NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study details

Title	Observational study to IDEntify patients with advanced/metastatic NSCLC and ALK and ROS1 translocation and to establish their therapeutic management (IDEALK&ROS)
Protocol Code	A-8081057// PFI-ALK-2015-01
Protocol Version	Version 2.0
Date	18 MARCH 2020
Active substance	Crizotinib Protein kinase inhibitors (L01XE16)
Medicinal product	XALKORI.
Hypothesis and objectives	To determine the actual incidence of patients with advanced/metastatic NSCLC and ALK translocation To describe the ALK- and ROS1-positive patient population and to establish their therapeutic management
Author	PPD Tel.: PPD E-mail: PPD.

1. CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
SAE	Serious Adverse Event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios [Spanish Agency of Medicines and Medical Devices]
ALK	Anaplastic Lymphoma Kinase
ACs	Autonomous Communities
CBC	Complete Blood Count
IEC	Independent Ethics Committee
IC	Informed Consent
NSCLC	Non-Small Cell Lung Cancer
CRF	Case Report Form
eCRF	Electronic Case Report Form
CTC	Common Terminology Criteria
DOR	Duration of Response
DOT	Duration of treatment
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group Quality of Life Scale
SD	Stable Disease
EML	Echinoderm microtubule-associated protein-like
EORTC	European Organisation for Research and Treatment of Cancer
PAS	Post-Authorisation Study
PAPFS	Post-authorisation Prospective Follow-up Study
FDA	US Food and Drug Administration
PIS	Patient Information Sheet
HR	Hazard Ratio
TKI	Tyrosine-kinase inhibitor
DP	Disease Progression
PFS	Progression-Free Survival
CR	Complete Response
ROS1	V-Ros Avian UR2 Sarcoma Virus Oncogene Homolog 1
PR	Partial Response
SAE	Serious Adverse Event
OS	Overall Survival
PFS	Progression-Free Survival
CT	Computed axial tomography
TNM	Tumour (cancer) staging system. T, tumour size, N, spread to lymph nodes, M, metastasis.
RR	Response Rate

ORR	Objective Response Rate
Q4	Fourth Quarter

3. STUDY COORDINATORS

Coordinating Investigator(s)

Name	Post	Affiliation	Address
PPD	Coordinating Investigator	PPD Madrid	PPD Madrid
PPD	Coordinating Investigator	PPD Barcelona	PPD Barcelona
PPD	Sr. Medical Advisor	PPD	PPD (Madrid)
PPD	Sr. CRA	PPD	PPD (Madrid)

4. ABSTRACT

4.1. SPONSOR:

PPD (Madrid)

Contact person: PPD

PPD Lung Cancer

Tel.: PPD / Email: PPD

4.2. STUDY DETAILS

STUDY TITLE: Prospective observational study to IDEntify patients with advanced/metastatic NSCLC and ALK and ROS1 translocation and to establish their therapeutic management "IDEALK&ROS"

PROTOCOL CODE: PFI–ALK–2015–01

Pfizer's Protocol No.: A8081057

Version: 2.0, of 18 March 2020

4.3. STUDY COORDINATORS

COORDINATING INVESTIGATORS:

The scientific coordinators shall be responsible for maintaining the methodological rigour of the study, both in the design phase and in the evaluation of results and writing of the final report. They will guarantee the ethical conduct of the study, maintaining the scientific support for all participating doctors until the publication of the study results:

Study coordinators:

PPD
Medical Oncology Department
PPD Madrid
PPD
Madrid

PPD
Barcelona

4.4. STUDY SITES:

It has been deemed most appropriate to enrol patients at sites spread across Spain. Annexed to the protocol are the sites expected to participate in the study.

4.5. IEC ASSESSING THE STUDY

This protocol will be evaluated by the following IEC, as the central IEC of the study:

PPD

MADRID

Tel. PPD Email: PPD

4.6. PRIMARY OBJECTIVE

The objective of this study is to determine the actual incidence of ALK translocations in patients with advanced/metastatic NSCLC in Spain and to describe the clinical characteristics of these patients (ALK Incidence Sub-study) and the efficacy and safety of crizotinib in routine clinical practice in ALK (ALK Treatment Sub-study) and ROS1 (ROS1 Treatment Sub-study) patients.

