Clinical Study Protocol	
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A prospective, multicenter, Phase-IV clinical trial to assess safety of TAGRISSO™ (Osimertinib) in Indian adult patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive nonsmall cell lung cancer (NSCLC)

Sponsor:

AstraZeneca Pharma India Limited

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Rechenahalli, Outer Ring Road, Bangalore-560045.

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

VERSION HISTORY

Version 1.0, 06 November 2017
Initial creation

PROTOCOL SYNOPSIS

A prospective, multicenter, Phase-IV clinical trial to assess safety of TAGRISSO™ (Osimertinib) in Indian adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC)

Study site(s) and number of patients planned

No. of total screened patients: Approximately 70

No. of total enrolled patients: Approximately 60

No. of study sites: 10

Total planned Study period	
Estimated date of first patient in	01-April-2018
Estimated date of last patient in	30-December-2018
Estimated date of last patient last visit	30-June-2019
Estimated date of data base lock	31-July-2019

BACKGROUND & RATIONALE

Lung cancer is the leading cause of cancer related mortality world-wide and amongst males in India. About 85% of lung cancers are non-small cell lung cancers (NSCLC) and the most common form of NSCLC is Adenocarcinoma (Howlader N et al. 2016). Mutations in the Epidermal growth factor receptor (EGFR) tyrosine kinase are observed in approximately 10-15% of NSCLC adenocarcinomas in the Caucasians (Nguyen, Neal, and Wakelee 2014). Studies from India report a much higher frequency of EGFR mutations 23% to 44% (Noronha et al. 2016). Patients harbouring activating EGFR mutation often respond well when treated with Tyrosine kinase inhibitors (TKIs).

Resistance mutations confer resistance to EGFR TKIs in NSCLC tumors and can be de novo or acquired. T790M is one such mutation associated with resistance to TKI inhibitors like gefitinib and Erlotinib. Clinical data suggests that T790M mutation is found in <5% - 11% of TKI-naïve patients (Primary T790M mutation) and about 50% of TKI resistant patients (acquired resistance to T790M mutation) (Sequist et al. 2011; Yu et al. 2013; Camidge, Pao, and Sequist 2014).

Findings from 2 Phase II clinical trials (AURA extension and AURA2) evaluating safety and efficacy of osimertinib indicated an objective response rate (ORR) of 66.1% (95% confidence interval [CI] 61.2, 70.7%) among patients (n = 398) with a T790M mutation (Goss et al. 2016; Chen et al. 2017), suggesting that this drug will help address an unmet need in this patient population setting. The phase III clinical trial AURA3, presented in World Conference on Lung Cancer on December 2016 and published on February 2017 (Mok et al. 2017), compared the treatment with osimertinib 80 mg orally once a day to intravenous pemetrexed (500 mg per square meter of body-surface area) plus either carboplatin (target area under the curve, 5 [AUC5]) or cisplatin (75 mg per square meter) every 3 weeks for up to six cycles (maintenance pemetrexed was allowed). 419 patients with T790M-positive advanced non-small-cell lung cancer, who had disease progression after first-line EGFR-TKI therapy were randomized (in a 2:1 ratio; 279 and 140 patients, respectively). The median duration of progression-free survival was significantly longer with osimertinib than with platinum therapy plus pemetrexed (10.1 months versus 4.4 months; hazard ratio; 0.30; 95% confidence interval [CI], 0.23 to 0.41; P<0.001). The objective response rate was significantly better with osimertinib (71%; 95% CI, 65 to 76) than with platinum therapy plus pemetrexed (31%; 95% CI, 24 to 40) (odds ratio for objective response, 5.39; 95% CI, 3.47 to 8.48; P<0.001).

Osimertinib, a third-generation EGFR-TKI has been approved in the USA, Canada, Mexico, European Union, Switzerland, Israel, Japan, Brazil, China, and South Korea for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

The USA-based National Comprehensive Cancer Network (NCCN) guidelines included osimertinib as one of the recommended treatment options following first-line therapy with erlotinib, afatinib or gefitinib ("NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)- Non-Small Cell Lung Cancer (Version 8.2017)" 2017).

51st patient expert committee (SEC) of oncology and hematology on 21-Mar-2017 has given positive recommendations for approval of osimertinib for "the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive nonsmall cell lung cancer (NSCLC), as detected by an appropriate test, who have progressed on or after EGFR TKI therapy" with a condition to conduct phase IV clinical trial as per the requirements of Indian Good Clinical Practices (GCP) and schedule Y of Drugs and Cosmetics Rules, 1945.

As per recommendation, current phase-IV study is planned with the aim to assess the safety of osimertinib in Indian patients as a post-marketing requirement. The data obtained from the present study will help to understand the safety profile of osimertinib in Indian patients with EGFR-T790M mutation-positive NSCLC and add to the limited burden of safety data on osimertinib currently available.

