Study report

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Observational, Retrospective, Real World Study of Osimertinib for Patients with Locally advanced/Metastatic T790M Mutation-Positive NSCLC progressed on previous EGFR TKI

An observational, retrospective study conducted among locally advanced or metastatic T790M mutation-positive NSCLC patients progressed after EGFR TKI treatment to evaluate osimertinib effectiveness in a real world setting

Sponsor: AstraZeneca

CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Events
AESI	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Chemical
BM	Brain Metastases
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food And Drug Administration
FFPE	Formalin fixed paraffin embedded
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LM	Leptomeningeal Metastases
MC	Marketing Company
MedDRA	Medical Dictionary for Regulatory Activities
NSCLC	Non-Small Cell Lung Cancer
PD	Progressive Disease
PS	Performance status
PFS	Progression Free Survival
PR	Partial Response
PT	Preferred Term
RR	Response Rate

Abbreviation or special term	Explanation
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
SS	Safety Set
TKI	Tyrosine Kinase Inhibitor
TTE	Time To Event

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STUDY REPORT SYNOPSIS

Observational, Retrospective, Real World Study of Osimertinib for Patients with Locally advanced/Metastatic T790M Mutation-Positive NSCLC progressed on previous EGFR TKI

An observational, retrospective study conducted among locally advanced or metastatic T790M mutation-positive NSCLC patients progressed after EGFR TKI treatment to evaluate osimertinib effectiveness in a real world setting

Milestones:	CSP approved	Dec 2016
	Final protocol	Jan 2017
	Site initiation	Apr 2017
	Statistical Analysis Plan	Jan 2018
	Statistical Analysis Report	Oct 2018
	Clinical study report	Nov 2018
Phase of development:	Real word study	
Sponsor:	AstraZeneca	

This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Background/rationale:

Epidermal growth factor receptor (EGFR) gene mutations are detected in approximately 30-40% of non-small-cell lung cancer (NSCLC) in Asian population. EGFR tyrosine kinase inhibitor (TKI) can significantly improve objective response rate (ORR) and prolong progression free survival (PFS) in EGFR mutated locally advanced or metastatic NSCLC patients compared to platinum-based chemotherapy, with less adverse events and higher quality of life (QoL). However, the majority of patients will acquire resistance and have disease progression in 1 to 2 years. In approximately 60% of patients, the mechanism of acquired resistance is due to an amino acid substitution at position 790 in EGFR from a threonine to a methionine (T790M). Osimertinib is an oral, potent, irreversible third-

generation EGFR TKI that is selective for EGFR TKI sensitizing mutation and the T790M resistance mutation. Two phase 2 studies (AURA extension, AURA2) have demonstrated encouraging efficacy and tolerable toxicity. The pooled analysis of these two studies indicates an ORR of 66% (95% confidence interval [CI] 61, 71%), and a PFS of 11 months (95% CI 9.6, 12.4) in T790M mutation positive patients resistant to prior EGFR TKI treatment (James C-H Yang, 2016).

Based on these promising data, Osimertinib has been approved in major countries/districts worldwide, including US, Europe, Japan, and Korea. As a novel medicine approved based on phase II trials, the effectiveness, safety and QoL needs to be further investigated in a real world setting, where the patient population is less restricted and management is more flexible than in Phase II or Phase III trials.

Besides, T790M mutation has been proved to be an effective biomarker to select patients benefiting from osimertinib. Per indication use of osimertinib and other third generation TKIs will require confirmation for the presence of a T790M mutation. However, local data reflecting testing status including testing platform, sample tested, and turnaround time in China is still lacking. The current study will not only assess the effectiveness of osimertinib treatment in a real world setting, but will also help us to understand the real-world testing patterns among T790M mutation positive locally advanced or metastatic NSCLC patients who have progressed after EGFR TKI treatment.

Objectives:

Primary objectives

To assess the real world effectiveness of osimertinib treatment in locally advanced or metastatic Non-small cell lung cancer (NSCLC) patients with an epidermal growth factor receptor (EGFR) T790M mutation in terms of response rate (RR)

Secondary objectives

(1) To assess the real world effectiveness of osimertinib treatment in locally advanced or metastatic NSCLC patients with an EGFR T790M mutation in terms of progression free survival (PFS)
(2) To describe the pattern of T790M mutation testing, including turnaround time, sample type, testing techniques, EGFR subtype, T790M mutation abundance if tested quantitatively.
(3) To assess the real world safety profile of osimertinib
(4) To describe the treatment pattern including treatment lines and combination therapy (radiotherapy, surgery, etc.) in a real world setting

Study design:

This was an observational retrospective cohort study of locally advanced or metastatic T790M mutation positive NSCLC patients who progressed after EGFR tyrosine kinase inhibitor (TKI) therapy and received osimertinib treatment by treating physicians.

Patients who received osimertinib treatment at the participating site in Macau between May 1st 2016 and Oct 31st 2016 were enrolled consecutively. It was estimated that approximately 50 patients will be enrolled. Two sequential retrospective reviews were done at two time points mainly for two effectiveness end points, PFS and response rate respectively. Patients were followed historically forward in time. All study measures were collected through medical records.

Data source:

An eCRF was used to collect data required to address the study objectives. All study data collected were entered into the eCRF by the site investigator (or site staff). The site investigator was responsible for ensuring that the required data is extracted from the medical charts and entered in the eCRF accurately.

Study population:

The study cohort included locally advanced or metastatic T790M mutation positive NSCLC patients who progressed after EGFR TKI therapy (i.e., gefitinib, erlotinib, icotinib, afatinib) and received osimertinib treatment per the judgement of treating physicians in the participating site in Macau. 50 patients are anticipated to be enrolled in the study, the majority of which are estimated to be from mainland China.

Inclusion criteria:

- Above 18 years of age
- Locally advanced (stage IIIB) or metastatic (stage IV) NSCLC, not amenable to curative surgery or radiotherapy
- Confirmed T790M mutation
- Progressed on previous EGFR TKI treatment. Patients may have also received additional lines of treatment
- Received osimertinib treatment in the participating site between May 1st and Oct 31st 2016

Exclusion criteria:

- Enrollment in studies that prohibit any participation in this observational study

Statistical methods:

All analyses were descriptive in nature and no formal hypothesis testing were performed. Continuous study measures (e.g., age, duration of therapy) were reported descriptively with mean, standard deviation, median, minimum and maximum. Frequencies and percentages were used to document categorical measures of interest (e.g., number and proportion of patients undergoing tissue testing, cytology testing, and plasma testing respectively, number and proportion of patients with response per investigator assessment) and included 95% CIs for key outcome variables. Finally, Kaplan-Meier curves were generated and median PFS were reported, overall and by testing pattern and other characteristics of interest, if sample size permits (e.g., T790M mutation positive by tissue testing vs. plasma testing).

Results:

The primary efficacy endpoint is response rate (RR), was defined as the proportion of patients with a best response of "responding" to treatment by investigator assessment.

The best overall response of the 47 subjects included in FAS: 3 (6.4%) subjects were CR, 22(46.8%) were PR and 18 (38.3%) subjects were SD. The objective response rate with its 95% CI were 53.2% (38.1%, 67.9%).

Secondary endpoints include:

PFS, defined as the time from the date of first dose of osimertinib to the date of investigator-assessed disease progression or death from any cause during study. Subjects who have not progressed or died at the time of analysis were censored at the time of the latest date of assessment.

A total of 32 (68.1%) subjects were progression or death, in which 27 (57.4%) subjects were progression and 5 (10.6%) subjects were died without progression during study. The median PFS and the corresponding 95% CI were 10.25 months (6.08, 11.56).

Conclusion:

Efficacy Summary:

3 (6.4%) subjects were CR, 22(46.8%) were PR , 18 (38.3%) subjects were SD,4 (8.5%) subjects were PD. 25 (53.2%) subjects were CR+PR.The objective response rate with its 95% CI were 53.2% (38.1%, 67.9%).

A total of 32 (68.1%) subjects were progression or death, in which 27 (57.4%) subjects were progression and 5 (10.6%) subjects were died without progression during study. A total of 15 (31.9%) subjects were censored.

As the month increased, the PFS showed a downward trend and at risk showed a downward

trend. The median PFS and the corresponding 95% CI were 10.25 months (6.08, 11.56).

Safety Summary:

Of the 47 subjects included in SS, 1 subject died due to AE during the study, and the event was judged not related to osimertinib.

18 (38.3%) subjects were reported at least one on-treatment AE. The most frequently reported AEs were rash (7 subjects, 14.9%), fatigue (6 subjects, 12.8%) and nausea (5 subjects, 10.6%).

13 (27.7%) subjects were reported at least one adverse drug reaction. The most frequently reported adverse drug reactions were rash (7 subjects, 14.9%), fatigue (5 subjects, 10.6%) and nausea (4 subjects, 8.5%).

The reported AE (subject 0142) was chest discomfort, which was judged not related to osimertinib.

2 (4.3%) subjects experienced 2 SAEs. Each event occurred to one subject and only fatigue was judged related to osimertinib.

