow-up visit falls before the 28-day follow-up visit, then AEs and concomitant medications will be assessed at this visit in addition to the 28-day follow-up visit.
m In addition to tumour assessments, patients will be followed for the earlier of first subsequent anticancer therapy (including surgical) after discontinuing osimertinib or death.
n At progression, a whole blood sample will be obtained within 7 days of when the tissue biopsy is performed.
o The progression biopsy should be done prior to the start of subsequent anticancer treatment.
p Monthly pregnancy testing and monitoring of WOCBP is recommended, however this schedule may be modified to comply with local legislation.

AE = adverse event; C = cycle; CT = computed tomography; ctDNA = circulating tumour deoxyribonucleic acid; D = day; ECG = electrocardiogram; IVRS/IWRS = interactive voice response system/interactive web response system; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; RECIST = Response Evaluation Criteria in Solid Tumours; WHO = World Health Organization; WOCBP = women of childbearing potential.

4.2 Treatment Period

Estimated treatment duration is 24 to 36 months; however, there is no maximum duration of treatment. Patients may continue to receive osimertinib beyond RECIST 1.1-defined progression if they continue to show clinical benefit to treatment as judged by the Investigator.

Descriptions of the procedures for this period are included in Table 2.

4.2.1 Cycle 1 to 6 inclusive

The first 6 cycles will be 4 weeks (28 days) each.

4.2.2 Cycle 7 and subsequent cycles

Cycle 7 to 3.5 years (Day 1277) will be 8 weeks (± 7 days) each. After that, cycles will be every 10 weeks (± 14 days) until disease progression.

4.2.3 Treatment discontinued

A treatment discontinuation visit will be performed at the time the study drug is permanently stopped. Study procedures should be conducted as shown in Table 2.

4.3 Follow-up Period

1. All patients will be followed up for safety at approximately 28 days.

2. All patients will be followed up for RECIST 1.1-defined progression.

3. All patients will be followed up for subsequent anticancer treatment/death.

4.3.1 28 days after treatment discontinued

As a minimum, telephone contact should be made with the patient 28 days (+ 7 days) following the discontinuation of osimertinib (last dose of IP) to collect new AEs and follow-up on any ongoing AEs and concomitant medications (including any subsequent anticancer treatment). Refer to Section 6.3.1 for full details on AE recordings during follow-up.

4.3.2 Follow-up for RECIST 1.1-defined progression

Patients who discontinue study drug for reasons other than RECIST 1.1-defined progression will continue RECIST assessments every 8 weeks (± 7 days) (relative to study enrolment) up to 3.5 years (1277 days) and every 10 weeks (± 14 days) from Day 1278 to objective progression.

In addition to tumour assessments, the following assessments are also required during this follow-up period:

- First subsequent anticancer therapy (including surgical) after discontinuing osimertinib or death
- WHO performance status (once at start of first subsequent anticancer therapy)
- Concomitant medication and procedures (only in the first scheduled progression follow-up visit)
- AEs (only in the first scheduled progression follow-up visit)

5 STUDY ASSESSMENTS

A 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 eCRFs as specified in the Clinical Study Protocol and in accordance with the instructions provided.

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

5.1 Efficacy Assessments

5.1.1 Tumour evaluation

Following the screening assessment, subsequent tumour assessments will be conducted every 8 weeks (± 7 days) from study enrolment until 3.5 years (Day 1277), and then every 10 weeks (± 14 days) until RECIST 1.1-defined progression, even if a patient discontinues treatment prior to progression or receives other anticancer treatment. Tumour assessment will be performed using computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen (including liver and adrenal glands) and pelvis. Any other sites where disease is suspected or known at screening must also be imaged. Scans will continue to be submitted up to the point of progression as assessed by the Investigator.

5.2 Safety Assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan (see Section 4).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

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

The following laboratory variables will be measured:

Table 3 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Hb	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-ALP
B-Platelet count	S/P-AST
	S/P-ALT
Urinalysis (dipstick)	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Protein/Albumin	S/P-Calcium, total
U-Glucose	S/P-Sodium
	S/P-Magnesium
	Creatine phosphokinase

ALP = alkaline phosphatase, ALT = alanine aminotransferase; AST = aspartate aminotransferase; B = blood; Hb = haemoglobin; P = plasma; S = serum; U = urine.

At each visit, approximately 6 mL of blood for clinical chemistry and 9 mL for haematology will be taken.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. In case a patient shows an AST **or** ALT ≥ 3 x ULN **or** TBL ≥ 2 x ULN, please refer to Appendix D for further instructions.

5.2.2 Physical examination

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

5.2.3 Electrocardiogram

5.2.3.1 Resting 12-lead electrocardiogram

Twelve-lead ECG will be performed at the visits indicated in the Study Plan.

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

After the paper ECG has been recorded, the Investigator or designated physician will review the ECG and may refer to a local cardiologist if appropriate. A copy of the ECG 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.

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

5.2.4 Echocardiogram/Multigated acquisition scan

An echocardiogram or multigated acquisition scan (MUGA) to assess LVEF will be performed at screening (prior to first dose of osimertinib) and at least every 16 weeks throughout the treatment period until patients have reached 3.5 years on the study. Thereafter, echocardiogram or MUGA will be performed at least every 20 weeks for the remainder of the treatment period. Additional assessments of LVEF should be performed as clinically indicated. The modality of the cardiac function assessments must be consistent within a patient, ie, if echocardiogram is used for the screening assessment, then echocardiogram should also be used for subsequent scans. The patients should also be examined using the same machine and operator whenever possible, 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

The assessment of vital signs includes blood pressure, pulse, and temperature (see Table 1 and Table 2).