OBJECTIVES

Primary Objective:	**Primary Outcome Measure:**
To assess the safety of osimertinib among T790M positive NSCLC patients of India	Number, frequency and proportion of patients with adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI) including interstitial lung disease/pneumonitis-like events, and on-study deaths.

STUDY DESIGN

This is a prospective, single-arm, multicenter, phase-IV trial investigating the safety of osimertinib in Indian adult patients with locally advanced or metastatic EGFR-T790M mutation-positive NSCLC. Investigator will be trained on the locally approved prescribing information before the enrolment of the first patient at their site to ensure compliant and proper dosing of the study drug. Patients will be monitored throughout the study period for AEs of osimertinib.

The decision of patients to participate in this study must not, in any way, impact upon the standard of care that they are receiving or any benefits to which they are otherwise entitled. Prior to data collection, all patients must sign an informed consent form (ICF) allowing data collection and source data verification in accordance with local requirements and sponsor policy.

Patients with metastatic EGFR T790M mutation-positive NSCLC, who are eligible to osimertinib treatment as per locally approved prescribing information and ratified by an independent clinical judgment of treating physician will be evaluated for the inclusion into the current phase-IV study based on eligibility criteria. EGFR T790M positivity on plasma or tissue biopsy on PCR-based platform will be considered appropriate test. EGFR T790M must be performed after progressive disease on last line of therapy (on or after EGFR TKI therapy). In order to enroll approximately 60 patients, it is expected that approximately 70 patients will be screened.

Patient participation will include a Screening/Enrolment Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 7 days prior to Cycle 1, Day 1. The Treatment Phase will extend from Cycle 1, Day 1 to Cycle 6, Day 21; or until study drug discontinuation due to either disease progression or unacceptable toxicity; or other reasons whichever occurs first, as listed in Section 3.9. Each cycle of treatment is defined as 21 days of once daily osimertinib treatment. The Follow-up Phase will begin once a patient discontinues study drug or on completion of Treatment

Phase, and will continue until 28 days after last dose, death, loss to follow up, consent withdrawal for study participation, or study end, whichever occurs first (see Section 3.9, 3.10, 3.11).

Osimertinib will be provided free of cost by the sponsor to clinical trial patient in the Treatment Phase. The sponsor shall provide the laboratory investigations for safety evaluation including hematology, biochemistry and ECG as mentioned in the Time and Event Schedule to monitor the safety throughout the study period.

SCREENING PHASE (VISIT 0)

Patients, or their legally acceptable representative, will provide written informed consent before any trial-specific procedures are performed. During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Time and Event Schedule. Screening procedures will be performed within 7 days before Cycle 1, Day 1. All baseline disease characteristics will be captured based evaluation performed as a part of routine clinical practice. The Screening laboratory tests, if any, must be completed within 7 days before Cycle 1, Day 1.

TREATMENT PHASE

The Treatment Phase will extend from Cycle 1, Day 1 to Cycle 6, Day 21; or until study drug discontinuation due to either disease progression or unacceptable toxicity; or other reasons whichever occurs first, as listed in Section 3.9. Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedules. Patients will be closely monitored for adverse events and other safety evaluations including laboratory investigations, concomitant medications. If disease progression is diagnosed before Cycle 6, Day 21, then the patient will discontinue study drug with completion of the End-of-Treatment Visits on the day of progression, and will enter the Follow-up Phase.

END-OF–TREATMENT VISIT (EOT)

An End-of-Treatment Visit is to be scheduled on Cycle 6, Day 21 of the study drug administration. In a case where patient discontinues the study treatment for any reason listed in Section 3.9 before Cycle 6, Day 21, last visit of the patient will be considered as End-of-treatment visit. Every effort should be made to conduct the telephonic End-of-Study Visit before the patient starts subsequent treatment.

FOLLOW UP PHASE (END-OF-STUDY)

A telephonic follow-up will be conducted 28 days after the EOT Visit. This will be considered as End-of-study visit.

The observation period including the Enrolment Visit and telephonic end-of-study visit will be up to a maximum duration of approximately 23 weeks for each patient.

PATIENT POPULATION

Key eligibility criteria include the patients of either sex who are ≥18 years of age with metastatic EGFR T790M mutation-positive NSCLC, as detected by an appropriate test, who have progressed on or after EGFR TKI therapy by an independent clinical judgment of treating physician based on locally approved prescribing information. Patient with either the history of hypersensitivity to excipients of the study drug or to drugs with a similar chemical structure or class to the study drug OR with pregnant and/or lactating women OR patients participating in any current or future interventional trial will not be enrolled in the current study.

DURATION OF TREATMENT

The Treatment Phase will extend from Cycle 1, Day 1 to Cycle 6, Day 21; or until study drug discontinuation due to either disease progression or unacceptable toxicity; or other reasons whichever occurs first, as listed in Section 3.9. 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.