The proposed objectives for each type of sub-study are:

- ALK Incidence Sub-study:

Primary Objective: To determine the actual incidence of ALK translocation in patients with advanced/metastatic ALK-positive NSCLC enrolled in this study in Spain.

Secondary Objectives:

- To describe the population of patients with advanced/metastatic NSCLC whose ALK is being determined.

- To compare the characteristics of the population with advanced/metastatic NSCLC that has tested positive for ALK translocation with advanced/metastatic NSCLC with negative ALK translocation.

-ALK Treatment Sub-study:

Primary Objective: To study the efficacy of treatment with crizotinib in patients with advanced/metastatic NSCLC with ALK translocation in terms of progression-free survival (PFS).

Secondary Objectives:

- To describe the clinical characteristics of these patients.
- To assess the efficacy of crizotinib treatment in these patients in terms of objective response rate (ORR), duration of response (DOR) and duration of treatment (DOT).
- To evaluate the survival of these patients in terms of overall survival (OS).
- To study the quality of life of the patients during treatment.
- To study the safety profile of the drug.

-**ROS1 Treatment Sub-study:**

Primary Objective: To study the efficacy of treatment with crizotinib in patients with advanced/metastatic NSCLC with ROS1 translocation in terms of progression-free survival (PFS).

Secondary objectives:

- To describe the clinical characteristics of these patients.
- To evaluate the efficacy of treatment with crizotinib in these patients in terms of ORR, DOR and DOT.
- To evaluate the survival of these patients in terms of OS.
- To study the safety profile of the drug, especially for potentially serious adverse events (prolonged QTc interval, bradycardia, skin photosensitivity, vision disorders, oedema, elevated liver enzymes and neutropenia).

4.7. DESIGN

This is a multicentre, observational post-authorisation study with retrospective and/or prospective follow-up for the ALK population and retrospective follow-up for the ROS1 population.

4.8. STUDY CONDITION

Advanced/metastatic non-small cell lung cancer (NSCLC).

4.9. STUDY POPULATION AND TOTAL NUMBER OF SUBJECTS

Patients with advanced/metastatic non-small cell lung cancer (NSCLC). Patients with this condition will be included in the following sub-studies of the study:

- ALK incidence sub-study: All patients with advanced/metastatic NSCLC diagnosed at the hospital will be registered. Subsequently, those who are to undergo ALK translocation molecular testing will be included in the incidence sub-study.

All patients who meet the inclusion criteria and none of the exclusion criteria may be enrolled in this sub-study for as long as the recruitment period of the treatment sub-study remains open to reach its sample size. As such, in this first sub-study, the number of patients to be enrolled is not predetermined.

- ALK Treatment Sub-study: Patients with advanced/metastatic NSCLC with confirmed ALK-positive translocation and who have been treated or are going to be treated with crizotinib. Within this population, data will be collected on the patients' treatment.

An estimated 100 patients with advanced/metastatic ALK+ NSCLC being treated with crizotinib as routine clinical practice will be included in the treatment sub-study (retrospective inclusion from January 2014 of 50% of the patients is allowed, plus prospective inclusion).

It is planned to conduct the study in 20-30 sites across Spain in order to include the planned number of study patients.

- ROS1 Treatment Sub-study: Patients with advanced/metastatic NSCLC with confirmed ROS1-positive translocation and who have been treated with crizotinib. Within this population, data on the treatment of patients who have received crizotinib according to routine clinical practice will be collected.

It is estimated that 50 patients will be included in this sub-study, all ROS1+ with advanced/metastatic NSCLC who have received treatment with crizotinib as per routine clinical practice (patients who started treatment with crizotinib on or after 8 February 2017, the market launch date of crizotinib in Spain for the ROS1 indication, will be included retrospectively, until the opening of the site).

The study is expected to be conducted in approximately 50 sites across Spain in order to include the planned number of study patients. This sample number is equivalent to the inclusion of at least 1 ROS1+ patient per site, considering the low incidence of the disease of 1-2% of all patients with non-small cell lung cancer.