5.2.6 Other safety assessments

5.2.6.1 Ophthalmologic exam

Full ophthalmic assessment, including slit lamp examination, should be performed if a patient experiences any visual symptoms (including blurring of vision). Ophthalmology examination results should be collected in the eCRF.

Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE.

5.3 Other Assessments

5.3.1 Resistance profiling

The samples will be collected and stored in a central laboratory/repository. Further details on sample processing, handling, and shipment are provided in the Laboratory Manual.

Mandatory tissue collection

The first mandatory tumour tissue biopsy will be collected at screening for baseline resistance profiling. Tumour tissue may be an archival or fresh tissue sample. An archival tissue sample is acceptable as long as there has been no intervening anticancer treatment since the biopsy was acquired and enrolment into this study, and as long as it is within 60 days of study entry.

The Investigator will be asked to provide formalin-fixed, paraffin-embedded tumour tissue blocks, or a at least 15 re-cut unstained sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides. Each section is to be 5 μm thick.

Biopsy samples taken from bone metastasis and cytology samples are unsuitable for testing and should not be provided. Samples may be collected from primary or metastatic tumour deposits. The mandatory screening tumour biopsy must not be taken from a previously irradiated lesion. The biopsy must not be taken from the lesion(s) selected for inclusion criterion #6 (unless only one measurable lesion exists, in which case the baseline tumour assessment scans are to be done at least 14 days after the screening biopsy).

The second mandatory tumour tissue biopsy will be performed any time between Investigator-assessed, RECIST 1.1-defined progression and before the start of any new anticancer treatment. If a patient discontinues osimertinib before RECIST 1.1-defined progression, the second biopsy will not be performed.

Optional tissue collection

Patients will be asked to consent to provide additional tumour tissue during treatment. The biopsy may be performed between Day 15 and Day 21 of Cycle 1.

5.3.2 Circulating tumour deoxyribonucleic acid and blood-borne biomarkers

Plasma (generated from blood) samples will be taken at every visit for ctDNA and blood-borne biomarkers. The samples will be collected and stored in a central laboratory/repository and analysed at a later date. Individual patients' test results from stored plasma samples will not be available in real time and will not be provided to the Investigators for use in clinical management of patients.

At progression, a whole blood sample will be taken within 7 days of the time the tissue biopsy is obtained. This will be analysed in real time as described below.

5.4 Biomarker Analysis

Tissue and whole blood samples obtained at progression will be collected to carry out real time analysis using a Next Generation Sequencing (NGS) targeted panel to identify the mechanism of resistance to first-line osimertinib, and to inform patient treatment following progression on first-line treatment with osimertinib.

CCI [redacted]

5.4.1 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last 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. CCI [redacted].

5.4.2 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'International Airline Transportation Association (IATA) 6.2 Guidance Document.' Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

5.4.3 Chain of custody of biological samples

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

The Principal Investigator at each centre 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 sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca Biobank or its designee (see details in the Laboratory Manual) during the entire life cycle.

5.4.4 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.

The Principal 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 site, 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 site.
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

6 SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a subject or clinical study subject 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 (eg, 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 study treatment 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 one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject 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 subject or may require medical intervention to prevent one of the outcomes listed above

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

6.3 Recording of Adverse Events

6.3.1 Time period for collection of adverse events

AEs will be collected from the time of signature of informed consent throughout the treatment period and including the follow-up period. The safety follow-up period is defined as 28 days after study drug is discontinued.

SAEs occurring in the safety follow-up period should be reported to AstraZeneca in the usual manner (see Section 6.4).

Following discontinuation of study treatment, SAEs considered related to study procedures should continue to be collected while patients are followed up for disease progression as outlined in Table 2.

6.3.2 Follow-up of unresolved adverse events

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

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum CTCAE Grade
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused patient's withdrawal from study *(*yes or no)
- Outcome

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

- Date AE met criteria for serious AE
- 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)
- 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.

6.3.4 Causality collection

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

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

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

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

6.3.6 Adverse events based on examinations and tests

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

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

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

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

6.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 x ULN together with TBL ≥ 2 x ULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law (HL).

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. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.3.9 New cancers

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

6.3.10 Handling of deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of IP (28 days post last dose 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 eCRF module, but should not be reported as a SAE during the study.
- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.
- Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes.

6.4 Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 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 the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

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

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

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

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

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

6.5 Overdose

A maximum tolerated dose has not been established for osimertinib. An overdose is any dose which exceeds the daily dose that is defined in the clinical study protocol.

Such overdoses should be recorded as follows:

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

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

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 dose of osimertinib.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study IP should be discontinued immediately.

Pregnancy itself is not regarded as an 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 (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study or within 6 weeks of the final dose of the IP, then the Investigator or other site personnel 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 provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 4 months after dosing ends should be followed up and documented.

6.7 Medication Error, Drug Abuse, and Drug Misuse

6.7.1 Timelines

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

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

6.7.2 Medication Error

For the purposes of this clinical study, a medication error is an **unintended** failure or mistake in the treatment process for an AstraZeneca study drug 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 drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error.