POST STUDY ACCESS TO STUDY TREATMENT

Patients receiving osimertinib at the time of study completion (i.e. after completion of treatment phase) may continue to receive osimertinib, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment or have not progressed clinically. They will be provided osimertinib treatment as per recommendation from treating physician on ethical basis. Post-trial access to osimertinib will be provided from local commercial supply though local distribution channel. Such patients will not be monitored after EOS visit.

STUDY DRUG, DOSAGE AND MODE OF ADMINISTRATION

Osimertinib is an oral, potent, selective, irreversible inhibitor of both EGFR-TKI sensitizing and resistance mutations in NSCLC with a significant selectivity margin over wild-type EGFR. osimertinib will be administered orally as one 80 mg tablet once a day. A cycle of treatment is defined as 21 days of once daily osimertinib treatment. Dose modification will be done as per locally approved prescribing information with the use of 40 mg tablet strength if required.

SAFETY EVALUATIONS

Safety evaluations will include adverse event monitoring, physical examinations, ECG monitoring, clinical laboratory parameters (hematology and biochemistry), vital sign measurements, and WHO performance status and death as observed by the investigator. Based on the previous human experience with osimertinib, in vitro studies, and animal toxicological findings, interstitial lung disease (ILD), QT_c interval prolongation, cardiomyopathy and keratitis will be closely monitored. Any of the safety monitoring assessments may be performed more frequently, and adverse events should be evaluated by the investigator according to the standard practice if clinically indicated.

Statistical methods

SAMPLE SIZE JUSTIFICATION

The primary objective of the trial is to describe the safety profile of osimertinib in routine clinical practice and add to the limited burden of safety data on osimertinib currently available as assessed by the incidence of adverse events (AEs) (Serious and Non-serious AEs) observed during trial. Considering the epidemiology of metastatic NSCLC- adenocarcinoma subtype which are positive for EGFR sensitizing mutation and have progressed after EGFR-TKI based treatment in first line setting and prevalence of T790M-mutation after such progression, a sample size of 60 patients is expected to provide the following exact two sided 95% confidence interval for a list of percentages of patients reporting at least one AE (Julious and Campbell 2012).

Observed rate expressed as % (number of patients reporting at least one AE*)	**Lower Limit of CI (%)**	**Upper Limit of CI (%)**
0%	0	6.0
1%	0	7.8
2%	0.1	9.5
5%	1.0	13.9
10%	3.8	20.5
20%	10.8	32.3
30%	18.8	43.2
40%	27.6	53.5
50%	36.8	63.2

*the symptom could be any of the expected AE, unexpected AE or SAE. The calculation is based on the link between binomial and beta distributions.

Hypothesis

No formal hypothesis testing will be conducted.

Statistical Analysis

Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, coefficient of variation, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. Shift tables will be provided to determine the change in reported outcomes from baseline.

The safety analysis population will include all patients who sign the ICF and receive at least one dose of osimertinib.

Adverse Events (both in terms of 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 study drug (ie, the last dose 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.

TIME AND EVENTS SCHEDULE

Table 1. Time and Event Schedule

Study Phase	**Screening Phase[a]**	**Treatment Phase**		**Follow-up Phase**
Cycle		**Cycles 1-6**	**EOT**	**EOS**
Visit No.	**1**	**2-7 (Day 1 of each cycle)**	**8**	
Study Days	**-6 to 0**	**1-109 (21 day per cycle)**	**131**	**28 days post-EOT**
Screening/Enrolment visit				
Informed consent[b]	Patients must sign the informed consent form before any study-specific procedures are performed.			
Eligibility Criteria	X			
Demographics/ Review medical history	X			
WHO Performance Status	X	X	X	
General Physical examination	X	Symptom-directed physical examination only		
Concomitant medication recording	Continuous from time of ICF until 28 days after last osimertinib dose in treatment phase.			
Study Drug Administration				
Osimertinib dosing		The recommended dose is 80 mg osimertinib once a day until disease progression or unacceptable toxicity. Each cycle is of 21 days.		
Disease Evaluations (Disease characteristics will be performed as per routine clinical practice)				
Baseline Disease Characteristics	X			
Safety Evaluations				
Physical examination	X	Symptom-directed physical examination only		
Vital parameters	X	X	X	
Adverse event monitoring	Continuous from time of ICF until 28 days after last study osimertinib dose			
12-lead ECG	X	X	X	
Hematology & Biochemistry	X	X	X	

Footnotes:

a. The Screening Phase begins when the first Screening procedure is conducted. Screening tests should be performed within 7 days of Cycle 1 Day 1 except for disease evaluations (performed as routine clinical practice).