Only 1(2.1%) subject experienced on-treatment Interstitial lung disease/Pneumonitis-type events. And the AESI was judged with causality to osimertinib

Publications:

not applicable

AMENDMENT HISTORY

Date	Section of study report	Amendment or update	Reason
N/A	N/A	N/A	N/A

MILESTONES

Milestone	Date
CSP approved	Dec 2016
Final protocol	Jan 2017
Site initiation	Apr 2017
Statistical Analysis Plan	Jan 2018
Statistical Analysis Report	Oct 2018
Clinical study report	Nov 2018

1. BACKGROUND AND RATIONALE

1.1 Background

Lung cancer has been the most common cancer in the world for several decades. In 2012, there were an estimated 1.8 million new cases globally, representing 12.9% of all new cancers. It was also the most common cause of death from cancer, with 1.59 million deaths (19.4% of the total) (GLOBOCAN, 2012). NSCLC represents approximately 85% of all lung cancers (Howlader et al., 2015). At the time of diagnosis approximately 70% of NSCLC patients already have locally advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage (30-55%) of early stage NSCLC patients who have undergone surgery subsequently develop distant metastases and die as a result of their lung cancer (Pisters and Le Chevalier, 2005; Uramoto and Tanaka, 2014).

Treatment of patients with NSCLC is increasingly driven by the underlying molecular mutation. Epidermal growth factor receptor (EGFR) gene mutations are detected in approximately 30-40% of NSCLC in Asian population. EGFR tyrosine kinase inhibitor (TKI) can significantly improve objective response rate (ORR) and prolong progression free survival (PFS) in EGFR mutated locally advanced or metastatic NSCLC patients compared to platinum-based chemotherapy, with less adverse events and higher quality of life (QoL). However, the majority of patients will acquire resistance and have disease progression in 1 to 2 years. In approximately 60% of patients, the mechanism of acquired resistance is due to an amino acid substitution at position 790 in EGFR from a threonine to a methionine (T790M).

Several third generation EGFR-TKIs (e.g., osimertinib, rociletinib, HM61713) are currently under development specifically targeting T790M-mutant NSCLC.

osimertinib is a potent irreversible inhibitor of both the single EGFRm (TKI sensitivity-conferring mutation) and dual EGFRm/T790M (TKI resistance-conferring mutation) receptor forms of EGFR. Therefore osimertinib has the potential to provide clinical benefit to patients with advanced NSCLC harbouring both the single sensitivity mutations and the resistance mutation following prior therapy with an EGFR TKI, and could potentially prevent or delay the development of acquired resistance when used as a first line therapy in the EGFRm NSCLC patient population.

Non-clinical data provides evidence to warrant clinical investigation of osimertinib in first-line advanced and early stage EGFRm NSCLC. Unlike gefitinib, erlotinib, and afatinib, emergence of T790M does not appear to be a mechanism of preclinical resistance to osimertinib (Cross et al 2014a) and in vitro data supports a slower time to resistance in response to osimertinib treatment than that of currently approved EGFR TKIs. In a non-clinical mouse model of EGFRm NSCLC, osimertinib achieved superior durable complete

responses compared to those achieved with gefitinib (Cross et al 2014a).

Non-clinical and clinical studies continue to investigate mechanisms of resistance to EGFR TKIs including osimertinib, and as such a number of combination strategies. For instance, bypass signalling mechanisms such as MET amplification (Engelman et al 2007; Cross et al 2014b) or RAS-MAPK signalling (Cross et al 2014b; Ercan et al 2012) have been implicated in EGFR TKI resistance. Furthermore combination with immunotherapy checkpoint inhibitors such as anti-PD-L1 may provide alternative approaches to increase duration of benefit in EGFR mutant disease (Akbay et al 2013; Cross et al 2014b). Such emerging combination strategies warrant further clinical investigation.

Recently, TAGRISSO^{TM}（osimertinib）, an oral, potent, irreversible third-generation EGFR TKI selective for EGFR TKI sensitizing mutation and the T790M resistance mutation, gained approval by both the Food and Drug Administration (FDA) in the United States and European Medicines Agency (EMA) in the European Union. The US FDA in November 2015 granted accelerated approval of osimertinib for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA approved test, who have progressed on or after an EGFR TKI therapy. The EMA in February 2016 granted conditional approval of osimertinib for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

Those approval are based on two phase 2 studies (AURA extension, AURA2) demonstrating encouraging efficacy and tolerable toxicity. The pooled analysis of these two studies indicates an ORR of 66% (95% confidence interval [CI] 61, 71%), and a PFS of 11 months (95% CI 9.6, 12.4) in T790M mutation positive patients resistant to prior EGFR TKI treatment (James C-H Yang, 2016), suggesting that this drug will help address an unmet need in this patient population.

1.2 Rationale

As a novel medicine approved based on phase II trials, the effectiveness, safety and QoL needs to be further investegated in a real world setting, where the patient population is less restricted and management is more flexible than in Phase II or Phase III trials. Besides, T790M mutation has been proved to be an effective biomarker to select patients benefiting from osimertinib. Per indication use of osimertinib and other third generation TKIs will require confirmation for the presence of a T790M mutation. However, local data reflecting testing status including testing platform, sample tested, and turnaround time in China is still lacking. The current study will not only assess the effectiveness of osimertinib treatment in a real world setting, but will also help us to understand the real-world testing patterns among T790M mutation positive locally advanced or metastatic NSCLC patients who have progressed after EGFR TKI treatment.

2. OBJECTIVES AND HYPOTHESES

The objective of this study is to assess osimertinib effectiveness among locally advanced or metastatic T790M mutation positive NSCLC patients who have progressed after EGFR TKI therapy.

The specific study objectives that will be assessed include the following:

2.1 Primary objectives and hypotheses

To assess the real world effectiveness of osimertinib treatment in locally advanced or metastatic Non-small cell lung cancer (NSCLC) patients with an epidermal growth factor receptor (EGFR) T790M mutation in terms of response rate (RR).

2.2 Secondary objectives and hypotheses

(1) To assess the real world effectiveness of osimertinib treatment in locally advanced or metastatic NSCLC patients with an EGFR T790M mutation in terms of progression free survival (PFS)

(2) To describe the pattern of T790M mutation testing, including turnaround time, sample type, testing techniques, EGFR subtype, T790M mutation abundance if tested quantitatively.

(3) To assess the real world safety profile of osimertinib

(4) To describe the treatment pattern including treatment lines and combination therapy (radiotherapy, surgery, etc.) in a real world setting

2.3 Exploratory objectives and hypotheses

not applicable.

3. METHODOLOGY

3.1 Study design – general aspects

This was an observational retrospective cohort study of locally advanced or metastatic T790M mutation positive NSCLC patients who progressed after EGFR TKI therapy and received osimertinib treatment by treating physicians.

Patients who received osimertinib treatment at the participating site in Macau between May 1st 2016 and Oct 31st 2016 were enrolled consecutively. It was estimated that approximately 50 patients will be enrolled. Two sequential retrospective reviews were done at two time points mainly for two effectiveness end points, PFS and response rate respectively. Patients

were followed historically forward in time. All study measures were collected through medical records.

The study plan is depicted in Table 3-1 below.

Table 3-1 Study Plan

	Enrolment visit	**Treatment visit**	**Treatment Discontinuation visit**
	Index date	**(every 2months)**	**Treatment discontinue date**
Windows (days)	+/- 14 days	+/- 14 days	+/- 14 days
Inclusion/Exclusion criteria check	X		
Demographic characteristics	X		
Disease characteristics	X		
Molecular testing patterns	X		
Treatment received prior to osimertinib	X		
ECOG Performance status	X	X	X
CNS metastasis status	X	X	X
Treatment in combination with osimertinib	X	X	X
Concomitant medications	X	X	X
Osimertinib dosing (daily): - start dose; dose modification; interruption/discontinuation and reason for any dose change		X	X
Investigator-reported effectiveness		X	X
ADRs, SAEs, AESIs, AEs leading to dose modification and drug discontinuation		X	X

3.1.1 Data source

An eCRF was used to collect data required to address the study objectives. All study data collected were entered into the eCRF by the site investigator (or site staff). The site investigator was responsible for ensuring that the required data is extracted from the medical charts and entered in the eCRF accurately.

3.2 Study population

The study cohort included locally advanced or metastatic T790M mutation positive NSCLC patients who progressed after EGFR TKI therapy (i.e., gefitinib, erlotinib, icotinib, afatinib) and received osimertinib treatment per the judgement of treating physicians in the participating site in Macau. 50 patients are anticipated to be enrolled in the study, the majority of which are estimated to be from mainland China.

3.3 Inclusion criteria

- Above 18 years of age
- Locally advanced (stage IIIB) or metastatic (stage IV) NSCLC, not amenable to curative surgery or radiotherapy
- Confirmed T790M mutation
- Progressed on previous EGFR TKI treatment. Patients may have also received additional lines of treatment
- Received osimertinib treatment in the participating site between May 1st and Oct 31st 2016

3.4 Exclusion criteria

- Enrollment in studies that prohibit any participation in this observational study

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

4.1 Exposure

Drug exposure of patients is osimertinib treatment. Treatment duration, treatment dose and dose modification of osimertinib was at the discretion of the treating physician. Concomitant treatment, such as radiation therapy and surgery, was not restricted per the clinical practice of treating physician.

4.2 Outcomes

The following outcome measures were collected among patients included in the study cohort:

- Demographic characteristics: patient characteristics including age, gender, smoking status, family history of cancer will be collected.

- Disease characteristics: relevant medical history and clinical manifestation of tumor including tumor stage, histology, secondary metastasis, CNS metastasis, comorbidity burden, performance status.