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

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

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, eg, wrong route dose (error greater than +/- 10%), or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature

- Wrong patient received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

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

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(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 SoC medication in open-label studies, even if an AstraZeneca product, patient failed to return unused medication or empty packaging.

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

If a medication error occurs in the course of the study, then the Investigator or other site personnel 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 a SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

6.7.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of AstraZeneca study drug for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 1.

6.7.4 Drug Misuse

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

The full definition and examples of Drug Misuse can be found in Appendix B 1.

6.8 Management of Investigational Product-Related Toxicities

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

Table 4 Osimertinib Dose Adjustment Information for Adverse Reactions

Target organ	Adverse reaction	Dose modification
Pulmonary	Interstitial lung disease/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 more than 481 msec within 3 weeks of interruption, then restart at a reduced dose (40 mg) or at 80 mg (at the discretion of the Investigator, to allow for situations where causality in relation to osimertinib may be difficult to determine)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib
Cutaneous	Stevens-Johnson Syndrome and toxic epidermal necrolysis (TEN)	Permanently discontinue osimertinib
Blood and lymphatic system	Aplastic anaemia	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

Note: The intensity of clinical adverse events graded by the NCI CTCAE version 4.0.
ECG = electrocardiogram; CTCAE = Common Terminology Criteria for Adverse Event; NCI = National Cancer Institute; QTc = QT interval corrected for heart rate; TEN = toxic epidermal necrolysis.

If a patient experiences a CTCAE Grade 3 or higher adverse reaction, and/or unacceptable toxicity, including a dose-limiting toxicity (DLT), 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 a toxicity resolves or reverts to ≤CTCAE Grade 2 within 3 weeks of withholding osimertinib, treatment with osimertinib may be restarted at the same dose or a lower dose

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 of withholding osimertinib, 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	80 mg
Reduced dose – 1	40 mg

On resolution of toxicity within 3 weeks:

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

6.8.1 Interstitial lung disease/pneumonitis-like toxicity

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of ILD is observed, an interruption in study treatment dosing is recommended, and the AstraZeneca study team should be informed. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema or pulmonary haemorrhage. The results of the full diagnostic workup (including high-resolution CT [HRCT], blood and sputum culture, haematological parameters) will be captured in the CRF. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered and study treatment permanently discontinued.

In the absence of a diagnosis of ILD, study treatment may be restarted following consultation with the AstraZeneca Study Team Physician.

6.8.2 QTc prolongation

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

Patients with QT interval corrected using Fridericia's correction (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 40 mg, or 80mg at the discretion of the Investigator. If the

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

6.8.3 Keratitis

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

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

Case reports of EM and TEN have been uncommonly reported, and SJS have been rarely reported, in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of EM, SJS and TEN. If signs and symptoms suggestive of EM develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. If signs and symptoms suggestive of SJS appear, osimertinib should be interrupted. Osimertinib should be discontinued immediately if diagnosis of SJS or TEN is confirmed.

6.8.5 Aplastic anaemia

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

Permanent discontinuation due to toxicity

Patients experiencing ILD, QTc prolongation with signs/symptoms of serious arrhythmia or Grade 3 or higher adverse reaction that does not improve to Grade 0 to 2 after withholding for up to 3 weeks will not be permitted to restart study treatment.

6.8.6 Changes in cardiac contractility

Based on the available clinical trial 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

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

AstraZeneca will supply osimertinib as tablets (35 tablets per bottle) for oral administration as a single daily dose of 80 mg or 40 mg. Osimertinib tablets are packed in high-density polyethylene bottles with desiccant and child-resistant closures.

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

7.2 Dose and Treatment Regimens

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

Doses should be taken approximately 24 hours apart at the same time point each day. Doses should not be missed. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their osimertinib, they should not make up for this dose, but should take the next scheduled dose.

The dose of 80 mg osimertinib daily can be reduced to 40 mg osimertinib once daily under circumstances described in Section 6.8. Further dose reductions are not possible. Once a dose has been reduced, it should not be re-escalated at future cycles.

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

7.3 Labelling

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

7.4 Storage

All study drugs 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 study drugs (including IPs) should be recorded in the appropriate sections of the eCRF.

7.6 Accountability

The study drug provided for this study will be used only as directed in the Clinical Study Protocol.

The study site staff will account for all study drugs dispensed to and returned from the patient.

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

7.7 Concomitant and Other Treatments

Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided in Section 3.5 and Appendix E.

7.7.1 Other concomitant treatment

Other medication, other than that described above, which is 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 eCRF.

7.8 Post-study Access to Study Treatment

Patients receiving study treatment at the time of study completion (ie, after final DCO date) will be switched to commercial supply and/or another study to ensure continuation of treatment, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment. Such patients will continue to be monitored and all safety assessments will be performed until study treatment is discontinued. These patients will then be followed up for a period of 28 days after the last study treatment dose is administered for any new treatment-related SAEs. A CSR addendum will be prepared if any additional safety data are collected.

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

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

informed consent, as applicable.

8 STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical Considerations

The primary aim of the study is to examine the molecular profile of patients at the point of disease progression and to compare it to the profile prior to initiation of treatment in patients receiving osimertinib as first-line therapy. A comprehensive statistical analysis plan (SAP) will be prepared and finalised prior to the final analysis. All analyses will be performed by AstraZeneca or its representatives.