b. Must be signed before first study-related activity.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event
BCRP	Breast Cancer Resistance Protein
CI	Confidence Interval
CRF	Case Report Form (electronic/paper)
CTCAE	Common Terminology Criteria for Adverse Event
ECG	Electrocardiogram
EGFR	Epidermal Growth Factor Receptor
EGFRm	EGFR Mutation positive; EGFR Sensitizing Mutation positive
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ILD	Interstitial Lung Disease
INR	International Normalized Ratio
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective response rate
PFS	Progression Free Survival
PT	Preferred Term
QT	Interval on the electrocardiogram representing the duration of depolarization and repolarization of the heart
QTc	The QT interval corrected for heart rate
QTcF	QT interval corrected per Fredericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
T790M	An amino acid substitution at position 790 in EGFR, from a Threonine (T) to a Methionine (M). Presence of T790M
TKI	Tyrosine Kinase Inhibitor
WBDC	Web based data capture

1. Introduction

1.1 Background and rationale for conducting this study

Lung cancer is the leading cause of cancer related mortality world-wide and amongst males in India. About 85% of lung cancers are non-small cell lung cancers (NSCLC) and the most common form of NSCLC is Adenocarcinoma (Howlader N et al. 2016). Mutations in the Epidermal growth factor receptor (EGFR) tyrosine kinase are observed in approximately 10-15% of NSCLC adenocarcinomas in the Caucasians. Studies from India report a much higher frequency of EGFR mutations 23% to 44% (Noronha et al. 2016). Patients harbouring activating EGFR mutation often respond well when treated with Tyrosine kinase inhibitors (TKIs).

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As per recommendation, current phase-IV study is planned with the aim to assess the safety of osimertinib in Indian patients as a post-marketing requirement. The data obtained from the present study will help to understand the safety profile of osimertinib in Indian patients with EGFR-T790M mutation-positive NSCLC.

1.2 Rationale for study design, doses and control groups

51st patient expert committee (SEC) of oncology and hematology on 21-Mar-2017 has given positive recommendations for approval of osimertinib for "the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive nonsmall cell lung cancer (NSCLC), as detected by an appropriate test, who have progressed on or after EGFR TKI therapy" with a condition to conduct phase IV clinical trial as per the requirements of Indian Good Clinical Practices (GCP) and schedule Y of Drugs and Cosmetics Rules, 1945.

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1.3 Benefit/risk and ethical assessment

Not applicable.

1.4 Study Design

This is a prospective, single-arm, multicenter, phase-IV trial investigating the safety of osimertinib in Indian adult patients with metastatic EGFR-T790M mutation-positive NSCLC. Investigator will be trained on the locally approved prescribing information before the enrolment of the first patient at their site to ensure compliant and proper dosing of the study drug. Patients will be monitored throughout the study period for AEs of osimertinib.

2. Study Objectives

Primary Objective:	**Primary Outcome Measure:**
To assess the safety of osimertinib among T790M positive NSCLC patients of India	• Number, frequency and proportion of patients with adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI) including interstitial lung disease/pneumonitis-like events, and on-study deaths.

3. Patient Selection, Enrolment, Randomisation, Restrictions, Discontinuation and Withdrawal

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

3.1 Inclusion criteria

Each potential patient must satisfy all of the following criteria to be enrolled in the study.

1 Patient of either sex and ≥18 years of age

2 Patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an appropriate test, who have progressed on or after EGFR TKI therapy by an independent clinical judgment of treating physician based on locally approved prescribing information

3 Each patient (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. Patients must be willing and able to adhere to the prohibitions and restrictions specified in this protocol, as referenced in the informed consent form (ICF).

3.2 Exclusion criteria

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

1 Patient with either the history of hypersensitivity to excipients of the study drug or to drugs with a similar chemical structure or class to the study drug.

2 Pregnant and/or lactating women

3 Patients participating in any current or future interventional trial will not be enrolled in the current study

Procedures for withdrawal of incorrectly enrolled patients see section 3.4.

3.3 Patient enrolment and randomization

- Approximately 70 patients meeting all inclusion and none of the exclusion criteria will be screened for the study to enroll 60 patients in the current study.
- Patients will be in open label treatment.
- Patients who discontinue the study will not be replaced.
- The E-code is the only patient identification number to be used in CSRs and high level documents.
- Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.
- The Investigator(s) will:
    - Obtain signed informed consent from the potential patient before any study specific procedures are performed.
    - Assign potential patient a unique enrolment number code.
    - Determine patient eligibility.
    - Enroll only eligible patients. If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused.

3.4 Procedures for handling incorrectly enrolled or 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 Methods for assigning treatment groups

Not applicable- This is a single arm study.

3.6 Methods for ensuring blinding

Not applicable – This is an open-label study.

3.7 Methods for unblinding

Not applicable – This is an open label study.