- Molecular testing patterns, including turnaround time, sample type, testing techniques, EGFR subtype, T790M mutation abundance if tested quantitatively

- Relevant Concomitant medication: in case of AEs, SAEs, AESIs, AE leading to dose modification/study medication discontinuation.

- Osimertinib dosing: start dose, dose modification, dose interruptions, dose discontinuation and reason for any dose change.

- Disease assessment: as per institutional standard of care, data collected in the CRF includes date, assessment methods (e.g. CT scan), and response status at each follow-up visit. In case of disease progression, the progression assessment, progression date and methods used as per standard definitions and routine institutional standard of care will be collected in CRF.

- ADRs, SAEs, AESIs, AEs leading to dose modification and drug discontinuation: AE diagnosis/description, AE start and end date, AE intensity, maximum CTCAE grade, whether it's SAE or AESI, causality to osimertinib treatment, action taken and outcome of AE will be collected from medical record.

- Treatment Patterns including treatment received prior to and in combination with osimertinib treatment.

4.3 Other variables and covariates

not applicable

5. STATISTICAL ANALYSIS

5.1 Statistical methods – general aspects

5.1.1 Statistical Analysis Considerations

5.1.1.1 General Considerations

Unless otherwise specified, all descriptive statistics for continuous variables were reported using number of subjects (N), mean, standard deviation (SD), median, minimum and maximum. Categorical variables were summarized as number (percent) of subjects.

Unless otherwise specified in the description of the analyses, the confidence intervals (CIs) is 95% and all statistical tests (where appropriate) were performed using a two-sided test at a 5% significance level.

P-values was rounded to three decimal places. If a p-value is less than 0.001 it was reported as "<0.001." If a p-value is greater than 0.999 it was reported as ">0.999."

All analyses were descriptive in nature and no formal hypothesis testing was performed.

5.1.1.2 Definitions of Analysis Sets

Full Analysis Set (FAS): All enrolled subjects who received at least one dose of study drug with efficacy data collected.

Safety Set (SS): All enrolled subjects who received at least one dose of study drug with safety data collected.

5.1.1.3 Examination of Subgroups

No subgroup analyses were performed for this study.

5.1.1.4 Pooling of Centers

Not applicable.

5.1.2 Statistical Analysis

5.1.2.1 Subject Information

5.1.2.1.1 Disposition of Subjects

The number of subjects enrolled was calculated.

The number (percentage) of subjects who are in FAS/SS, who completed the study and who discontinued from the study and primary reasons for discontinuation were tabulated.

Subject disposition data was listed for all enrolled subjects.

5.1.2.1.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics for the FAS were tabulated using descriptive statistics.

Continuous demographic variables included：

- Age
- Years of smoking

Categorical variables included:

- Gender
- Age group (<65 years, and >=65 years)

- Smoking status (current smoker, previous smoker, non-smoker, and unknown)
- Daily smoking number category (<1pack, and >=1pack)
- Family history of cancer

Demographic and baseline characteristics data were also listed by subject.

5.1.2.1.3 Disease Characteristics

Disease characteristics for the FAS were presented using descriptive statistics. Disease characteristics variables included:

- Disease diagnosis
- Stage (at index date)
- Tumor TNM stage (at index date)
- Tumor histology at diagnosis
- Organs and location of metastases
- Were there any CNS metastases at progression
- Were there any BM metastases at progression
- Were there any LM metastases at progression
- Were there any CNS metastases at index date
- Were there any BM metastases at index date
- Were there any LM metastases at index date
- Presence of other primary malignancy (at diagnosis)
- Other comorbidities of interest (at index date)

Disease Characteristics were listed by subject.

5.1.2.1.4 Medical History

Medical history was analyzed for the FAS.

The Medical History was coded by using Medical Dictionary for Regulatory Activities (MedDRA 19.1).

Medical history was summarized by System Organ Class (SOC) alphabetically and Preferred Term (PT) in decreasing order of frequency.

Medical history was also listed by subject.

5.1.2.1.5 Prior and Concomitant Therapy

Prior and Concomitant Therapy were analyzed for the FAS.

Concomitant medications were coded using the World Health Organization (WHO) Drug Reference List and the Anatomical Therapeutic Chemical (ATC) code.

Prior and concomitant medication were summarized by ATC classification 1st level (alphabetically) and ATC classification 2nd level (in decreasing order of frequency). These medications will be tabulated separately for:

1) Prior medication, defined as medications that stopped prior to the first dose of study drug (i.e. with end date before date of 1st osimertinib administration)

2) Concomitant medication, defined as medications that (1) started before the first dose of study drug and are continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the last dose (i.e. medication that was not stopped before date of 1st osimertinib administration and not started after the study end visit)

If the timing of the dose of a concomitant medication cannot be established in relation to the administration of osimertinib, it was considered as concomitant medication.

Concomitant medications were also listed by subject.

5.1.2.1.6 Treatment received before osimertinib

The analyses of Treatment received before osimertinib were performed in FAS.

The treatment types (chemotherapy, surgery, immunotherapy, targeted therapy or radiation) were summarized as number (percent) of subjects. For each treatment type, line (s) of treatment, average treatment duration and evidence of treatment related to central nervous system (CNS) metastases were calculated.

A listing of treatment received before osimertinib was generated.

5.1.2.1.7 Treatment received in combination with osimertinib

The analyses of Treatment received in combination with osimertinib were performed in FAS.

The treatment types (surgery, radiation or other treatment) were summarized as number (percent) of subjects. For each treatment type, subtype, average treatment duration and evidence of treatment related to CNS metastases were calculated.

A listing of treatment received in combination with osimertinib was also generated.

5.1.2.1.8 Molecular Testing Patterns

5.1.2.1.8.1 Turnaround Time

Turnaround time was tabulated using descriptive statistics (i.e. N, mean, SD, median, minimum, maximum) for the FAS.

5.1.2.1.8.2 Sample Type

Sample type include tissue, plasma, cytology, urine or other. The "Fresh frozen tissue" and "Formalin fixed paraffin embedded (FFPE) tissue" reported on the CRF were classified as tissue. The numbers and percentages of patients for each type were calculated for FAS.

5.1.2.1.8.3 Testing Techniques Performed

The numbers and percentages of patients for each testing techniques were calculated for FAS.

5.1.2.1.8.4 Testing Laboratory Type

The same analysis methods used for testing techniques performed were used for testing laboratory type.

5.1.2.1.8.5 EGFR Mutation Subtype

The same analysis methods used for testing techniques performed were used for EGFR mutation subtype.

5.1.2.1.8.6 T790M Mutation Tested by Quantitative Method

The same analysis methods used for testing techniques performed were used for T790M mutation tested by quantitative method.

A listing of T790M mutation testing was also be generated.

5.1.2.2 Efficacy Analysis

5.1.2.2.1 Primary Efficacy Analysis

The primary analyses were performed for the FAS.

The primary efficacy endpoint is response rate (RR), defined as the proportion of patients with a best response of "responding" to treatment by investigator assessment. The numbers and percentages of patients with a best response of complete response (CR) or partial response (PR) and its 95% confidence interval were calculated based on the evaluable patients.

The response data were also listed by subject.

5.1.2.2.2 Secondary Efficacy Analyses

5.1.2.2.2.1 Progression Free Survival (PFS)

PFS, defined as the time from the date of first dose of osimertinib to the date of investigator-assessed disease progression or death from any cause during study. Subjects who have not progressed or died at the time of analysis were censored at the time of the latest date of assessment.

PFS was performed for the FAS.

PFS was analyzed using the Kaplan-Meier product-limit method. Summary statistics, including median progression free survival time and the corresponding 95% CI, and related curves were presented.

5.1.2.3 Safety Analysis

All safety analyses were performed on the Safety Set.

5.1.2.3.1 Extent of Exposure

Mean, SD, median, minimum, and maximum were provided for time on treatment.

Time on treatment in days was derived from the following formula:

Time on treatment (days) = (date of last dose) – (date of first dose) + 1;

The number (percentage) of subjects who have dose change were calculated. In addition, type and the reason for dose change were also summarized.

A separated data listing was provided for exposure.

5.1.2.3.2 Adverse Events

AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA 19.1).

Adverse Events were collected from the time of starting osimertinib treatment under study throughout the treatment period.

Only on-treatment period AEs were presented in summary tables. AEs in the on-treatment period are defined as those with onset from the day of starting osimertinib treatment under study throughout the treatment period. If an AE has a missing onset date then unless the end date of the AE indicates otherwise, this was considered an on-treatment event. Similarly, if an AE has a partial onset date, then unless the partial onset date or the end date indicates otherwise, this was considered an on-treatment AE.

Missing values were treated as missing.

A separated data listing was also provided for AEs.

5.1.2.3.2.1 Overview of On-treatment Period Adverse Events

An on-treatment period AEs summary table was presented including the number and percentage of subjects reporting at least one AE, and the total number of events reported for each of the following categories:

- All AEs
- All adverse events of special interest (AESI)
- AESI related to osimertinib
- Severe AEs
- Adverse drug reactions (ADRs), defined as AEs with causality to osimertinib judged as yes
- AEs leading to withdrawal
- Serious AEs
- Deaths.

5.1.2.3.2.2 Incidence of Adverse Events

Summary tables were prepared for the incidence of on-treatment period AEs by MedDRA SOC sorted alphabetically and PT sorted in decreasing frequency of occurrence.

The number and percentage of subjects reporting at least one AE, and the total number of events reported were presented.