The final analysis will be performed at study end (see Section 9.3 for definition of "end of study"), and when approximately 50 patients have evaluable paired biopsies upon progression. Assuming a 70% rate of patients having a biopsy at both baseline and progression, and with an assumed technical failure rate of 30% of the samples (assume an overall failure rate of 51%), then we should expect approximately 50 evaluable paired biopsies to be available when approximately 103 of the 150 patients have progressed, which would be expected to occur approximately 38 months after the first patient is enrolled.

This calculation assumes patients are recruited over 12 months, exponentially distributed progression times with a 19-month median and a 2-piece recruitment function, assuming an exponentially distributed recruitment rate.

The first 100 patients to be enrolled within the first 5 months (ie, from first patient inclusion to the timing of the global protocol amendment). This will be followed by a pause in recruitment of 6 months to account for the issue and approval of the global protocol amendment. This will further be followed by 1 month of recruitment to enrol the remaining 50 patients, assuming an exponentially distributed recruitment rate to account for the regional differences in approval times and slow uptake of recruitment following the protocol amendment.

This is an exploratory study which may inform other studies in the osimertinib development programme and therefore earlier interim analyses may be performed, such interim analyses may not be reported in a formal CSR.

If a patient progresses in the ELIOS study and then enrols in a subsequent AZ study, and if appropriate consent is provided, the biomarker results from a progression biopsy (generated in either the other study or ELIOS), may be shared between both studies and the data may be analysed as part of the ELIOS study.

8.2 Sample Size Estimate

Recruitment of 150 patients is appropriate to characterise the frequency of genetic and proteomic markers at disease progression regardless of their prevalence. The following table

displays the precision of the estimated proportion, for example, when 50 evaluable paired biopsies are available.

Table 6 Precision of Estimates of Marker Frequency with 50 Available and Evaluable Paired Biopsies

Marker Frequency	95% confidence interval [a]
10%	(3%, 22%)
30%	(18%, 45%)
50%	(36%, 64%)

[a] Exact binomial confidence intervals.

8.3 Definitions of Analysis Sets

The primary analysis set (PAS) will include all patients with evaluable paired biopsies. This analysis set will be used for the analysis of the primary endpoint. The full analysis set will include all patients who receive at least one dose of osimertinib and will be used for all other efficacy and safety analyses.

8.3.1 Primary analysis set

The PAS will include all patients with evaluable paired biopsies, which are defined as follows: the first biopsy taken prior to osimertinib treatment and the second biopsy taken at any time between Investigator-assessed, RECIST 1.1-defined progression and before the start of any new anticancer treatment. If the Investigator judges the patient to have progressed but the programmatically defined RECIST progression does not occur, the patient will still be considered evaluable. This analysis set will be used for the analysis of the primary endpoint.

8.3.2 Full analysis set

The full analysis set will include all patients who receive at least one dose of osimertinib. The full analysis set will be used for all efficacy and safety analyses.

8.4 Outcome Measures for Analyses

8.4.1 Calculation or derivation of primary endpoint variables

The primary endpoint is the proportion of patients with a given genetic and proteomic marker (including, but not limited to, EGFR mutations, HER2, and cMET expression and/or amplification) at the point of disease progression as defined by the Investigator; the choice of markers is dependent on the profile comparison at the point of disease progression and prior to treatment initiation. The number of patients with a given genetic and proteomic marker will be divided by the number of patients who have evaluable biopsies and have progressed according to the Investigator to calculate the proportion with a given marker at progression.

8.4.2 Calculation or derivation of efficacy variables

Investigator RECIST based assessments

From the Investigator's review of the imaging scans, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST version 1.1. At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of complete response, partial response, stable disease or progressive disease depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment, which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (unless there is evidence of progression in which case the response will be assigned as progressive disease).

Please refer to Appendix F for the definitions of complete response, partial response, stable disease and progressive disease.

Progression-free Survival

PFS is defined as the time from first dose of osimertinib until the date of RECIST 1.1-defined progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment. If the patient has no evaluable visits or does not have baseline data, they will be censored at day 1 unless they die within 2 visits of baseline.

The PFS time will always be derived based on scan/assessment dates not, visit dates. RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression
- When censoring a patient for PFS the patient will be censored at the latest of the dates contributing to a particular overall visit assessment

Objective Response Rate

ORR rate is defined as the number (%) of patients with at least one visit response of complete response or partial response that is confirmed at least 4 weeks later. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, any complete response or partial response, which occurred after a further anticancer therapy was received, will not be included in the numerator for the ORR calculation.

In the case where a patient has 2 non-consecutive visit responses of partial response, then, as long as the time between the 2 visits of partial response is greater than 4 weeks and there is no

progressive disease between the partial response visits, the patient will be defined as a responder. Similarly, if a patient has visit responses of complete response, not evaluable, complete response then, as long as the time between the 2 visits of complete response is greater than 4 weeks, then a best response of complete response will be assigned.

Duration of Response

DoR will be defined as the time from the date of first documented response, (that is subsequently confirmed) until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of partial response or complete response. If the response is not confirmed, it will not be included.

If a patient does not progress following a response, then their DoR will use the PFS censoring time.

Disease control rate

DCR is defined as the percentage of patients who have a best overall response of complete response or partial response or stable disease.