3.8 Restrictions

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

1 Females of child-bearing potential should use reliable methods of contraception from the time of screening until 6 weeks after discontinuing study treatment. Acceptable contraception methods are: Total sexual abstinence (abstinence must be for the total duration of the trial and the follow-up period); vasectomised sexual partner plus male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia); tubal occlusion plus male condom; intra-uterine device (IUD) - provided coils are copper-banded, plus male condom; intra-uterine system (IUS) levonorgestrel intra-uterine system, plus male condom; medroxyprogesterone injections plus male condom; etonogestrel implants plus male condom; normal and low dose combined oral contraceptive pills, plus male condom; norelgestromin / ethinylestradiol transdermal system plus male condom; intravaginal device (eg ethinylestradiol and etonogestrel) plus male condom; desogestrel plus male condom.

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

3 Once enrolled all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods that are known to be potent inducers of CYP3A4 whenever feasible, but patients may receive any medication that is

clinically indicated for treatment of adverse events. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 months after the last dose of TAGRISSO. All concomitant medications should be captured on the eCRF.

4 If medically feasible, patients taking regular medication, with the exception of potent inducers of CYP3A4 (see above), should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon BCRP and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving TAGRISSO.

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.

3.9 Discontinuation from study treatment

If a subject's study treatment must be discontinued, this will not result in automatic withdrawal of the subject from the study. If a subject discontinues study treatment for any reason before the end of the treatment phase, end-of-treatment assessments should be obtained and scheduled follow-up phase assessments should continued as specified in the Time and Events Schedule.

Patients may be discontinued from the study drug treatment in the following situations:

- The subject experiences disease progression (as per participating physician's assessment)
- Adverse Event (including laboratory abnormality or intercurrent illness) which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the patient
- The subject (or the subject’s legally acceptable representative) withdraws consent for administration of study drug
- The subject received concurrent (non-protocol) anti-cancer treatment for NSCLC
- ILD/Pneumonitis
- Corneal ulcerations
- QTc interval prolongation with signs/symptoms of serious arrhythmia
- Pregnancy
- Any adverse event deemed to be related to osimertinib that requires a dose hold of more than 21 days will result in permanent discontinuation of osimertinib.
- Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks

The primary reason for discontinuation of study treatment is to be recorded in the eCRF.

3.9.1 Procedures for discontinuation of a patient from study drug

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

Enrolled patients who discontinue the study prematurely should immediately stop taking study drug and complete the procedures described for End of Treatment Visit, as soon as possible but not later than 7 days after discontinuation of study drug.

If a patient is withdrawn from study, see Section3.9, 3.10, 3.11.

3.10 Criteria for withdrawal

3.10.1 Withdrawal of the informed consent

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

Reasons for withdrawal from the study:

- Eligibility criteria not fulfilled
- Death
- Withdrawal of consent.
- Lost to follow up (unsuccessful contact with patient despite every effort made by investigator)

Patients who withdraw consent for further participation in the study will not receive any further study drug or further study observation. Note that the patient may be offered additional tests to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn patients will not be replaced.

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the patient's status at that time. Patients who refuse continuing participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and any evaluations should resume according to the protocol.

3.11 Discontinuation of the study

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

- meet individual stopping criteria or are otherwise considered significant

- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

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

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

4. Study Plan and Timing of Procedures

Study is planned to be conducted according to plan described in Table 1.

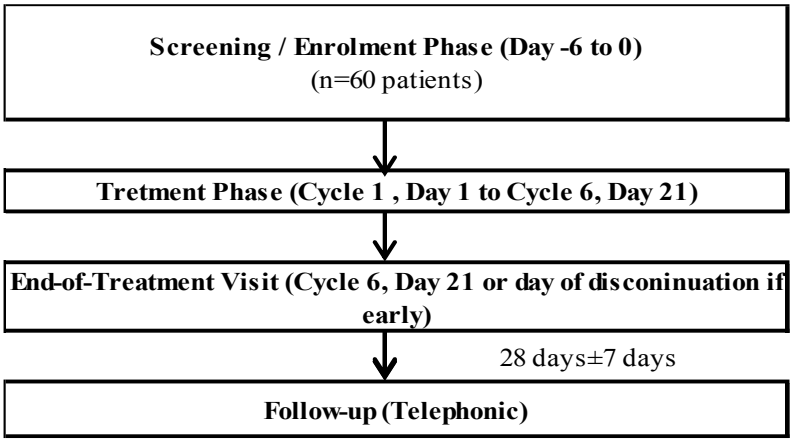
The decision of patients to participate in this study must not, in any way, impact upon the standard of care that they are receiving or any benefits to which they are otherwise entitled. Prior to data collection, all patients must sign an informed consent form (ICF) allowing data collection and source data verification in accordance with local requirements and sponsor policy.

Patients with metastatic EGFR T790M mutation-positive NSCLC, who are eligible to osimertinib treatment as per locally approved prescribing information and ratified by an independent clinical judgment of treating physician will be evaluated for the inclusion into the current phase-IV study based on eligibility criteria. EGFR T790M positivity on plasma or tissue biopsy on PCR-based platform will be considered appropriate test. EGFR T790M must be performed after progressive disease on last line of therapy (on or after EGFR TKI therapy). In order to enrol approximately 60 patients, it is expected that approximately 70 patients will be screened.