Summary tables were prepared for

- All AEs
- Serious AEs
- AEs by causality (rating as yes/ no)
- AEs by intensity (mild/moderate/severe)
- AEs by CTCAE grade (Grade 1/Grade 2/ Grade 3/ Grade 4/ Grade 5)
- ADRs by intensity (mild/moderate/severe)

5.1.2.3.2.3 AESI

Interstitial lung disease/Pneumonitis-type events and QTc-prolongation events are the AESI of this study. Only AESI related to osimertinib were analysed.

Summary tables were provided for the incidence of AESI by PT sorted in decreasing frequency of occurrence.

The number and percentage of subjects reporting at least one AESI, and the total number of events reported were presented.

Summary tables were prepared for

- All AESI
- Serious AESI
- AEs by causality (rating as yes/ no)
- AEs by intensity (mild/moderate/severe)
- AEs by CTCAE grade (Grade 1/Grade 2/ Grade 3/ Grade 4/ Grade 5)

5.1.2.3.2.4 ECOG Performance status

The numbers and percentages of each grade were calculated by visit.

5.1.3 Changes to the Statistical Analysis Plan

There were no changes to these planned statistical analyses.

5.2 Bias

not applicable

5.2.1 Methods to minimize bias

not applicable

5.2.2 Adjustment for multiple comparisons

not applicable

5.3 Sample size and power calculations

Precision estimates were calculated considering a time to event (TTE) end point (i.e., PFS of osimertinib treatment) and a categorical end point (i.e., response rate). The following assumptions were considered in estimating precision around the TTE outcome:

- TTE: PFS of osimertinib treatment is estimated to be around 10 month
- Categorical end point: response rate is estimated to be approximately 60%

Sample size and corresponding precision estimates for the two outlined measures are shown in Tables 5-1 and 5-2:

Table 5-1: Precision estimates* for TTE outcome (progression free survival)

N	Assumed median PFS (months)					
	9		10		11	
	n events	95% CI median PFS*	n events	95% CI median PFS*	n events	95% CI median PFS*
50	37	6.5 — 12.4	35	7.2 — 13.9	34	7.9 — 15.4
100	75	7.2 — 11.3	72	7.9 — 12.6	68	8.7 — 14
150	114	7.5 — 10.8	109	8.3 — 12.1	105	9.1 — 13.3
200	150	7.7 — 10.6	141	8.5 — 11.8	134	9.3 — 13

*based on the formula in Collett 1994

Table 5-2 Precision estimates* for categorical endpoint (response rate)

N	Assumed response rate 60%
	95% CI for RR
50	46.4-73.6
100	50.4-69.6

* using normal approximation

Sample size of the study is estimated to be 50 patients. As shown in charts above, this sample size will be sufficient to estimate a median PFS of 10 months with 95% confidence interval of 7.2-13.9 months and allow a precision of ±13.6% around a point estimate for response rate of 60% in a real-world setting.

5.4 Data quality

Data Collection

Data were entered in the web-based data capture (WBDC) system at the Investigator's site. The Investigator (or delegate) was responsible for entering data into the WBDC system and according to the Investigator Instructions Manual. The Investigator Instructions Manual also provided the study site with data entry instructions.

Data entered in the WBDC system were immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered, reviewed and edited, the Investigator was notified to sign the CRF electronically as per the agreed project process. A copy of the CRF was archived at the Investigator's site.

Monitoring

Before the first subject was recruited into the study, the local Marketing Company, MEOR Delivery Director, MEOR Operations Lead or CRO Representative would:

- Establish the adequacy of the facilities and the investigator's capability to appropriately select the sample

- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regards to protocol compliance, and the responsibilities of AstraZeneca or its representatives. This will be documented in an Observational Study Primary Agreement between AstraZeneca/delegate and the investigator.

- During the study the local MC representative or delegate can implement different activities to assure compliance with AZ standards of quality. These activities could include but are not limited to:

Contacts with the sites to:

- Provide information and support to the investigator(s)

- Confirm that the research team was complying with the protocol and that data were being accurately recorded in the case report forms (CRFs)

- Ensure that the CRFs were completed properly and with adequate quality.

Monitoring activities for:

- Checking that subjects exist in medical records

The extent and nature of monitoring were decided during the study planning based on design, complexity, number of subjects, number of sites, etc. Observational Research Center (multi country) /Marketing Company (MC) gave some recommendations that could be locally adapted.

Different signals (e.g., high rejection rate in a site) should be used as potential identification of low protocol compliance by investigators.

If these or any other signal occurs or if the local coordinator is suspicious of a potential non-optimal level of protocol compliance by the site investigator, specific measures should be adopted to evaluate the situation, identify the issue and implement specific action plans to correct the situation.

Training of Study Site Personnel

The Principal Investigator ensured that appropriate training relevant to the Observational Study was given to investigational staff, and that any new information relevant to the performance of this Observational Study was forwarded to the staff involved.

6. RESULTS

6.1 Study participation

A total of 47 subjects were enrolled and all of them received at least one dose of study drug with safety data and efficacy data.

Subject disposition with respect to the number of completed and discontinued subjects including reasons for discontinuation and analysis sets are summarized in Table 6-1.

Among 47 subjects in the FAS, 34 (72.3%) subjects completed the study, 13 (27.7%) subjects discontinued from the study and all the reasons for discontinuation were death.

Individual disposition data are listed in Appendix Listing 12.2.1.

Table 6-1 Subject Disposition

	Osimertinib (N=47)
All Enrolled	47
Full Analysis Set [1]	47 (100%)
Safety Set [2]	47 (100%)
Completed	34 (72.3%)
Discontinued	13 (27.7%)
Death	13 (27.7%)

Percentages are based on the number of subjects in Full Analysis Set.
[1] Full Analysis Set includes all enrolled subjects who received at least one dose of study drug with efficacy data collected.
[2] Safety Set includes all enrolled subjects who received at least one dose of study drug with safety data collected.
Source Date：Appendix Table 10.1.1.

6.2 Main results

6.2.1 Demographics and Baseline Characteristics

Demographics Characteristics of FAS are summarized in Table 6-2.

Of the 47 subjects included in FAS, the average age was 58.2 years, ranging from 37 to 83 years,

and majority (33 subjects,70.2%) of subjects were included in "<65 years". Female subjects (32 subjects,68.1%) were more than male subjects (15 subjects,31.9%). The status of smoking in most subjects (34 subjects,72.3%) was "Unknown", 12 subjects (25.5%) were non-smokers, 1 subject was current smoker with 20 years of smoking.

Relatives (parents, siblings) of 3 (6.4%) subjects (subject 0111、subject 0123 and subject 0132) were suffered from cancer, and all of them were suffered from lung cancer; relatives of 13(27.7%) subjects had no cancer; relatives of the others (31 subjects,66.0%) were "Unknown".

The demographic data are listed in Appendix Listing 12.2.2.1 and Appendix Listing 12.2.2.2.

Table 6-2 Demographics Characteristics - Full Analysis Set

	Osimertinib (N=47)
Age	
N	47
Mean (SD)	58.2 (11.35)
Median	59.0
Min, Max	37, 83
Age Group	
<65 years	33 (70.2%)
>=65 years	14 (29.8%)
Gender	
Male	15 (31.9%)
Female	32 (68.1%)
Smoking Status	
Current Smoker	1 (2.1%)
Non-smoker	12 (25.5%)
Unknown	34 (72.3%)
Years of Smoking	
N	1
Mean (SD)	20.0 (-)
Median	20.0
Min, Max	20, 20
Daily Smoking Number Category [1]	
>=1 pack	1 (100%)

	Osimertinib (N=47)
Relatives (parents, siblings) Suffer from Any Cancer	
Yes	3 (6.4%)
No	13 (27.7%)
Unknown	31 (66.0%)
Relatives (parents, siblings) suffer from lung cancer [2]	
Yes	3 (100%)

Percentages are based on the number of subjects in Full Analysis Set.
[1] Percentages are based on the number of current smoker or previous smoker.
[2] Percentages are based on the number of subjects whose relatives suffered from any cancer.
Source Date：Appendix Table 10.1.2.

6.2.2 Disease Characteristics

Disease Characteristics of FAS are summarized in Table 6-3.

All 47 (100%) subjects were diagnosed with metastatic T790 mutation-positive NSCLC, and all of them were diagnosed as adenocarcinoma.

At index date, all of the subjects were stage IV, 28 (59.6%) subjects had bone metastases, 25 (53.2%) subjects had lymph nodes metastases, 17 (36.2%) subjects had Pleura metastases. 11 (23.4%) subjects were known to have central nervous system (CNS) metastases, 1 (2.1%) subject was known to have brain metastases(BM), 1 (2.1%) subject was known to have leptomeningeal metastases(LM). At progression, 11 (23.4%) subjects were known to have CNS metastases.

The individual disease characteristics data are listed by subject in Appendix Listing 12.2.2.3.