4.10. SCHEDULE

The study's administrative procedures with the central IEC and the AEMPS are expected to start in September/October 2015, with the following provisional schedule:

For the ALK population:

Expected date of approval by the central IEC: November 2015

Expected date of opening the first site: January/February 2016

Recruitment period: 24 months

Expected date for closing data collection: 1st quarter 2019

Expected date of final study report: 4th quarter 2019

For the ROS1 population:

Expected date of approval by the central IEC for ROS1: 1 May 2020

Start of data collection for ROS1: 1 July 2020

End of data collection for ROS1: 15 July 2021

Final study report for ALK and ROS1: 28 February 2022.

4.11. SOURCE OF FUNDING

Pfizer SLU, as sponsor of the study, will provide financial compensation to the sites/investigators participating in the study. Such compensation will be explicit and transparent, without prejudice to the internal rules of their employers and in accordance with specific regulations in the ACs and sites at which the study is conducted

5. AMENDMENTS AND UPDATES

Amendment No.	Date	Amended protocol section(s)	Summary of change(s)	Reason
Administrative notification 1	28 June 2018		Extend the study recruitment period until June 2019.	To recruit the number of patients stipulated in the treatment sub-study (100 patients) given that it is the primary objective of the study
Administrative notification 2	13 July 2018		Clarify that the number of retrospective patients in the treatment sub-study can be around 50%, maintaining the sample size. Also, report the performance of an interim analysis when approximately half of the patients have been recruited for the treatment sub-study.	To recruit the number of patients stipulated in the treatment sub-study (100 patients), allowing the inclusion of retrospective patients to be approximately 50% given that crizotinib is no longer the only treatment in this group of patients (entry of competitors). The interim analysis is performed due to the fact that a scientific communication of the data is intended to be published when approximately half of the patients recruited in the treatment sub-study are available.
Amendment 1	18 March 2020	Several	Add the ROS1 patient population to the protocol and adapt the protocol to the new submission template for non-interventional studies. The Pfizer study team is updated	Subsequent approval in Spain of the ROS1 indication for crizotinib, so it is of interest to us to collect this information retrospectively. According to internal regulations, adaptation to the new submission template for non-interventional studies is a mandatory requirement in the event of submitting amendments to the protocol.

6. MILESTONES

Milestone	Expected date
Expected date of approval by the central IEC for ALK	*30 November 2015*
Expected date of approval by the central IEC for ROS1	*1 May 2020*
Start of data collection for ALK	*1 February 2016*
Start of data collection for ROS1	*1 July 2020*
End of data collection for ALK	*31 December 2019*
End of data collection for ROS1	*15 July 2021*
Results report for the ALK population	*30 June 2020*
Final study report for ALK and ROS1	28 February 2022

7. BACKGROUND AND RATIONALE

Lung cancer is a disease with a significant social and public health impact, which for decades has been one of the most common types of cancer worldwide. In 2008, there were an estimated 1.61 million new cases, accounting for 12.7% of all new cancers worldwide. Its large incidence also has an impact on mortality rates, and with 1.38 million deaths it is one of the leading causes of death from cancer[1]. In 2012, approximately 160,000 people were expected to die of lung cancer in the United States[2] and 262,000 in the European Union[3].

The World Health Organisation (WHO) divides lung cancer into two main categories based on their biology, therapy and prognosis: non-small cell lung cancer (NSCLC) and small cell lung cancer. Non-small cell lung cancer accounts for more than 85% of all cancer cases and includes 2 important types: (1) non-squamous carcinoma (including adenocarcinoma, large cell carcinoma, other cell types); and (2) squamous cell carcinoma (epidermoid). Adenocarcinoma (40% of lung cancers) is the most common type of lung cancer recorded in the USA and is also the most common cell type among non-smokers[4].