Patient participation will include a Screening/Enrolment Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 7 days prior to Cycle 1, Day 1. The Treatment Phase will extend from Cycle 1, Day 1 to Cycle 6, Day 21; or until study drug discontinuation due to either disease progression or unacceptable toxicity; or other reasons whichever occurs first, as listed in Section 3.9. Each cycle of treatment is defined as 21 days of once daily osimertinib treatment. The Follow-up Phase will begin once a patient discontinues study drug or on completion of Treatment Phase, and will continue until 28 days after last dose, death, loss to follow up, consent withdrawal for study participation, or study end, whichever occurs first (see Section 3.9, 3.10, 3.11).

Osimertinib will be provided free of cost by the sponsor to clinical trial patient in the Treatment Phase. The sponsor shall provide the laboratory investigations for safety evaluation including hematology, biochemistry and ECG as mentioned in the Time and Event Schedule to monitor the safety throughout the study period.

Figure 1. Schematic Overview of the Study



SCREENING PHASE (VISIT 0)
Patients, or their legally acceptable representative, will provide written informed consent before any trial-specific procedures are performed. During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Time and Event Schedule. Screening procedures will be performed within 7 days before Cycle 1, Day 1. All baseline disease characteristics will be captured based evaluation performed as a part of routine clinical practice. The Screening laboratory tests, if any, must be completed within 7 days before Cycle 1, Day 1.

TREATMENT PHASE
The Treatment Phase will extend from Cycle 1, Day 1 to Cycle 6, Day 21; or until study drug discontinuation due to either disease progression or unacceptable toxicity; or other reasons whichever occurs first, as listed in Section 3.9. Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedules. Patients will be closely monitored for adverse events and other safety evaluations including laboratory investigations, concomitant medications. If disease progression is diagnosed before Cycle 6, Day 21, then the patient will discontinue study drug with completion of the End-of-Treatment Visits on the day of progression, and will enter the Follow-up Phase.

END-OF–TREATMENT VISIT (EOT)
An End-of-Treatment Visit is to be scheduled on Cycle 6, Day 21 of the study drug administration. In a case where patient discontinues the study treatment for any reason listed in Section 3.9 before Cycle 6, Day 21, last visit of the patient will be considered as End-of-treatment visit. Every effort should be made to conduct the telephonic End-of-Study Visit before the patient starts subsequent treatment.

FOLLOW UP PHASE (END-OF-STUDY)
A telephonic follow-up will be conducted 28 days after the EOT Visit. This will be considered as End-of-study visit.

The observation period including the Enrolment Visit and telephonic end-of-study visit will be up to a maximum duration of approximately 23 weeks for each patient.

5. Study Assessments

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.

5.1 Safety assessments

5.1.1 Laboratory safety assessments

Blood sample for laboratory measurement will be performed at local laboratory.

Table 2. Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
	S/P-Albumin
	S/P-Potassium
	S/P-Calcium, total
	S/P-Sodium
	S/P-Creatine kinase (CK)

5.1.2 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, musculo-skeletal (including spine and extremities) and neurological systems.

5.1.3 12-Lead ECG

A 12-lead ECG will be taken (supine position, standard ECG with a recommended paper speed of 50 mm/second covering at least 6 sequential beats) after the patient has been lying down resting for at least 5 minutes. The ECG will be evaluated by the investigator and entered as “Normal” or “Abnormal” in the eCRF. If the ECG is evaluated as “Abnormal” the abnormality should be further specified.

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 and is responsible for reporting all SAEs and other AEs.

6.1 Definition of adverse events

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

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

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie screening, treatment, follow-up), that fulfils one or more of the following criteria:

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

For further guidance on the definition of a SAE, see

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"NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)- Non-Small Cell Lung Cancer (Version 8.2017)." 2017. National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf.

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Appendix A to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from patient actually taking the study drug throughout the entire treatment period and during the follow-up period until the end of the study. SAEs will be collected from the time at which informed consent is obtained until the end of the study.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment 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 collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the study drug (yes or no)
- Action taken with regard to study drug
- 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 serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE.

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

shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

Maximum intensity refers to the complete course of the AE. The patient (parents/legal guardians) will be asked to assess the maximum intensity of the reported AEs according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities).

6.3.4 Causality collection

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

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

A guide to the interpretation of the causality question is found in APPENDIX A. ADDITIONAL SAFETY INFORMATION to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF. The question will be put to each patient (or parent/legal guardian) in local language from Visit 2 to the last follow-up telephone contact. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests, vital signs and other safety assessments will be summarized in the CSR. Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the study drug.

If deterioration in a laboratory value, vital sign or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or other finding will be considered as additional information. In the absence of clinical signs and symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product 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 that are unequivocally due to disease progression should not be reported as AEs during the study.**

6.3.8 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.