Table 6-3 Disease Characteristics - Full Analysis Set

	Osimertinib (N=47)
Disease Diagnosis	
Metastatic T790M Mutation-Positive NSCLC	47 (100%)
Stage (at index date)	
IV	47 (100%)
Tumor Histology at Diagnosis	
Adenocarcinoma	47 (100%)
Organs and Location of Metastases at Index Date	

	Osimertinib (N=47)
None	3 (6.4%)
Liver	4 (8.5%)
Bone	28 (59.6%)
Brain	11 (23.4%)
Adrenal	2 (4.3%)
Lymph Nodes	25 (53.2%)
Pericardial Effusion	1 (2.1%)
Pleura	17 (36.2%)
Other	6 (12.8%)
Were There Any CNS Metastases at Progression	
Yes	11 (23.4%)
No	33 (70.2%)
Unknown	3 (6.4%)
Were There Any BM Metastases at Progression	
Unknown	11 (23.4%)
Missing	36 (76.6%)
Were There Any LM Metastases at Progression	
Unknown	11 (23.4%)
Missing	36 (76.6%)
Were There Any CNS Metastases at Index Date	
Yes	11 (23.4%)
No	33 (70.2%)
Unknown	3 (6.4%)
Were There Any BM Metastases at Index Date	
Yes	1 (2.1%)
Unknown	10 (21.3%)

	Osimertinib (N=47)
Missing	36 (76.6%)
Were There Any LM Metastases at Index Date	
Yes	1 (2.1%)
Unknown	10 (21.3%)
Missing	36 (76.6%)
Presence of Other Primary Malignancy (at diagnosis)	
None	45 (95.7%)
Breast	1 (2.1%)
Unknown	1 (2.1%)
Other Comorbidities of Interest (at index date)	
None	34 (72.3%)
Hypertension	7 (14.9%)
COPD	1 (2.1%)
Pneumonia	3 (6.4%)
Pulmonary Fibrosis	1 (2.1%)
Other	8 (17.0%)

Percentages are based on the number of subjects in Full Analysis Set.
Source Date：Appendix Table 10.1.3.

6.2.3 Medical History

All medical history events were coded using MedDRA 19.1 and summarized by SOC alphabetically and PT in decreasing order of frequency in Appendix Table 10.1.4.

A total of 47 (100%) subjects had at least one medical history event. The most frequently reported medical history events in SOC were: neoplasms benign, malignant and unspecified (incl cysts and polyps) (100%); Surgical and medical procedures (31.9%) ; respiratory, thoracic and mediastinal disorders (17.0%).

Medical history data are listed by subject in Appendix Listing 12.2.3.1.

6.2.4 Prior and Concomitant Therapy

No prior medication was recorded for this study.

Concomitant medications were coded with WHODD ATC classification (version Dec 1, 2016) and summarized in Appendix Table 10.1.5.2.

A total of 8 (17%) subjects received at least one concomitant medication. No medication was taken more than 10% of the subjects.

Prior and concomitant medication data are listed by subject in Appendix Listing 12.2.3.2.

6.2.5 Treatment Received Before Osimertinib

All treatment received before osimertinib are summarized in Appendix Table 10.1.6.1.

Before osimertinib, 22 (46.8%) subjects received chemotherapy, 38 (80.9%) subjects received at least one surgery, 1(2.1%) subject received immunotherapy, all (100%) subjects received targeted therapy and 9 (19.1%) subjects received radiation.

Treatment received before osimertinib are listed by subject in Appendix Listing 12.2.3.3.

6.2.6 Treatment Received in Combination with Osimertinib

All treatment received in combination with osimertinib are summarized in Appendix Table 10.1.7.1.

A total of 1 (subject 0107) subjects received radiation (stereotactic body radiation therapy used for bone metastasis).

Treatment received in combination with osimertinib are listed by subject in Appendix Listing 12.2.3.4.

6.2.7 Molecular Testing Patterns

Molecular Testing Patterns are summarized in Appendix Table 10.2.3.1.

Of the 47 subjects included in FAS, all subjects were performed molecular testing.

6.2.7.1 Turnaround Time

Only 34 subjects had the records of turnaround time, the average time was 5.1 days, ranging from 0 to 14 days, median was 6.0 days.

6.2.7.2 Sample Type

Samples from 22 (46.8%) subjects were plasma, 16 (34.0%) subjects were tissue, 4 (8.5%) subjects were cytology and 5 (10.6%) subjects were other.

6.2.7.3 Testing Techniques Performed

ARMS was performed for 13 (27.7%) subjects, NGS was performed for 4 (8.5%) subjects, DdPCR was performed for 2 (4.3%) subjects and other testing techniques were performed for 28 (59.6%) subjects.

6.2.7.4 Testing Laboratory Type

Commercial laboratory made up 42.6%, and others made up 57.4%.

6.2.7.5 EGFR Mutation Subtype

14 (29.8%) subjects were T790M+Exon 21 L858R, 13 (27.7%) subjects were T790M only, 13 (27.7%) subjects were T790M+Exon 19 deletions, 5 (10.6%) subjects were T790M+Exon 19 other, 1 (2.1%) subjects were T790M+Exon 21 other and 1 (2.1%) subjects were T790M+Exon 19 other+ Exon 21 L858R.

6.2.7.6 T790M Mutation Tested by Quantitative Method

BRAF KRAS and Immunohistochemical local excision biopsy examination were performed on one subject separately.

7. EFFICACY EVALUATION

7.1.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is response rate (RR), was defined as the proportion of patients with a best response of “responding” to treatment by investigator assessment. The best response rate is summarized in Table 7-1.

The best overall response of the 47 subjects included in FAS: 3 (6.4%) subjects were CR, 22(46.8%) were PR and 18 (38.3%) subjects were SD. The objective response rate with its 95% CI were 53.2% (38.1%, 67.9%).

The individual response data are listed by subject in Appendix Listing 12.2.4.1.

Table 7-1 Best Response Rate - Full Analysis Set

	Osimertinib (N=47)
Evaluable Subjects	47
Complete Responses (CR)	3 (6.4%)
95% CI	1.3%, 17.5%
Partial Responses (PR)	22 (46.8%)
95% CI	32.1%, 61.9%

	Osimertinib (N=47)
Stable Disease (SD)	18 (38.3%)
95% CI	24.5%, 53.6%
Progressive Disease (PD)	4 (8.5%)
95% CI	2.4%, 20.4%
CR+PR	25 (53.2%)
95% CI	38.1%, 67.9%

Percentages are based on the number of evaluable subjects.

Clopper Person method is used to calculate the 95% CI.

Source Date：Appendix Table 10.2.1.1.

7.1.2 Secondary Efficacy Endpoint(s)

7.1.2.1 Progression Free Survival (PFS)

PFS, defined as the time from the date of first dose of osimertinib to the date of investigator-assessed disease progression or death from any cause during study. Subjects who have not progressed or died at the time of analysis were censored at the time of the latest date of assessment. The results based on Kaplan-Meier product-limit method of PFS are summarized in Table 7-2 and presented in Figure 7-1.

A total of 32 (68.1%) subjects were progression or death, in which 27 (57.4%) subjects were progression and 5 (10.6%) subjects were died without progression during study. The median PFS and the corresponding 95% CI were 10.25 months (6.08, 11.56).

The PFS data are listed by subject in Appendix Listing 12.2.4.2.

Table 7-2 Kaplan-Meier Estimates for Progression-Free Survival - Full Analysis Set

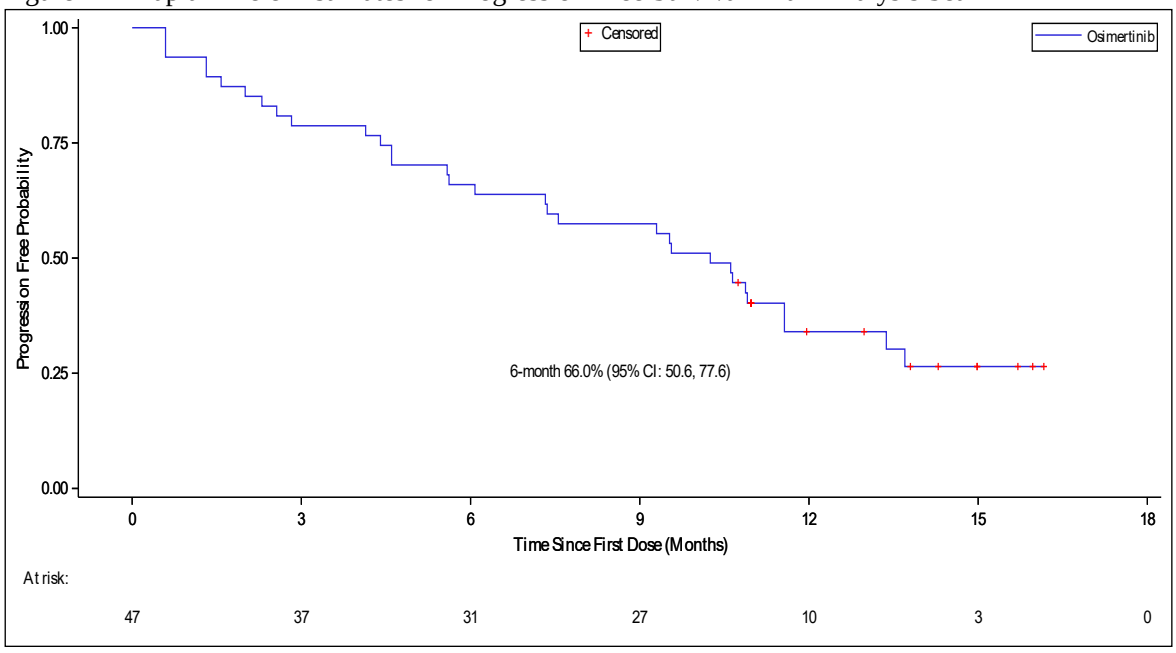
	Osimertinib (N=47)
Number of Events (%)	32 (68.1)
Progression	27 (57.4)
Death	5 (10.6)
Censored (%)	15 (31.9)
Median Progression Free Survival in Months (95% CI)	10.25 (6.08, 11.56)
Probability (95% CI) / at Risk	

	Osimertinib (N=47)
Month 3	0.787 (0.641, 0.879)/37
Month 6	0.660 (0.506, 0.776)/31
Month 9	0.574 (0.421, 0.701)/27
Month 12	0.340 (0.204, 0.482)/10
Month 15	0.265 (0.135, 0.414)/3

Percentages are based on the number of subjects in the Full Analysis Set.

