Protocol A8081067

AN OPEN-LABEL, SINGLE-ARM STUDY OF THE LONG-TERM SAFETY OF XALKORI® IN PATIENTS FROM CHINA WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) HARBORING A TRANSLOCATION OR INVERSION EVENT INVOLVING THE ANAPLASTIC LYMPHOMA KINASE (ALK) OR ROS1 LOCUS WHO HAVE PREVIOUSLY BEEN TREATED ON A STUDY OF XALKORI®

Statistical Analysis Plan
(SAP)

Version: 2.0

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study A8081067 is based on the protocol amendment 1 dated 02Aug2019.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	Extended the study treatment duration until disease progression, unacceptable toxicity, consent withdrawal, death, whichever comes first, to provide longer treatment access to the patients. Updated AE and SAE collections. Updated the primary/safety endpoints per the updated AE and SAE collections.	Protocol amendment 1

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study A8081067. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

To evaluate the long-term safety of crizotinib in patients with advanced NSCLC harboring a translocation or inversion of the ALK gene or ROS1 gene locus.

2.2. Study Design

This is a multi-center, open-label, single arm study in China only. Eligible patients include those with advanced NSCLC harboring a translocation or inversion of the ALK gene or ROS1 gene locus who were enrolled and treated in Studies A8081005, A8081007, A8081014, A8081029, or A8081063 and are still receiving crizotinib treatment at the time of enrollment into this study. In addition, patients, randomized to the chemotherapy arm in Studies A8081014 or A8081029 and have not yet crossed over to receive crizotinib treatment at the time of enrollment into this study are eligible to enroll into this study after investigator-assessed disease progression. Approximately 75 patients will be enrolled into this study. Patients will continue single-agent crizotinib treatment on this study until disease progression, unacceptable toxicity, consent withdrawal, death, whichever comes first. Dose reductions and re-escalations are allowed based on tolerability.

Adverse Events (AEs) and Serious Adverse Events (SAEs) will be collected for each patient from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last administration of crizotinib ("active collection period"). If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period. Specifically, for those patients who roll-over from the parent studies A8081029 and A8081063:

- All SAEs that occurs within 28 calendar days from the last dose of Crizotinib in the parent study are recorded in the AE page of the CRF of the parent study and as medical history in the CRF of the rollover study A8081067.

- All Non-serious AEs that occur within 28 calendar days from the last dose of Crizotinib in the parent study are recorded in the AE page of the CRF of the parent study and are recorded as medical history in the CRF of the rollover study A8081067.

After the end of the active reporting period for the parent studies A8081029 and A8081063 (ie, 28 calendar days after the last dose), study recording in the CRF for the rollover study (A8081067) follows the standard process as per protocol.

Medical history data and limited additional data will be collected as described in the Study Protocol Table 1 and Table 2, Schedule of Activities.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

All Grade 3-5 AEs, all AEs leading to permanent treatment discontinuation and all Serious Adverse Events (SAEs) as assessed by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03).

3.2. Secondary Endpoint(s)

No secondary endpoints are planned in this protocol.

3.3. Other Endpoints

No other endpoints are planned in this protocol.

3.4. Baseline Variables

Demographic characteristics, such as patient age, gender, height, weight, ethnicity, and medical history information, such as medical history and ECOG performance status, which are collected within 28 days Prior to Cycle 1 Day 1, will serve as baseline variables. Baseline variables will be summarized and listed.

3.5. Safety Endpoints

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment period is defined as the time from the first dose of study treatment through a minimum of 28 calendar days after the last administration of study drug or start of new anticancer therapy, whichever occurs first. However SAEs reported on the CRF after the last administration of study drug even though after the start of new anticancer therapy will also be included in the safety analyses and will be flagged.

An adverse event is considered treatment emergent (TEAE) relative to a given treatment if:

- the event occurs for the first time during the on-treatment period and was not seen prior to the start of treatment, or
- the event was seen prior to the start of treatment but increased in severity during the on-treatment period.

Adverse events will be classified by type, incidence, severity, timing, seriousness, and relatedness to study treatment (severity graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03).

4. ANALYSIS SETS

Data for all patients will be assessed to determine if patients meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per Pfizer's standard operating procedures.

Only patients who signed informed consent will be included in the analysis sets below.

4.1. Full Analysis Set

The Full Analysis Set (FAS) is defined as all patients who have been enrolled in the study, regardless of whether treatment was received.

4.2. Per Protocol Analysis Set

Not applicable.

4.3. Safety Analysis Set

The Safety Analysis Set (SAS) is defined as those patients who received at least one dose of the study treatment. The safety analysis set is the primary population for safety analysis.

4.4. Other Analysis Sets

Not applicable.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and Sample Size Determination

There is no hypothesis testing planned for this study.

The number of patients to be enrolled is not predefined. However, it is expected that approximately 75 patients will be enrolled.

5.1.2. Decision Rules

The objective of this study is to evaluate the long-term safety, decision rules are not applicable.

