Statistical Analysis Plan	
Drug Substance	OSIMERTINIB
Study Code	D5161C00005
Version	1.0
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Protocol D5161C00005

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 non small cell lung cancer (NSCLC)

Redacted Statistical Analysis Plan

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Abbreviation	Term
AE	Adverse Event
ALP	Alkaline phosphatise
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomic Therapeutic Class
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
EGFR	Epidermal Growth Factor Receptor
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
PT	Preferred Term
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
WHO	World Health Organization

1. Introduction

This statistical analysis plan (SAP) contains definition of analysis population(s), derived variables and statistical methods for safety analysis.

This SAP is created on the basis of clinical study protocol D5161C00005 version 1.0 dated 06NOV2017 and case report form (CRF) version 1.0 dated 10JAN2018.

Note: In this document any text taken directly from the protocol is ***italicised***.

1.1 Study Rationale

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

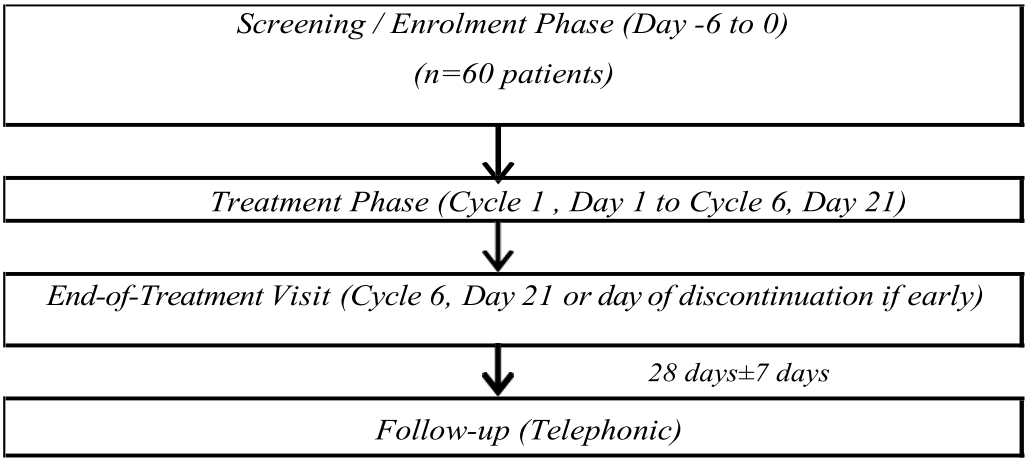
2. Study Objectives

To assess the safety of osimertinib among T790M positive NSCLC patients of India.

3. 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.

Schematic Overview of the Study



4. Sample Size and Power Considerations

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.*

In order to enroll approximately 60 patients, it is expected that approximately 70 patients will be screened.

5. Analysis Planned

5.1 General Analysis Definition

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 statistical analyses will be performed using Statistical Analysis System (SAS®), Version 9.4 or higher.

5.2 Visit Schedule

Patient participation will include a Screening/Enrolment Phase, a Treatment Phase, and a Follow-up Phase.

Phase/Visit	Definition
The Screening Phase	Up to 7 days prior to Cycle 1, Day 1.
The Treatment Phase	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. Each cycle of treatment is defined as 21 days of once daily Osimertinib treatment.
An End-of-Treatment (EoT) Visit	On Cycle 6, Day 21 of the study drug administration. 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.

The Follow-up Phase.	It 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. 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.

5.3 Pooling Strategy for Analysis Centers (if applicable)

Not Applicable

5.4 Analysis Population

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

Note: All the data for this study will be summarized using this population.

6. Randomization and Blinding

Not applicable - This is a single arm and open-label study.

7. Method of Analysis

7.1 Statistical Hypotheses

No formal hypothesis testing will be conducted.

7.2 Interim Analysis

Not Applicable

7.3 Handling of Missing Data

Missing results/events will not be imputed

Adverse events and concomitant medications with completely or partially missing assessment dates will have imputation performed as explained below for the purposes of calculation of durations or relativity to study medication.

For the end of a concomitant medication or adverse event:

- **If only Day of end date is missing**:

The last date of the month and year reported or the date of the final contact with the subject, whichever is earlier, will be used as the end date;

- **If Day and Month of end date are missing**:

The last date of year i.e. December 31 of the year reported or the date of the last study contact with the subject, whichever is earlier, will be used as the end date;

- **If Year of end date or complete end date is missing**:

If the adverse event or concurrent medication continues after the last study contact date, then no end date or time will be estimated.

For the start of a concomitant medication or adverse event:

- **If only Day of start date is missing:**
  - If the start year and month of medication/event are the same as that for the first dose date, then following approach will be used:
    - If the end date of medication/event is NOT before the first dose date or end date of medication/event is completely missing, then
      - Impute the start day as the day of first dose date;
    - Otherwise, impute the start day as 1.
  - If the start year and month of medication/event are NOT same as that for the first dose date, then
    - Impute the start day as 1.

- **If Day and Month of start date are missing:**
  - If start year of medication/event is same as first dose year, then following approach will be used:

i. For medication, impute the start Month as January and the Day as 1;
ii. For adverse event,
    - If the end date of event is NOT before the first dose date or end date of event is completely missing, then
      - Impute the start Month and Day as the Month and Day of first dose date;
    - Otherwise, impute the start Month as January and the Day as 1;
  - If start year of medication/event is NOT same as first dose year, then
    - Impute start Month as January and the Day as 1.