6.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day 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 adverse events 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.

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

The reference document for definition of expectedness/listedness is the Product Information for the osimertinib Overdose.

6.5 Overdose

The risks associated with over dosage of osimertinib are considered to be small.

In phase I/II clinical trials a limited number of patients were treated with osimertinib daily doses of up to 240 mg without dose limiting toxicities. In these studies, patients who were treated with osimertinib daily doses of 160 mg and 240 mg experienced an increase in the frequency and severity of a number of typical EGFR TKI-induced AEs (primarily diarrhoea and skin rash) compared to the 80 mg dose. There is limited experience with accidental overdoses in humans. All cases were isolated incidents of patients taking an additional daily dose of osimertinib in error, without any resulting clinical consequences. There is no specific

treatment in the event of osimertinib overdose. In case of suspected overdose, osimertinib should be withheld and symptomatic treatment initiated.

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

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

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 occurring during the course of the study and within 6 weeks of the last dose of TAGRISSO should be reported to Astrazeneca.

6.6.1 Maternal exposure

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

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject 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 investigational product, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section X) 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 subject's partners is not considered to be an adverse event. 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 subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome; the male subject 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 Management of study drug related toxicities

If a patient experiences a CTCAE grade 3 and/or unacceptable toxicity not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines.

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

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

Table 3. OSIMERTINIB dose adjustment information for adverse reactions

Target organ	Adverse reaction[a]	Dose modification
Pulmonary	ILD/Pneumonitis	Permanently discontinue OSIMERTINIB
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold OSIMERTINIB until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue OSIMERTINIB
Other	Grade 3 or higher adverse reaction	Withhold OSIMERTINIB for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding 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

[a] Note: The intensity of clinical adverse events graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

On resolution of toxicity within 3 weeks:

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

ILD/Pneumonitis-like toxicity
If new or worsening pulmonary symptoms (e.g., dyspnoea) or radiological abnormality suggestive of interstitial lung disease 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 edema, or pulmonary hemorrhage. The results of the full diagnostic workup (including high-resolution computed tomography, blood and sputum culture, haematological parameters) will be recorded in the CRF by the investigator. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease (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.

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

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.

Changes in cardiac contractility
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.

Patients experiencing corneal ulceration, Interstitial Lung Disease (ILD) or QTc prolongation with signs/symptoms of serious arrythmia will not be permitted to restart study treatment.

For the details, please refer to the local prescribing information.

7. Study Drug and Other Treatments

Osimertinib is an oral, potent, selective, irreversible inhibitor of both EGFR-TKI sensitising and resistance mutations in NSCLC with a significant selectivity margin over wild-type EGFR. osimertinib will be administered orally as one 80 mg tablet once a day. A cycle of

treatment is defined as 21 days of once daily osimertinib treatment. Dose modification will be done as per locally approved prescribing information with the use of 40 mg tablet strength if required.

The study drug	Dosage form and strength
Osimertinib	40 mg Tablets 80 mg Tablets

The tablets can be taken with or without food and should be swallowed whole with water. The tablet should not be crushed, split or chewed.

If the patient is unable to swallow the tablet, it may first be dispersed in 50 mL of non-carbonated water. The tablet should be dropped in the water, without crushing, stirred until dispersed and immediately swallowed. An additional 100mL of water should be added to ensure that no residue remains and then immediately swallowed.

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

Any change from dosing schedule, dose interruptions, or dose reductions must be recorded in the CRF.

The study drug will be administered according to the prescribing information of the approved label by the investigator.

7.1 Concomitant and other treatments

As this study will be performed under clinical practice, the investigator may prescribe any other concomitant medication that he/she considers necessary for the patient as locally approved. Please refer to section 3.8 for restrictions.

7.2 Post Study Access to Study Treatment

The Treatment Phase will extend from Cycle 1, Day 1 to Cycle 6, Day 21; or until study drug discontinuation due to either disease progression or unacceptable toxicity; or other reasons whichever occurs first, as listed in Section 3.9. 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.

Patients receiving osimertinib at the time of study completion (i.e. after completion of treatment phase) may continue to receive osimertinib, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment or have not progressed clinically. They will be provided osimertinib treatment as per recommendation from treating physician on ethical basis. Post-trial access to osimertinib will be provided from local commercial supply though local distribution channel. Such patients will not be monitored after EOS visit.

8. Statistical Analyses by AstraZeneca

8.1 Statistical considerations

- Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first patient enrolled and any subsequent amendments will be documented.