Time to treatment discontinuation or death

TTD is defined as the time from the date of first dose of osimertinib to the earliest of treatment discontinuation or death. Any patient not known to have discontinued treatment or not known to have died at the time of the analysis will be censored at the last known time to have not discontinued treatment, ie, the last follow-up visit where this was confirmed.

Time to first subsequent therapy or death

The TFST will be defined as the time from the date of first dose of osimertinib to the earlier of the date of anticancer therapy start date following study treatment discontinuation, or death. Any patient not known to have had a subsequent anticancer treatment or not known to have died at the time of the analysis will be censored at the last known time to have not received subsequent anticancer treatment, ie, the last follow-up visit where this was confirmed.

8.4.3 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, ECG, and vital signs. These will be collected for all patients.

Adverse events

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

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

Any AE occurring within 28 days of discontinuation of osimertinib will be included in the AE summaries. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of osimertinib) will be flagged in the data listings.

Other significant adverse events

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

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

8.5 Methods for Statistical Analyses

8.5.1 Analysis of the primary variables

The proportion of patients with a given genetic and proteomic marker at the point of disease progression will be calculated and presented alongside the associated exact binomial 95% CIs. If a reasonable proportion of patients have a given marker at baseline, the difference in the proportion of patients with that marker between progression and baseline, together with its 95% CI, may also be calculated.

8.5.2 Analysis of the secondary variables

Secondary variables PFS, DoR, TTD, and TFST will be summarised using a Kaplan-Meier plot from which the median and event rates from clinically important landmarks such as 1 and 2 years will be calculated. The standard error of the natural log of survival time will be used to calculate CIs. The CI for the median will be calculated by determining the earliest and latest survival times whose 95% CIs contain 0.5. If the 95% CI for survival at the largest event time contains 0.5 then the upper confidence limit will be described as Not Calculated.

For DoR only those patients who have responded (a confirmed response) will be included.

ORR and DCR will be summarised as the proportion of patients with a response or disease control along with the associated exact binomial 95% CIs.

8.5.3 Subgroup analysis

A full list of exploratory subgroup analyses will be defined in the SAP but will include, if numbers allow, comparing groups of patients with different patterns of genetic and proteomic markers at disease progression according to:

- PFS according to RECIST 1.1
- ORR
- Tumour shrinkage, defined as the best change from baseline in target lesion tumour size
- TTD
- Important patient and disease characteristics (eg, prior use of chemotherapy)

8.5.4 Exploratory analysis

The analyses associated with the exploratory objective will be reported separately and will not form part of the CSR. Any HER2/tissue/plasma analysis may be published outside of the CSR.

9 STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of Study Site Staff

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

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

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

9.2 Monitoring of the Study

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

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

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

The AstraZeneca representative may apply a risk-based monitoring approach during visits: source document review (a holistic review of source documents to determine source adequacy, overall eligibility, Good Clinical Practice (GCP), protocol compliance, and patient safety throughout the study), and source document verification (cross-checking specific variables in the source documents against the eCRF to confirm the accuracy of data transcription).

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

9.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

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

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

9.3 Study Timetable and End of Study

A patient is considered to have completed the study when he/she has progressed or died.

The end of the study is defined as when the earliest of these scenarios is met:

- All enrolled patients complete their participation in the study either through disease progression or withdrawal for other reasons.
- The study will end in by Q2 2023, as it is estimated that by then there will be sufficient data to support study endpoints. If, at this time (Q2 2023 or at another time if AstraZeneca

or Regulatory Authorities decide to stop study due to any concerns, eg, patient safety), there are ongoing patients who are drawing benefit from study treatment, they will be switched to commercial supply and/or another study to ensure continuation of treatment, and the study will close using the available data for the final analysis. A CSR will be written at this time, including all data collected during the study.

For any patients who continue in progression follow-up, any additional safety data will be collected and summarised in the CSR.

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

The study may be terminated at individual centres if there are no ongoing patients.

9.3.1 End of Study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under Food and Drug Administration (FDA) and European Union (EU) regulatory requirements:

- European Union requirements define study completion as the last visit of the last patient for any protocol related activity.
- Food and Drug Administration requirements defines 2 completion dates:
  - Primary Completion Date – the date that the final patient is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.
  - Study Completion Date – is defined as the date the final patient is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last patient's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

The study may be stopped if, in the judgement of AstraZeneca, study patients are placed at undue risk because of clinically significant findings.

As this study is event driven, the accrual of the predetermined number of events included in the study endpoints will determine the duration of the data collection phase of the study. There will be a final DCO, defined by when approximately 50 patients have evaluable paired biopsies upon progression. At this time, the clinical database will close to new data.

Should the study meet the primary endpoint at any of the prescribed interim analyses, additional data cuts may be needed per local health authority requirements.

See Section 7.8 for details on patient management following the final DCO, as well as following study completion.

9.4 Data Management

Data management will be performed by Parexel according to the Data Management Plan.

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

AEs and medical/surgical history will be classified according to the terminology of the latest version the MedDRA. Medications will be classified according to the WHO Drug Dictionary. All coding will be performed by the Medical Coding Team at Parexel.

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

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

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

ILD-like events

ILD/pneumonitis are to be reported as AEs in the CRF, with additional details captured in the "ILDIS" eCRF.