- **If Year of start date or complete start date is missing:**

If the year of start of medication/event is missing or start date is completely missing then no start date or time will be imputed.

Also for AE, compare the end date to the first dose date. If the AE end date is before the first dose date then the AE should be considered as a medical history. Otherwise, the AE will be considered as TEAE.

8. Statistical Analysis

8.1 Patient Disposition

A tabular presentation of the patient disposition will be provided. It will include the number of patients screened, enrolled/ assigned treatment, completed, as well as the number of dropouts, with reasons for discontinuation. All patients entered in the study will be accounted for in this. A listing will be presented to describe dates of screened,

assigned treatment, screen failed with reason, completion, early withdrawal, and the reason for early discontinuation, if applicable, for each patient.

8.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics data will be listed and summarized as appropriate using the safety analysis set.

8.3 Medical and Surgical History

Medical and Surgical history data will be listed and summarized by System Organ Class and Preferred Term according to MedDRA version 23.0 using the safety analysis set.

8.4 Prior and Concomitant Medications

Prior medications/procedures are those that are taken only prior to initial dose of study drug and concomitant medications/procedures are those taken while on study drug including the ones that started before the initial dose of study drug.

All prior and concomitant medications will be coded by Anatomic Therapeutic Class (ATC) and Preferred Term (PT) according to the World Health Organization (WHO) Drug Dictionary version March 1, 2020 and all prior and concomitant procedures will be coded using MedDRA Version 23.0.

Subjects using various prior or concomitant medications or who have undergone prior or concomitant procedures will be listed and summarized with numbers and percentages by ATC level 2 and Preferred Terms.

8.5 Study Drug Exposure

The extent of exposure to the study medication will be summarized and listed for safety analysis set. The extent of exposure to the study medication will be calculated as below:

Exposure (days) = Last date of dosing – First date of dosing + 1.

8.6 Efficacy Analysis

Not Applicable

8.7 Safety Analysis

8.7.1 Adverse Events

All adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. The intensity of adverse events is graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 or higher.

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 (i.e., 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.

An overall summary will be provided in terms of count and percentages for:

- AEs
- TEAEs
- Grade 3 and above TEAEs
- Grade 3 and above related TEAEs
- Treatment-related TEAEs
- Treatment-related serious TEAEs
- TEAEs leading to dose change/ interruption/ discontinuation
- Treatment related TEAEs leading to dose change/ interruption/ discontinuation
- Serious TEAEs
- Fatal TEAEs
- Related Fatal TEAEs

Summaries in terms of count and percentages by SOC and PT will be provided for the following:

- TEAEs
- Treatment-Emergent SAEs
- Grade 3 and above TEAEs
- Treatment-related TEAEs
- Grade 3 and above treatment-related TEAEs
- TEAEs leading to dose change/ interruption/ discontinuation
- Adverse Events of special interest

8.7.2 Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics (N, Mean, SD, Median, Minimum and Maximum) will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each cycle.

The baseline measurement is the last predose measurement taken before Cycle1 Day1.

Haematology/Haemostasis (whole blood)	***Clinical Chemistry (serum or plasma)***
Haemoglobin (Hb)	*Creatinine*
Leukocyte count	*Bilirubin, total*

Leukocyte differential count (absolute count) *Platelet count*	*Alkaline phosphatise (ALP)* *Aspartate transaminase (AST)* *Alanine transaminase (ALT)* *Albumin* *Potassium* *Calcium, total* *Sodium* *Creatine kinase (CK)*

Changes from baseline results will be presented in pre- versus post treatment 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.

Lab toxicity grades will be derived using NCI-CTCAE version 5.0.

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.

Physical Examinations

A listing of physical examinations will be provided.

8.7.3 Vital Signs

Descriptive statistics (N, Mean, SD, Median, Minimum and Maximum) will be provided for vital signs parameters (pulse rate, Systolic blood pressure, Diastolic blood pressure, weight) for the observed values and change from baseline at each cycle. The corresponding listing will be provided.

The baseline measurement is the last predose measurement taken before Cycle1 Day1.

8.7.4 Electrocardiogram

QTc Interval data will be descriptively summarized. Descriptive statistics (N, Mean, SD, Median, Minimum and Maximum) will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. *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 is further specified. *Frequency tabulations of the abnormalities will be made.*

The baseline measurement is the last predose measurement taken before Cycle1 Day1.

The number (%) of participants with maximum post-dose QTc values and maximum increases from baseline in the following categories will be tabulated for each cycle.

Safety QTc interval

QTc interval			
Absolute value	≥450 <480	>=480-<500 ≥480	>=500
Absolute change	30- <60	≥60	

8.7.5 Other Safety Parameters

WHO performance status will be summarized with number and percentage for each status per cycle.

A listing will be provided for each of the following:

- WHO performance status
- Pathology at Diagnosis
- Tumour sample
- Extent of disease
- Previous cancer therapy
- Previous radiotherapy
- Receptor status
- Pregnancy test
- Ejection fraction measurements
- Skin Reaction
- Pregnancy report
- Drug administration
- Drug accountability
- Drug Overdose
- Hospital admission details

9. Protocol Deviations

A full list of protocol deviations reported during the study will be compiled prior to database closure. This data will be listed as appropriate.