5.2. General Methods

5.2.1. Analyses for Continuous Data

Descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values, will be provided for continuous variables.

5.2.2. Analyses for Categorical Data

The number and percentage of patients in each category will be provided for categorical variables.

5.3. Methods to Manage Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In compliance with Pfizer standards, CDISC Safety Rulebook[1] will be followed when handling the missing/partial dates, treatment emergent AE algorithm, missing AE grades, etc.

In all patient data listings imputed values will be presented. In all listings imputed information will be flagged.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

The primary endpoint analysis is to summary the frequencies of Grade 3-5 AEs, AEs leading to permanent treatment discontinuation and all SAEs in the safety analysis set (SAS) corresponding to system organ class (SOC) and preferred term (PT) according to MedDRA terminology and maximum NCI CTCAE v4.03 grade. AE incidence rates will be described both with and without regard to causality.

The following safety data will be summarized:

- Grade 3-5 AEs and AEs leading to permanent treatment discontinuation– number and percent of patients with all-causality and treatment-related AEs.
- SAEs – number and percent of patients with all-causality and treatment-related SAEs.
- All recorded safety data on the CRF will be listed.

6.2. Secondary Endpoint(s)

Not applicable.

6.3. Other Endpoint(s)

Not applicable.

6.4. Subset Analyses

Not applicable.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

The following analyses will be based on the Full Analysis Set (FAS).

6.5.1.1. Demographic and Physical Characteristics

Gender (male, female), Age (<65, >= 65) and Ethnicity will be summarized by number and percentage.

Age (continuous), height (cm), weight (kg), will be summarized with descriptive statistics (mean, median, standard deviation, minimum, and maximum).

6.5.1.2. Medical Characteristics

Medical history and ECOG performance status recorded in CRFs at screening will be summarized by number and percentage.

6.5.2. Study Conduct and Subject Disposition

A summary of the number of patients enrolled by site will be provided.

Permanent discontinuation of treatment and discontinuation of study will be summarized separately and by reason for discontinuation. Discontinuations of treatment will be summarized using the safety analysis set and discontinuations from other phases will be summarized using the full analysis set.

Discontinuations from study treatment due to adverse events will be identified as either related or not related to study treatment. If causality is missing the event will be considered related to treatment. If multiple events lead to study treatment discontinuation and at least one was considered related, discontinuation will be reported as related to study treatment. Discontinuation due to SAEs will be summarized separately.

6.6. Safety Summaries and Analyses

AE data will be summarized for the SA set.

6.6.1. Adverse Events

Adverse events (AEs) – All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of all AEs will be graded by the Investigator using NCI CTCAE Version 4.03.

An overall summary of AEs will be provided: the number and percentage of patients who experienced any all-causality AE (including Grade 3-5 AEs and AEs leading to permanent treatment discontinuation), all-causality SAE, treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades.

Because the frequency of certain medical concepts or conditions may be underestimated by reliance on single MedDRA preferred terms, certain preferred terms will be analyzed in aggregate using clustered terms. Patients having more than 1 AE preferred term within a clustered term will contribute 1 event to the clustered term at the highest grade observed. Clustered terms to be used for summary of data from this study will be defined prior to data summary based on information included in the current Safety Risk Plan maintained by the Sponsor.

- **All Causality Adverse Events**

A summary of AEs by System Organ Class (SOC), preferred term and maximum CTCAE grade will be presented. A summary of AEs by preferred term/clustered term and maximum CTCAE grade will be presented, in decreasing order of frequency. A summary of AEs by preferred term/clustered term and maximum CTCAE grade group (Grade 3-4 and Grade 5) will also be presented, in decreasing order of frequency. AEs associated with permanent discontinuation of the study drug will be summarized (taking into consideration the action taken from the AE CRF page).

- **Treatment-Related Adverse Event**

Treatment-related AEs are those judged by the Investigator to be at least possibly related to the study drug (with a cause related to study drug as indicated on the CRF) or for which relatedness is recorded as “unknown” by the Investigator. Similar summaries as noted for all causality AEs will be provided for treatment-related AEs.

- **Serious Adverse Events and Death**

Similar summaries as noted for all causality AEs will be provided for all causality and treatment-related SAEs. Patients who experienced a SAE as reported in the clinical database will be listed for all enrolled patients.

Deaths will be summarized, and by cause of death. Deaths that occurred on or after Cycle 1 Day 1 dose of crizotinib and within 28 days after the last dose of crizotinib are defined as on-study deaths. Death data will also be listed.

6.6.2. Laboratory Data

NCI CTCAE v4.03 will be used to determine if a laboratory-associated AE will be reported. Grade >=3 AEs, AEs leading to permanent treatment discontinuation and SAEs associated with a laboratory test abnormality will be recorded on the AE page of the CRF and will be summarized as described above.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analyses are planned.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

1. CDISC Safety Rulebook. Available from: http://urlretrieval.pfizer.com/webtop/component/getcontent?objectId=0901201b8416a018&docbase=Gnosis.