8.2 Sample size estimate

The primary objective of the trial is to describe the safety profile of osimertinib in routine clinical practice and add to the limited burden of safety data on osimertinib currently available as assessed by the incidence of adverse events (AEs) (Serious and Non-serious AEs) observed during trial. Considering the epidemiology of metastatic NSCLC-adenocarcinoma subtype which are positive for EGFR sensitizing mutation and have progressed after EGFR-TKI based treatment in first line setting and prevalence of T790M-mutation after such progression, a sample size of 60 patients is expected to provide the following exact two sided 95% confidence interval for a list of percentages of patients reporting at least one AE (Julious and Campbell 2012).

Observed rate expressed as % (number of patients reporting at least one AE*)	Lower Limit of CI (%)	Upper Limit of CI (%)
0%	0	6.0
1%	0	7.8
2%	0.1	9.5
5%	1.0	13.9
10%	3.8	20.5
20%	10.8	32.3
30%	18.8	43.2
40%	27.6	53.5
50%	36.8	63.2

*the symptom could be any of the expected AE, unexpected AE or SAE. The calculation is based on the link between binomial and beta distributions.

8.3 Description of outcome variables in relation to objectives

Analysis will be conducted to evaluate the following as available in the CRF:

- Baseline characteristics: demographics, relevant medical history, disease characteristics, cancer treatment history.
- Exposure to the study drug
- Adverse events SAEs, AEs leading to dose modification or discontinuation, and AEs of special interest (for example interstitial lung disease/pneumonitis-like events; QTc prolongation events)
- Death due to AE, or unknown cause (except death due to disease progression).

8.4 Definitions of analysis sets

8.4.1 Safety analysis set

Safety analysis set will include all enrolled patients who received at least one dose of study medication during treatment period.

8.5 Methods for statistical analyses

Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, coefficient of variation, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. Shift tables will be provided to determine the change in reported outcomes from baseline.

8.5.1 Analysis of the primary variable (s)

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and CTCAE grade and will be listed individually by patient. Treatment-emergent adverse events are adverse events with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized.

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 investigational product (ie, the last dose 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.

Adverse events of special interest (for example interstitial lung disease/pneumonitis-like events; QTc prolongation events]) will be summarized separately.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). Parameters with predefined National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Electrocardiogram (ECG)

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

9. Study and Data Management by AstraZeneca

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and 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 protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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

9.2.1 Source data

Study sites will maintain source data in accordance with Good Clinical Practice (GCP) or local regulations.

9.2.2 Study agreements

The investigator at each site must comply with all the terms, conditions, and obligations of the Study Agreement for this study. In the event of any inconsistency between this study

protocol and the Study Agreement, the terms of the 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 Study Agreement shall prevail.

Agreements between the sponsor and the investigator must be in place before any study-related procedures can take place.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.3 Data management by delegate of AstraZeneca

Data management will be performed by CRO, according to the Data Management Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by CRO.

Data collected will include patient demographics, information needed to determine patient eligibility (including medical history, past and current disease characteristics, and tumour EGFR mutational status), exposure of the study drug (including starting dose, dose adjustments or discontinuations), investigator-reported efficacy (including tumour response and disease progression), and safety (including SAEs, AEs leading dose-modification).

Data will be entered in the web-based data capture (WBDC) system at the Investigator's site. The Investigator (or delegate) will be responsible for entering data into the WBDC system and according to the Investigator Instructions Manual. The Investigator Instructions Manual will also provide the study site with data entry instructions. The data collected through third party sources will be obtained and reconciled against study data. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered, reviewed and edited, the Investigator will be notified to sign the CRF electronically as per the agreed project process. A copy of the CRF will be archived at the Investigator's site.

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

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

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

Serious Adverse Event (SAE) Reconciliation

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

10. Ethical and Regulatory Requirements

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the sponsor's policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation.

- Study data will be stored in a computer database, maintaining confidentiality in accordance with relevant data protection and privacy legislation
- Patient data will be maintaining confidentiality in accordance with relevant data protection and privacy legislation
- For data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an IRB may require direct access to parts of the hospital or practice source records relevant to the study, including patients' medical history
- All data computer processed by AstraZeneca will be identified by study code and enrolment code (E-code)

10.3 Ethics and regulatory review

An Institutional Review Board (IRB) should approve the final 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 IRB, and to the study site staff.

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

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

Before enrolment of any patient into the study, the final 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 will handle the distribution of any of these documents to the national regulatory authorities.

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

The environment where the process of consent is conducted should be determined by the type of research being conducted but there should always be a period where a private, confidential, and "safe" setting is afforded to facilitate a constructive dialogue between the prospective patient and the person(s) involved in obtaining consent.

10.5 Changes to the protocol and informed consent form

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

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

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

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

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's IRB are to approve the revised Informed Consent Form before the revised form is used. If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

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

10.6 Audits and inspections

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

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APPENDIX A ADDITIONAL SAFETY INFORMATION

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

Life threatening

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

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

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

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

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

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same

pharmacological class? Or could the AE be anticipated from its pharmacological properties?

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

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

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

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

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

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

- Is there a known mechanism?

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

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

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