In recent years, the improved understanding of the biology of NSCLC has led to the identification of molecular events that are crucial for the malignant transformation and survival of cancer cells, and the identification of 'molecular subgroups' of NSCLC patients who may be candidates for 'targeted therapy'. These aberrant molecular events are critical oncogenic drivers and therefore represent potential therapeutic targets[5]. As a result, new targeted treatment options have been developed and continue to evolve. Erlotinib and gefitinib, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), have been approved for the treatment of NSCLC[6]. EGFR TKIs in particular represent a new paradigm in the treatment of NSCLC. EGFR mutations are found in 10-12% of Caucasian patients and 30-40% of Asian patients with NSCLC, and are associated with a higher response to EGFR TKIs[6]. Multiple randomised clinical trials have shown that patients harbouring EGFR-activating mutations benefit more from EGFR TKIs than standard chemotherapy in terms of ORR, progression-free survival (PFS), toxicity profile and quality of life[6]. The success of EGFR TKIs highlights the importance of identifying specific molecular drivers of NSCLC so that the targeted agents can be properly directed at specific patient populations.

The discovery of anaplastic lymphoma kinase (ALK) gene rearrangement in NSCLC in 2007[7] represents another major milestone in the era of targeted molecular therapy in NSCLC. ALK was first identified as a fusion protein produced by chromosomal translocation in the majority of anaplastic large cell lymphomas (ALCL). When fused to other proteins, ALK becomes constitutively active, causing an increase in the kinase catalytic function, signal transduction activity and oncogenic function. The expression of EML4-ALK, a new fusion protein between ALK and the echinoderm microtubule-associated protein-like 4 (EML4) gene, has been shown in transgenic mice to induce tumour formation, suggesting the therapeutic potential of inhibiting the EML4-ALK fusion protein in NSCLC[7]. The frequency of EML4-ALK rearrangement in NSCLC patients is relatively low, being found in about 2-8% of analysed tumours[8,9,7]. However, although the incidence of this type of tumour in Spain is not known with any accuracy due to a lack of pertinent studies, the available scientific literature (especially with a North American population)

suggests that NSCLC patients with ALK rearrangement are similar to those with EGFR mutations (i.e. adenocarcinoma, non-smokers or light smokers and young people)[10].

Moreover, it is important to have a detailed description of the clinical features of patients with NSCLC who have ALK translocation and its incidence, since no data are available for the Spanish population.

Crizotinib, an oral inhibitor of the ALK, ROS and MET tyrosine kinases, has been developed for patients with advanced/metastatic NSCLC with ALK rearrangements who have progressed after first-line treatment. Crizotinib was associated with clinically significant response rates of 60% and 48%, respectively, in two single-arm trials in 136 and 119 patients, respectively, with locally advanced or metastatic ALK-positive NSCLC who had been previously treated with standard chemotherapy (75% with two or more regimens)[11]. The responses were fast, with the majority patients achieving an objective and lasting response in the first 8 weeks of treatment, with a median duration of response (DOR) of 48.1 and 47.3 weeks, respectively, in each of the studies[12].

The use of crizotinib monotherapy in the treatment of ALK-positive advanced NSCLC was studied in a phase III, randomised, open-label, multicentre, multinational study (Study 1), in which a second-line treatment with crizotinib was compared to a second-line treatment with standard chemotherapy.

Crizotinib significantly increased PFS compared to chemotherapy, as assessed by an independent radiologic review (IRR), with a median PFS of 7.7 months in the crizotinib arm versus 3.0 months in the chemotherapy arm (HR 0.49; 95% CI 0.37-0.64). The improvement in PFS obtained with crizotinib was homogeneous across the patient subgroups, taking their baseline characteristics into account, and crizotinib also significantly improved the ORR assessed by IRR compared with chemotherapy.

The median DOR was 32.1 weeks (95% CI: 26.4; 42.3) in the crizotinib arm and 24.4 weeks (95% CI: 15.0; 36.0) in the chemotherapy arm. Data on overall survival (OS) were not final at the time of the PFS analysis.

For the evaluation of quality of life, a total of 162 patients in the crizotinib arm and 151 patients in the chemotherapy arm had answered the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and LC-13 questionnaires at the baseline visit and at least one subsequent visit. Crizotinib led to an improvement in symptoms by significantly increasing the time to the worsening (median of 5.6 months versus 1.4 months) of chest pain, dyspnoea or cough reported by the patient, compared to chemotherapy (HR 0.54; 95% CI: 0.40; 0.71; logarithmic p adjusted by the Hochberg method <0.0001).