Source Date：Appendix Table 10.2.2.1.

Figure 7-1 Kaplan-Meier Estimates for Progression-Free Survival - Full Analysis Set



Source Date：Appendix Figure 10.2.2.1.

7.1.3 Efficacy Summary

The best overall responses of the 47 subjects included in FAS: 3 (6.4%) subjects were CR, 22(46.8%) were PR and 18 (38.3%) subjects were SD. The objective response rate with its 95% CI were 53.2% (38.1%, 67.9%).

A total of 32 (68.1%) subjects were progression or death, in which 27 (57.4%) subjects were progression and 5 (10.6%) subjects were died without progression during study. The median PFS and the corresponding 95% CI were 10.25 months (6.08, 11.56).

8. SAFETY EVALUATION

8.1 Extent of Exposure

Exposure data of osimertinib are summarized in Table 8-1.

Of the 47 subjects included in SS, the average duration of treatment was 37.736 weeks, and median value was 46.571 weeks.

During the trial, 1 (2.1%) subject experienced dose modifications and 31(66.0%) subjects experienced dose discontinuation. The primary reasons for dose discontinuation were disease progression (22 subjects, 46.8%), death (4 subjects, 8.5%), patients' preference (3 subjects, 6.4%) and other (2 subjects, 4.3%).

The individual exposure data are listed by subject in Appendix Listing 12.2.3.5.

Table 8-1 Extent of Exposure - Safety Analysis Set

	Osimertinib (N=47)
Duration of Treatment (weeks)[1]	
N	47
Mean (SD)	37.736 (20.614)
Median	46.571
Min, Max	4.571, 70.286
Cumulative Dose (mg)[2]	
N	47
Mean (SD)	21223.8 (11449.2)
Median	26080.0
Min, Max	2560, 39360
Patients with Dose Changes	31 (66.0%)
Dose Modification	1 (2.1%)
Reason for Dose Modification	
Other	1 (2.1%)
Dose Discontinuation	31 (66.0%)
Reason for Dose Discontinuation	
Disease Progression	22 (46.8%)
Patients' Preference	3 (6.4%)
Death	4 (8.5%)
Other	2 (4.3%)

[1] Duration of treatment (weeks) = (Date of last dose – date of first dose + 1)/7.
[2] Cumulative dose (mg) = Sum of all actual doses taken.
Source Date：Appendix Table 10.3.0.1.

8.2 Adverse events

8.2.1 Adverse Events

All AEs were coded using MedDRA, version 19.1.

8.2.1.1 Brief Summary of On-treatment Period Adverse Events

The overall on-treatment period AEs are summarized in Table 8-2.

A total of 18(38.3%) subjects experienced 31 on-treatment AEs; 13(27.7%) subjects experienced 21 adverse drug reactions events. Most of the on-treatment AEs were of the mild or moderate grade, only 2 (4.3%) subjects reported 2 severe on-treatment AEs. Only 1(2.1%) subject reported 1 AESI and the AESI was judged with causality to osimertinib. A total of 2 (4.3%) subjects experienced 2 on-treatment SAEs; one death was reported. One AE was reported to lead the subject withdrawn from the treatment.

Details of all on-treatment period AEs of SS are listed in Appendix Listing 12.2.5.1.1.

Table 8-2 Overview of On-treatment Period Adverse Events - Safety Analysis Set

Category	**Osimertinib (N=47) n (%) E**
Any AEs	18 (38.3%) 31
Any Adverse Events of Special Interest (AESI)	1 (2.1%) 1
AESI Related to Osimertinib	1 (2.1%) 1
Severe AEs [1]	2 (4.3%) 2
Adverse Drug Reactions (ADRs) [2]	13 (27.7%) 21
AEs Leading to Withdrawal	1 (2.1%) 1
Any Serious AEs [3]	2 (4.3%) 2
AEs Leading to Death	1 (2.1%) 1

E = number of events.
On-treatment AE is any AE with onset from the day of starting osimertinib treatment under study throughout the treatment period.
[1] Including any on-treatment adverse events with missing intensity.
[2] Defined as AEs with causality to osimertinib judged as yes.
[3] Including any on-treatment adverse event with missing seriousness.
Percentages are based on the number of subjects in Safety Analysis Set.
Source Date：Appendix Table 10.3.1.1.1.

8.2.1.2 Overall Incidence of On-treatment Period Adverse Events

The overall on-treatment period AEs by SOC and PT are summarized in Table 8-3.

The most frequently reported primary SOCs were gastrointestinal disorders (9 subjects, 19.1%), general disorders and administration site conditions (8 subjects, 17.0%) and skin and subcutaneous tissue disorders (7 subjects, 14.9%).

The most frequently reported ae was rash (7 subjects, 14.9%), fatigue (6 subjects, 12.8%) and nausea (5 subjects, 10.6%).

The most frequently reported adverse drug reactions were rash (7 subjects, 14.9%), fatigue (5 subjects, 10.6%) and nausea (4 subjects, 8.5%). The incidence of on-treatment period adverse drug reactions by SOC, PT are summarized in Appendix Table 10.3.1.2.5.

Table 8-3 Incidence of On-treatment Period AEs by System Organ Class and Preferred Term - Safety Analysis Set

System Organ Class Preferred Term	**Osimertinib (N=47)** **n (%) E**
Any On-treatment AEs	18 (38.3%) 31
Gastrointestinal disorders	9 (19.1%) 10
Nausea	5 (10.6%) 5
Gastritis	2 (4.3%) 2
Abdominal discomfort	1 (2.1%) 1
Dry mouth	1 (2.1%) 1
Gastrooesophageal reflux disease	1 (2.1%) 1
General disorders and administration site conditions	8 (17.0%) 10
Fatigue	6 (12.8%) 6
Chest discomfort	2 (4.3%) 2
Pain	1 (2.1%) 1
Pyrexia	1 (2.1%) 1
Infections and infestations	1 (2.1%) 1
Pneumonia	1 (2.1%) 1
Respiratory, thoracic and mediastinal disorders	3 (6.4%) 3
Dyspnoea	2 (4.3%) 2
Cough	1 (2.1%) 1
Skin and subcutaneous tissue disorders	7 (14.9%) 7

System Organ Class Preferred Term	**Osimertinib (N=47) n (%) E**
Rash	7 (14.9%) 7

E = number of events.
On-treatment AE is any AE with onset from the day of starting osimertinib treatment under study throughout the treatment period.
System Organ Classes are sorted alphabetically and preferred terms are sorted within system organ class in descending order of frequency. If there are still ties, sort preferred terms alphabetically.
Subjects with multiple occurrences of adverse events within a preferred term is counted only once within the preferred term.
Subjects with multiple occurrences of adverse events within a system organ class is counted only once within the system organ class.
Percentages are based on the number of subjects in the safety analysis set.
Adverse events are coded with MedDRA version 19.1
Source Date：Appendix Table 10.3.1.2.1.

8.2.1.3 AESI

Interstitial lung disease/Pneumonitis-type events and QTc-prolongation events are the AESI of this study.

There were no QTc-prolongation events reported in this study (Appendix Listing 12.2.5.1.6).

A total of 1 subject experienced 1 on-treatment Interstitial lung disease/Pneumonitis-type events. The AE was pneumonia, which was judged related to osimertinib. The overview of the on-treatment period AESI are summarized in Table 8-4.

Details of all on-treatment period AESI of SS are listed in Appendix Listing 12.2.5.1.5.

Table 8-4 Overview of On-treatment Period AESI

	Osimertinib (N=47) n (%) E
Interstitial lung disease/Pneumonitis-type events	
Any On-treatment Period Interstitial Lung Disease/Pneumonitis Type events	1 (2.1%) 1
Related to Osimertinib	1 (2.1%) 1
Severe or CTCAET Grade 3/4	0
Serious AEs	0
QTc-prolongation events	
Any On-treatment QTc-prolongation events	0

E = number of events.

Subjects with multiple occurrences of adverse events within a system organ class is counted only once within the system organ class.
Percentages are based on the number of subjects in the safety analysis set.
Adverse events are coded with MedDRA version 19.1
Source Date：Appendix Table 10.3.1.3.1, Table 10.3.1.3.2, Table 10.3.1.3.3, Table 10.3.1.3.4, Table 10.3.1.3.5, Table 10.3.1.4.1, Table 10.3.1.4.2, Table 10.3.1.4.3, Table 10.3.1.4.4, Table 10.3.1.4.5.

8.2.1.4 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

8.2.1.4.1 Deaths

A total of 13 subjects died during the study. The causes of death are study disease (9 subjects), adverse event (subject 0142), no specific cause (subject 0111) and missing (subjects 0101 and 0120).

The on-treatment period AEs leading to death by SOC and PT are summarized in Table 8-5.