Serious adverse event reconciliation

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

Data associated with human biological samples

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

10 ETHICAL AND REGULATORY REQUIREMENTS

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 as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines and are consistent with International Council for Harmonisation (ICH)/GCP, applicable laws and regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples. For details refer to Appendix A 1.

10.2 Patient Data Protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. For details refer to Appendix A 4.

10.3 Ethics and Regulatory Review

An Ethics Committee/Institutional Review Board (IRB) should approve the final Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee/IRB, and to the study site staff.

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

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

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the Clinical Study Protocol should be re-approved by the Ethics Committee/IRB annually.

Before enrolment of any patient into the study, the final Clinical Study Protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca or delegate will handle the distribution of any of these documents to the national Regulatory Authorities.

AstraZeneca or delegate will provide Regulatory Authorities, Ethics Committees/IRBs and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the Ethics Committees/IRBs with reports of any serious and unexpected ADRs from any other study conducted with the IP. AstraZeneca or delegate will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed Consent

The Principal Investigator(s) at each 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 Informed Consent Form(s) is/are stored in the Investigator's Study File.
- Ensure a copy of the signed Informed Consent Form is given to the patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the Informed Consent Form that is approved by an Ethics Committee/IRB.

  For details, refer to Appendix A 3

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

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

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant Ethics Committee/IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

AstraZeneca will distribute any new versions of the Clinical Study Protocol to each Principal Investigator(s). For distribution to Ethics Committee/IRB see Section 10.3.

If a change to a Clinical Study Protocol requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee/IRB are to approve the revised Informed Consent Form before the revised form is used.

10.6 Audits and Inspections

Authorised representatives of AstraZeneca, a regulatory authority or an Ethics Committee/IRB 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 Clinical Study Protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

11 LIST OF REFERENCES

Asami and Atagi 2016
Asami K, Atagi S. Comparing the efficacy of gefitinib, erlotinib, and afatinib in non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations. Austin J Lung Cancer Res. 2016;1(1):1003.

Cross et al 2014
Cross DAE, Ashton SE, Ghiorghiu S, Eberlein C, Nebhan CA, Spitzler PJ, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov. 2014;4(9):1046–61.

Gil-Bazo and Rolfo 2016
Gil-Bazo I, Rolfo C. AZD9291 in TKI EGFR resistance in non-small cell lung cancer and the new concept of phase I trials. Transl Lung Cancer Res. 2016;5(1):85-8.

Jänne et al 2015
Jänne PA, Yang JC-H, Kim DW, Planchard D, Ohe Y, Ramalingam SS, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med. 2015;372:1689-99.

Kuiper et al 2014
Kuiper JL, Heideman DAM, Thunnissen E, Paul MA, van Wijk AW, Postmus PE, et al. Incidence of T790M mutation in (sequential) rebiopsies in EGFR-mutated NSCLC-patients. Lung Cancer. 2014;85:19-24.

Li et al 2014
Li W, Ren S, Li J, Li A, Fan L, Li X, et al. T790M mutation is associated with better efficacy of treatment beyond progression with EGFR-TKI in advanced NSCLC patients. Lung Cancer. 2014;84:295-300.

Oxnard et al 2011
Oxnard GR, Arcila ME, Sima CS, Riely GJ, Chmielecki J, Kris MG, et al. Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: distinct natural history of patients with tumors harboring the T790M mutation. Clin Cancer Res. 2011;17(6):1616–22.

Soria et al 2018
Soria J-C, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee K.H, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018; 387: 113-25.

Yu et al 2013
Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res. 2013;19(8):2240–7.

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, revised protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organisation (CRO), but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- For all studies except those utilising medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reaction according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

- Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
    - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after they become aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
    - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and Investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the EMA CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The Investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach.
    - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca to submit complete and accurate financial certification or disclosure statements to the appropriate Regulatory Authorities. Investigators are responsible for providing information on financial interests during the study and for one year after completion of the study.

A 3 Informed Consent Process

- The Investigator or their representative will explain the nature of the study to the patient or their legally authorised representative and answer all questions regarding the study.

- Patients must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Patients or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study centre.

- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

- If new information requires changes to the ICF, consider if patients must be reconsented and if so, this must be to the most current version of the ICF(s) during their participation in the study.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional HBS. The Investigator or authorised designee will explain to each patient the objectives of the analysis to be done on the samples and any potential future use. Patients will be told that they are free to refuse to participate in any optional samples or the future use, and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Patients will be assigned a unique identifier by AstraZeneca. Any patient records or datasets that are transferred to AstraZeneca will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that their personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the patient in the informed consent.
- The patient must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from Regulatory Authorities.
- The patient must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business

activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.

- The patient must be informed that in some cases their data may be pseudonymised. The General Data Protection Regulation (EU) (GDPR) defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

CCI [redacted]

The patient's samples will not be used for any purpose other than those described in the study protocol.

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to Investigators.

A 6 Dissemination of Clinical Study Data

- Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.
- A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All patient data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits will be predefined in the state location(s) to identify systematic issues that can impact patient safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the quality tolerance limits and remedial actions taken will be summarised in the CSR.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plans.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plans.
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).

Study monitors will perform ongoing source data verification as per the Monitoring Plans to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

A 8 Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data and its origin can be found in site specific source data agreement and/or monitoring guidelines. All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Study and Site Start and Closure

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

- The first act of recruitment is the first site open is considered the first act of recruitment and will be the study start date.