The reported AE was chest discomfort, which was judged not related to osimertinib.

Details of all on-treatment period AEs leading to death are listed in Appendix Listing 12.2.5.1.4.

Table 8-5 On-treatment Period AEs Leading to Death by System Organ Class and Preferred Term - Safety Analysis Set

System Organ Class Preferred Term	**Osimertinib (N=47) n (%)**
Any On-treatment AEs Leading to Death	1 (2.1%)
General disorders and administration site conditions	1 (2.1%)
Chest discomfort	1 (2.1%)

Subjects with multiple occurrences of adverse events within a system organ class is counted only once within the system organ class.
Percentages are based on the number of subjects in the safety analysis set.
Adverse events are coded with MedDRA version 19.1
Source Date：Appendix Table 10.3.1.6.

8.2.1.4.2 Other Serious Adverse Events

The serious on-treatment period AEs by SOC and PT are summarized in Table 8-6.

A total of 2 (4.3%) subjects experienced 2 SAEs. The PTs were chest discomfort and fatigue. Only fatigue was judged related to osimertinib.

Details of all serious on-treatment period AEs are listed in Appendix Listing 12.2.5.1.2.

Table 8-6 Incidence of Serious On-treatment Period AEs by System Organ Class and Preferred Term - Safety Analysis Set

System Organ Class Preferred Term	**Osimertinib (N=47) n (%)**
Any Serious On-treatment AEs	2 (4.3%) 2
General disorders and administration site conditions	2 (4.3%) 2
Chest discomfort	1 (2.1%) 1
Fatigue	1 (2.1%) 1

On-treatment AE is any AE with onset from the day of starting osimertinib treatment under study throughout the treatment period.
System Organ Classes are sorted alphabetically and preferred terms are sorted within system organ class in descending order of frequency. If there are still ties, sort preferred terms alphabetically.
Subjects with multiple occurrences of adverse events within a preferred term is counted only once within the preferred term.
Percentages are based on the number of subjects in the safety analysis set.
Adverse events are coded with MedDRA version 19.1
Source Date：Appendix Table 10.3.1.2.2.

8.2.1.4.3 Other Significant Adverse Events

Other significant adverse events included on-treatment period AEs leading to withdrawal.

The on-treatment period AEs leading to withdrawal by SOC and PT are summarized in Table 8-7.

Details of all on-treatment period AEs leading to withdrawal are listed in Appendix Listing 12.2.5.1.3.

Table 8-7 On-treatment Period AEs Leading to Withdrawal by System Organ Class and Preferred Term - Safety Analysis Set

System Organ Class Preferred Term	**Osimertinib (N=47) n (%)**
Any On-treatment AEs	1 (2.1%)
General disorders and administration site conditions	1 (2.1%)
Chest discomfort	1 (2.1%)

On-treatment AE is any AE with onset from the day of starting osimertinib treatment under study throughout the treatment period.
System Organ Classes are sorted alphabetically and preferred terms are sorted within system organ class in descending order of frequency. If there are still ties, sort preferred terms alphabetically.
Subjects with multiple occurrences of adverse events within a preferred term is counted only once within the preferred term.
Percentages are based on the number of subjects in the safety analysis set.

Adverse events are coded with MedDRA version 19.1
Source Date：Appendix Table 10.3.1.5.

8.2.2 ECOG Performance status

The ECOG performance status are summarized in Appendix Table 10.2.4.1.

The individual ECOG data are listed by subject in Appendix Listing 12.2.4.3.

8.2.3 Safety Summary

Of the 47 subjects included in SS, 1 subject died due to AE during the study, and the event was judged not related to osimertinib.

18 (38.3%) subjects were reported at least one on-treatment AE. The most frequently reported AEs were rash (7 subjects, 14.9%), fatigue (6 subjects, 12.8%) and nausea (5 subjects, 10.6%).

13 (27.7%) subjects were reported at least one adverse drug reaction. The most frequently reported adverse drug reactions were rash (7 subjects, 14.9%), fatigue (5 subjects, 10.6%) and nausea (4 subjects, 8.5%).

2 (4.3%) subjects experienced 2 SAEs. Each event occurred to one subject and only fatigue was judged related to osimertinib.

Only 1(2.1%) subject experienced on-treatment Interstitial lung disease/Pneumonitis-type events.

9. DISCUSSION AND CONCLUSION

9.1 Discussion

This was an observational retrospective cohort study of locally advanced or metastatic T790M mutation positive NSCLC patients who progressed after EGFR TKI therapy and received osimertinib treatment by treating physicians. The objective of this study is to assess osimertinib effectiveness. A total of 47 subjects who received osimertinib treatment at the participating site in Macau between May1st 2016 and Oct 31st 2016 were enrolled consecutively.

The study limitation is a single site study. The site selected will be a sample from a specific region, and may or may not be representative of the geographic distribution, diagnostic standards, and resources available in each of the participating sites locally.

In this study, 47 subjects were included in the FAS and 47 subjects were included in the SS .

1.In the FAS:

34 (72.3%) subjects completed the study, 13 (27.7%) subjects discontinued from the study because of death.

the average age was 58.2 years. 32 subjects(68.1%) are female subjects. 15 subjects(31.9%)are male subjects . The status of smoking in most subjects (34 subjects,72.3%) was “Unknown”. Relatives of 3 (6.4%) subjects (subject 0111、subject 0123 and subject 0132) were suffered from lung cancer. The most frequently reported medical history events in SOC were: neoplasms benign, malignant and unspecified (incl cysts and polyps) (100%); Surgical and medical procedures (31.9%) ; respiratory, thoracic and mediastinal disorders (17.0%).

At index date:

(1)47 subjects were stage IV

(2)28 (59.6%) subjects had bone metastases>25 (53.2%) subjects had lymph nodes metastases>17 (36.2%) subjects had Pleura metastases>11 (23.4%) subjects were known to have central nervous system (CNS) metastases>1 (2.1%) subject was known to have brain metastases(BM)=1 (2.1%) subject was known to have leptomeningeal metastases(LM).

At progression:

11 (23.4%) subjects were known to have CNS metastases.

Efficacy analysis:

3 (6.4%) subjects were CR, 22(46.8%) were PR , 18 (38.3%) subjects were SD,4 (8.5%) subjects were PD. 25 (53.2%) subjects were CR+PR.The objective response rate with its 95% CI were 53.2% (38.1%, 67.9%).

A total of 32 (68.1%) subjects were progression or death, in which 27 (57.4%) subjects were progression and 5 (10.6%) subjects were died without progression during study. A total of 15 (31.9%) subjects were censored.

Probability (95% CI) / at Risk:

Month 3: 0.787 (0.641, 0.879)/37> Month 6: 0.660 (0.506, 0.776)/31> Month 9: 0.574 (0.421, 0.701)/27> Month 12: 0.340 (0.204, 0.482)/10> Month 15: 0.265 (0.135, 0.414)/3

2.In the SS:

During the trial, 1 (2.1%) subject experienced dose modifications and 31(66.0%) subjects experienced dose discontinuation. The primary reasons for dose discontinuation were disease progression (22 subjects, 46.8%)> death (4 subjects, 8.5%)>patients' preference (3 subjects, 6.4%) >other (2 subjects, 4.3%).

A total of 18(38.3%) subjects experienced 31 on-treatment AEs; 13(27.7%) subjects experienced 21 adverse drug reactions events. Most of the on-treatment AEs were of the mild or moderate grade, only 2 (4.3%) subjects reported 2 severe on-treatment AEs. Only 1(2.1%) subject reported 1 AESI(Interstitial lung disease/Pneumonitis) and the AESI was judged with causality to osimertinib. A total of 2 (4.3%) subjects experienced 2 on-treatment SAEs; one death was reported. One AE was reported to lead the subject withdrawn from the treatment.

The most frequently reported primary SOCs were gastrointestinal disorders (9 subjects, 19.1%)> general disorders and administration site conditions (8 subjects, 17.0%) >skin and subcutaneous tissue disorders (7 subjects, 14.9%).

The most frequently reported AE was rash (7 subjects, 14.9%)>fatigue (6 subjects, 12.8%) > nausea (5 subjects, 10.6%).

The most frequently reported adverse drug reactions were rash (7 subjects, 14.9%)> fatigue (5 subjects, 10.6%) > nausea (4 subjects, 8.5%).

A total of 13 subjects died during the study. The causes of death are study disease (9 subjects), adverse event (subject 0142), no specific cause (subject 0111) and missing (subjects 0101 and 0120). The reported AE (subject 0142) was chest discomfort, which was judged not related to osimertinib.

A total of 2 (4.3%) subjects(subject 0103 and subject 0142) experienced 2 SAEs. The PTs were chest discomfort and fatigue. Only fatigue(subject 0103) was judged related to osimertinib.

9.2 Conclusion

Efficacy Summary:

3 (6.4%) subjects were CR, 22(46.8%) were PR , 18 (38.3%) subjects were SD,4 (8.5%) subjects were PD. 25 (53.2%) subjects were CR+PR.The objective response rate with its 95% CI were 53.2% (38.1%, 67.9%).

A total of 32 (68.1%) subjects were progression or death, in which 27 (57.4%) subjects were progression and 5 (10.6%) subjects were died without progression during study. A total of 15 (31.9%) subjects were censored.

As the month increased, the PFS showed a downward trend and at risk showed a downward trend. The median PFS and the corresponding 95% CI were 10.25 months (6.08, 11.56).

Safety Summary:

Of the 47 subjects included in SS, 1 subject died due to AE during the study, and the event was judged not related to osimertinib.

18 (38.3%) subjects were reported at least one on-treatment AE. The most frequently reported AEs were rash (7 subjects, 14.9%), fatigue (6 subjects, 12.8%) and nausea (5 subjects, 10.6%).

13 (27.7%) subjects were reported at least one adverse drug reaction. The most frequently reported adverse drug reactions were rash (7 subjects, 14.9%), fatigue (5 subjects, 10.6%) and nausea (4 subjects, 8.5%).

The reported AE (subject 0142) was chest discomfort, which was judged not related to osimertinib.

2 (4.3%) subjects experienced 2 SAEs. Each event occurred to one subject and only fatigue was judged related to osimertinib.

Only 1(2.1%) subject experienced on-treatment Interstitial lung disease/Pneumonitis-type events. And the AESI was judged with causality to osimertinib

10. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

10.1 Demographic Data

Table Number	Table Name	Analysis Set
Table 10.1.1	Subject Disposition	FAS SS
Table 10.1.2	Demographics Characteristics	FAS
Table 10.1.3	Disease Characteristics	FAS
Table 10.1.4	Medical History by System Organ Class and Preferred Term	FAS
Table 10.1.5.1	Prior Medication by ATC 1st Level and ATC 2nd Level	FAS
Table 10.1.5.2	Concomitant Medication by ATC 1st Level and ATC 2nd Level	FAS
Table 10.1.6.1	Treatment Received Before Osimertinib	FAS
Table 10.1.7.1	Treatment Received in Combination with Osimertinib	FAS

10.2 Efficacy Data

Figure Number	Figure Name	Analysis Set
Figure 10.2.2.1	Kaplan-Meier Estimates for Progression-Free Survival	FAS

Table Number	Table Name	Analysis Set
Table 10.2.1.1	Best Response Rate	FAS
Table 10.2.2.1	Kaplan-Meier Estimates for Progression-Free Survival	FAS
Table 10.2.3.1	Molecular Testing Patterns	FAS
Table 10.2.4.1	ECOG Performance Status	FAS

10.3 Safety Data

Table Number	Table Name	Analysis Set
Table 10.3.0.1	Extent of Exposure	SS
Table 10.3.1.1.1	Overview of On-treatment Period Adverse Events	SS
Table 10.3.1.2.1	Incidence of On-treatment Period AEs by System Organ Class and Preferred Term	SS
Table 10.3.1.2.2	Incidence of Serious On-treatment Period AEs by System Organ Class and Preferred Term	SS
Table 10.3.1.2.3	Incidence of On-treatment Period AEs by System Organ Class, Preferred Term and Maximum Causality	SS
Table 10.3.1.2.4	Incidence of On-treatment Period AEs by System Organ Class, Preferred Term and Maximum Intensity	SS
Table 10.3.1.2.5	Incidence of On-treatment Period Adverse Drug Reactions by System Organ Class, Preferred Term and Maximum Intensity	SS
Table 10.3.1.2.6	Incidence of On-treatment Period AEs by System Organ Class, Preferred Term and Maximum CTCAE Grade	SS
Table 10.3.1.3.1	Incidence of On-treatment Period Interstitial Lung Disease/Pneumonitis Type events by Preferred Term	SS
Table 10.3.1.3.2	Incidence of Serious On-treatment Period Interstitial Lung Disease/Pneumonitis Type events by Preferred Ter	SS
Table 10.3.1.3.3	Incidence of On-treatment Period Interstitial Lung Disease/Pneumonitis Type events by Preferred Term and Maximum Causality	SS
Table 10.3.1.3.4	Incidence of On-treatment Period Interstitial Lung Disease/Pneumonitis Type events by Preferred Term and Maximum Intensity	SS
Table 10.3.1.3.5	Incidence of On-treatment Period Interstitial Lung Disease/Pneumonitis Type events Preferred Term and Maximum CTCAE Grade	SS

Table 10.3.1.4.1	Incidence of On-treatment Period QTc-prolongation Events by Preferred Term	SS
Table 10.3.1.4.2	Incidence of Serious On-treatment Period QTc-prolongation Events by Preferred Term	SS
Table 10.3.1.4.3	Incidence of On-treatment Period QTc-prolongation Events by Preferred Term and Maximum Causality	SS
Table 10.3.1.4.4	Incidence of On-treatment Period QTc-prolongation Events by Preferred Term and Maximum Intensity	SS
Table 10.3.1.4.5	Incidence of On-treatment Period QTc-prolongation Events by Preferred Term and Maximum CTCAE Grade	SS
Table 10.3.1.5	On-treatment Period AEs Leading to Withdrawal by System Organ Class and Preferred Term	SS
Table 10.3.1.6	On-treatment Period AEs Leading to Death by System Organ Class and Preferred Term	SS

11. LIST OF REFERENCES

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12. APPENDICES

12.1 Study Information

This appendix contains the following sections:

12.1.1 Protocol .

12.1.2 Sample Case Report Form (Unique Pages Only) .

12.1.3 List of IECs or IRBs .

12.1.4 List and Description of Investigator in the Study .

12.1.5 Doctor's license

12.1.6 Documentation of Statistical Methods

12.1.7 Important publications referenced in the Report .

12.1.1 Protocol and Protocol Amendments

This appendix contains:

- Final Protocol, version 1.0, dated: 2 January 2017

12.1.2 Sample Case Report Form (Unique Pages Only)

This appendix contains:

- List titles of eCRF pages included and then scan in copies.

12.1.3 List of IECs or IRBs

This appendix contains:

- ethics committee approval letter .

12.1.4 List and Description of Investigator in the Study

This appendix contains:

Curriculum Vitae's (CVs) of:

- Investigator

12.1.5 Doctor's license

Jinghu Hospital , Macau, China,Doctor's license dated 31 Dec 2014 .

12.1.6 Documentation of Statistical Methods

Final SAP, dated 25 Jan 2018 .

Final Analysis Table Shells, dated 25 Jan 2018 .

Changes to Planned Statistical Analyses Form : there were no changes to these planned statistical analyses.

12.1.7 Important Publications Referenced in the Report

No publications referred to in this report are appended. All references are available on request.

12.2 Subject Data Listings

This appendix contains the following sections:

12.2.1 Withdrawn Subjects. .

12.2.2 Demographic Data .

12.2.3 Treatment Data

12.2.4 Individual Efficacy Response Data .

12.2.5 Adverse Event Listings (each subject)

12.2.1 Withdrawn Subjects

This appendix contains:

Listing Number	Listing Name	Analysis Set
Listing 12.2.1	Disposition of Subjects	FAS SS

12.2.2 Demographic data

This appendix contains:

Listing Number	Listing Name	Analysis Set
Listing 12.2.2.1	Demographics and Baseline Characteristics	FAS
Listing 12.2.2.2	Smoking Status and Family History of Cancers	FAS
Listing 12.2.2.3	Disease Characteristics	FAS
Listing 12.2.2.4	Molecular Testing Patterns	FAS

12.2.3 Treatment data

This appendix contains:

Listing Number	Listing Name	Analysis Set
Listing 12.2.3.1	Medical History	FAS
Listing 12.2.3.2	Prior and Concomitant Medications	FAS
Listing 12.2.3.3	Treatment Received Before Osimertinib	FAS
Listing 12.2.3.4	Treatment Received in Combination with Osimertinib	FAS
Listing 12.2.3.5	Treatment Administration	FAS

12.2.4 Individual Efficacy Response Data

This appendix contains:

Listing Number	Listing Name	Analysis Set
Listing 12.2.4.1	Individual Primary Efficacy Response Data	FAS
Listing 12.2.4.2	Progression Free Survival (PFS)	FAS
Listing 12.2.4.3	ECOG Performance Status	FAS

12.2.5 Adverse Event Listings (each subject)

This appendix contains:

Listing Number	Listing Name	Analysis Set
Listing 12.2.5.1.1	Subjects with Adverse Events	SS
Listing 12.2.5.1.2	Subjects with Serious Adverse Events	SS
Listing 12.2.5.1.3	Subjects with Adverse Events That Resulted in Withdrawal	SS
Listing 12.2.5.1.4	Subjects with Adverse Events That Resulted in Death	SS

Listing 12.2.5.1.5	Interstitial Lung Disease/Pneumonitis-type events	SS
Listing 12.2.5.1.6	QTc-prolongation events	SS

12.3 Case Report Forms

This appendix contains the following sections:

12.3.1 CRFs for Deaths, Other Serious Adverse Events and Withdrawals for Adverse Events .

12.3.2 Other CRFs Submitted.

12.3.1 CRFs for Deaths, Other Serious Adverse Events and Withdrawals for Adverse Events

The following CRFs are included:

- [Serious adverse event] – CRFs from following subjects:
  subject 0103; subject 0142
- [Withdrawn because of deaths] – CRFs from following subjects:
  subject 0101
  subject 0106
  subject 0111
  subject 0113
  subject 0117
  subject 0118
  subject 0120
  subject 0123
  subject 0124
  subject 0126
  subject 0130
  subject 0140
  subject 0142

12.3.2 Other CRFs Submitted

The following CRFs are included – scan in copies:

- [except for Deaths, Serious Adverse Events and Withdrawn] – CRFs from following subjects: scan in copies