- The AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. 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 AstraZeneca or the 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, AstraZeneca's procedures, or GCP guidelines
    - Inadequate recruitment of patients by the investigator
    - Discontinuation of further study intervention development

- If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event

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 SAE, 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 jeopardise the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

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

- Angioedema not severe enough to require intubation but requiring intravenous 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) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

The causality assessment is performed based on the available data including enough information to make an informed 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.

B 1 Medication Error, Drug Abuse and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for AstraZeneca study drug 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 drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error:

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

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

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, eg, wrong route, dose (error greater than +/- 10%), or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong patient received the medication (excluding IVRS/RTSM errors)
- Wrong drug administered to patient (excluding IVRS/RTSM errors)

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

- Errors related to or resulting from IVRS/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging

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

Drug Abuse

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

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

Examples of drug abuse include but are not limited to:

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

Drug Misuse

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

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

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole

- Only half the dose is taken because the study patient feels that they were feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug.

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

Labelling and Shipment of Biohazard Samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations 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, HIV types 1 and 2. They are assigned the following UN number and proper shipping name:

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

Exempt – all other materials with minimal risk of containing pathogens

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

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

D 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report cases of HL. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Section 6.3.7 of the Clinical Study Protocol.

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 medicinal product (IMP).

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

D 2 Definitions

Potential Hy's Law

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

Hy's Law

AST or ALT ≥ 3 x ULN **together with** TBL ≥ 2 x ULN, where no other reason, other than the IMP, 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.

D 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 x ULN
- AST ≥ 3 x ULN
- TBL ≥ 2 x ULN

The Investigator will 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)
- Complete the appropriate unscheduled laboratory electronic case report form (eCRF) module(s) with the original local laboratory test result

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

- Determine whether the patient meets PHL criteria (see D 2 within this appendix for definition) by reviewing laboratory reports from all previous visits

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 D 2 within this appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

D 4 Follow-up

D 4.1 Potential Hy's Law Criteria Not Met

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

- Inform the AstraZeneca representative that the patient has not met PHL criteria

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol

D 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 D 6)

- Notify the AstraZeneca representative who will then inform the central study team

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

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician

- 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

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

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

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

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

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

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

- If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF accordingly and follow the AstraZeneca standard processes

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

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

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

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined

D 6 Actions Required When Potential Hy's Law Criteria Are Met Before and After Starting Study Treatment

This section is applicable to patients who meet PHL criteria on study treatment 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 D 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 TBL) 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.

D 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 D 6.

If No: follow the process described in D 4.2 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 D 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 TBL) 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.

D 8 References

US FDA 2009
United States Food and Drug Administration (FDA) [internet]. FDA Guidance for Industry; Drug-induced Liver Injury: Premarketing Clinical Evaluation; July 2009 [cited 08 Mar 2022]. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM174090.pdf.

Appendix E Guidance Regarding Potential Interactions with Concomitant Medications

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

E 1 Drugs inducing CYP3A4 metabolism that AstraZeneca strongly recommends 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 E1 Drugs Inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to osimertinib start
Carbamazepine, phenobarbital (phenobarbitone), phenytoin, rifampicin, rifabutin, rifapentine, St John's Wort	3 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 judgement is required. Please contact AstraZeneca with any queries you have on this issue.

Medicines whose exposures may be affected by osimertinib that AstraZeneca considers may be allowed with caution

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

Table E2 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 co-administration with osimertinib.
Sulfasalazine	
Doxorubicin	
Daunorubicin	
Topotecan	
Dabigatran	
Aliskiren	
Digoxin	

E 2 Drugs that prolong QT interval

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

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

E 2.1 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.

E 2.1.1 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 E3.

E 2.1.2 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 2 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 of 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 E3 Drugs With a Known Risk of TdP [a]

Drug name	Withdrawal period prior to study treatment start [b]
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 [c] , 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.
[b] Values determined from comprehensive review (internal to AZ) of each compound's PK half-life and determination of the washout period.
[c] Estimated value as PK of arsenic trioxide has not been studied.
AZ = AstraZeneca; PK = pharmacokinetics; TdP = Torsades de Pointes.

E 3 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 of ECGs and electrolytes is recommended.

Patients with **congenital long QT syndrome are excluded** from this study.

During study treatment and for a period of 2 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 of ECGs and electrolytes is recommended.

Appendix F Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

F 1 Introduction

This appendix details the implementation of RECIST 1.1 guidelines (Eisenhauer et al 2009) for the D5161C00003 study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

F 2 Definition of Measurable, Non-Measurable, Target and Non-Target Lesions

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated and not chosen for biopsy during the Screening Period.

Measurable:

A lesion, not previously irradiated and not chosen for biopsy during the Screening Period, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with CT or MRI and which is suitable for accurate repeated measurements. If only one measurable lesion exists, it is acceptable to be used (as a target lesion) as long as it has not been previously irradiated and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed.

Non-measurable:

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis at baseline*)
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses / abdominal organomegaly identified by physical examination that is not measurable by CT or MRI
- Previously irradiated lesions**
- Skin lesions assessed by clinical examination
- Brain metastasis
- Lesions biopsied within the Screening Period (exception: if only one measurable lesion exists, it is acceptable to be used [as a target lesion] as long as it has not been previously irradiated and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed)

*Nodes with < 10 mm short axis are considered non-pathological and should not be recorded or followed as a non-target lesion (NTL).

**Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as NTLs at baseline and followed up as part of the NTL assessment.

Special cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions.

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as target lesions (TL) at baseline.

Non-target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

F 3 Methods of Assessment

The same method of assessment and the same technique should be used to characterise each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

Table F1 Summary of Methods of Assessment

Target lesions	Non-target lesions	New lesions
CT (preferred) MRI	CT (preferred) MRI Clinical examination X-ray, Chest x-ray	CT (preferred) MRI Clinical examination X-ray, Chest x-ray Ultrasound Bone Scan FDG-PET

F 3.1 Computed Tomography or Magnetic Resonance Imaging

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D5161C00003 study it is recommended that CT examinations of the chest and abdomen (including liver and adrenal glands) and pelvis, will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or is medically contraindicated. For brain lesion assessment, MRI is the preferred method although CT is acceptable.

F 3.2 Clinical Examination

In the D5161C00003 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as TLs if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

F 3.3 X-ray

F 3.3.1 Chest X-ray

In the D5161C00003 study, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest x-ray can, however, be used to assess NTL and to identify the presence of new lesions.

F 3.3.2 Plain X-ray

In the D5161C00003 study plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

F 3.4 Ultrasound

In the D5161C00003 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed, then new lesions should be confirmed by CT or MRI examination.

F 3.5 Endoscopy and Laparoscopy

In the D5161C00003 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

F 3.6 Tumour Markers

In the D5161C00003 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

F 3.7 Cytology and Histology

In the D5161C00003 study histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

F 3.8 Isotopic Bone Scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or x-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the D5161C00003 study isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI, and x-ray is recommended where bone scan findings are equivocal.

F 3.9 FDG-PET Scan

In the D5161C00003 study FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: new lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

*A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

F 4 Tumour Response Evaluation

F 4.1 Schedule of Evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment (refer to Study Plan and Section 5.1 from the study protocol). Follow-up assessments will be performed every 8 weeks (± 7 days) (relative to study enrolment) up to 3.5 years (1277 days) and every 10 weeks (± 14 days) from Day 1278 to progression as defined by RECIST 1.1 even if a patient discontinues treatment prior to progression or receives other anticancer treatment. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

F 4.2 Target Lesions

F 4.2.1 Documentation of Target Lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimetres. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.

- If a TL splits into 2 or more parts, then record the sum of the diameters of those parts.
- If 2 or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention eg, radiotherapy, embolisation, surgery, during the study, the size of the TL should still be provided where possible.

F 4.2.2 Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL.

Table F2 Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides not evaluable as a target lesion response

F 4.3 Non-target Lesions

F 4.3.1 Evaluation of Non-target Lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table F3 Evaluation of Non-target Lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more NTL.
Progression (PD)	Unequivocal progression of existing non-target lesions. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not Evaluable (NE)	Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit.

To achieve ‘unequivocal progression’ on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

F 4.4 New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans

confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

F 4.5 Symptomatic Deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

F 4.6 Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table F4.

Table F4 Overall Visit Response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-D or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if there were no NTLs at baseline).

F 5 References

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Appendix G Definition of Women of Childbearing Potential and Highly Effective 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 postmenopausal (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, as required by the study protocol)
- Women will be considered postmenopausal if they are amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:
  - Women under 50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with luteinising hormone and follicle-stimulating hormone levels in the postmenopausal range
  - Women 50 years of age or more will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments

Highly effective contraception methods

Highly effective method of birth control is defined in Note 3 in International Conference on Harmonisation 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.

Highly effective 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 patient assurance that partner received post-vasectomy confirmation of azoospermia)
- Tubal occlusion plus male condom
- Intrauterine device (IUD) – provided coils are copper-banded, plus male condom
- Intrauterine system (IUS) levonorgestrel IUS (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 / ethinyl oestradiol transdermal system plus male condom
- Intravaginal device (eg, ethinyl oestradiol 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
- All progesterone-only pills except, Cerazette
- All barrier methods, if intended to be used alone
- Non-copper containing IUD
- Fertility awareness methods
- Coitus interruptus

Appendix H Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) during which patients may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the patient's safety. If in doubt, please contact the AZ Study Physician.

H 1 Reconsent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on-site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in the sections below. Local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

H 2 Rescreening of Patients to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened patients. The Investigator should confirm this with the designated Study Physician.

In addition, during study disruption there may be a delay between confirming eligibility of a patient and either enrolment into the study or commencing of dosing with study intervention. If this delay is outside the screening window specified in Table 1 and Table 2, the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to rescreen a patient in addition to that detailed in Section 3.7.1. The procedures detailed in Table 1 and Table 2 must be undertaken to confirm eligibility using the same randomization number as for the patient.

H 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or third-party vendor service will visit the patient's home or other remote location as per local Standard Operating Procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

H 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the patient using telecommunications technology, including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow AEs, concomitant medications, and targeted physical examinations to be reported and documented.

H 5 Data Capture During Telemedicine Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP (or site delegate) from the study site or third-party vendor service in the source documents.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d5161c00003-csp-v7		
Document Title:	D5161C00003 Clinical Study Protocol version 7	
Document ID:	Doc ID-003766187	
Version Label:	6.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
02-May-2023 13:15 UTC	PPD	Management Approval
25-Apr-2023 23:43 UTC	PPD	Management Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.