The speed with which crizotinib progressed from first being developed to approval has had a major impact on second-line treatment for patients with ALK+ NSCLC. However, this very fact means that the experience with and knowledge about its use is limited, with very little data to date on its use in routine clinical practice[13].

Crizotinib efficacy data for first-line treatment were presented in the PROFILE 1014 study, a comparative study of crizotinib versus cisplatin or carboplatin plus pemetrexed. Crizotinib obtained a median PFS of 10.9 months versus 7.0 months of chemotherapy, with an HR of 0.45 (95% CI 0.35 -0.60) and p <0.01. These data were later confirmed with the publication of the overall survival data from the same study, where the median OS for crizotinib had not been reached (NR) compared to 47.5 months of chemotherapy with an HR of 0.76 (95% CI 0.548 - 1.053) and p = 0.0978. The high OS achieved by chemotherapy reflects the high crossover allowed in the study (84%) and is the reason why statistical significance was not reached[14].

Another milestone of scientific importance is the discovery of the V-Ros Avian UR2 Sarcoma Virus Oncogene Homolog 1 (ROS1). The incidence of ROS1 disease in non-small cell lung cancer (NSCLC) patients is approximately 1-2% according to the different published series[15]. Given that approximately 29,000 patients were expected to have lung cancer in Spain in 2019 according to the Spanish Society of Medical Oncology[16], the incidence of the ROS1 disease would be around 500 patients per year. The real incidence of this condition in Spain is unknown.

Since its initial description as a biomarker for lung cancer in 2007, ROS1 disease began to gain diagnostic and therapeutic importance thanks to the 2016 EMA approval of crizotinib based on the results of an expansion cohort of the phase I PROFILE 1001 study evaluating 53 patients, which showed a median progression-free survival (PFS) of 19.2 months. The final overall survival (OS) results of the PROFILE 1001 study in the ROS1 cohort have recently been published, showing a median OS of 51.4 months[17]. These results further support the efficacy of crizotinib in this condition.

Currently, the diagnosis of ROS1 disease is indicated in all patients with a previous diagnosis of non-small cell lung cancer and in those where the phenotypic characteristics of a young patient, light/non-smoker and with adenocarcinoma histology suggest it. The ROS1 disease testing figures in Spain are unknown. According to an exploratory registry study of NSCLC cases collected since 2016, the ROS1 disease testing rate is around 20%[18]. It can be diagnosed using the immunohistochemical (IHC) technique that must then be confirmed with fluorescent in situ hybridisation (FISH). Another method currently being developed is next-generation sequencing, a cost-effective method in the diagnosis not only of this type of biomarker, but of many others at the same time and with a minimum amount of sample containing deoxyribonucleic acid (DNA)[19].

There are currently no data in Spain on the efficacy and safety of crizotinib in the ROS1 population; for these reasons, it is important and necessary to provide data on ROS1 disease and the benefit to these patients of a targeted therapy such as crizotinib, currently accepted as the only standard of treatment for these patients.

8. HYPOTHESIS AND OBJECTIVES

The objective of this study is to determine the actual incidence of ALK translocations in patients with advanced/metastatic NSCLC in Spain and to describe the clinical characteristics of these

patients (ALK Incidence Sub-study) and the efficacy and safety of crizotinib in routine clinical practice in ALK (ALK Treatment Sub-study) and ROS1 (ROS1 Treatment Sub-study) patients.

The proposed objectives of the study are:

- ALK Incidence Sub-study:

Primary Objective: To determine the actual incidence of ALK translocation in patients with advanced/metastatic ALK-positive NSCLC included in this study in Spain.

Secondary Objectives:

- To describe the population of patients with advanced/metastatic NSCLC whose ALK is being determined.

- To compare the characteristics of the population with advanced/metastatic NSCLC that has tested positive for ALK translocation with advanced/metastatic NSCLC with negative ALK translocation.

- ALK Treatment Sub-study:

Primary Objective: To study the efficacy of treatment with crizotinib in patients with advanced/metastatic NSCLC with ALK translocation in terms of progression-free survival (PFS).

Secondary Objectives:

- To describe the clinical characteristics of these patients.
- To evaluate the efficacy of treatment with crizotinib in these patients in terms of ORR, DOR and DOT.
- To evaluate the survival of these patients in terms of OS.
- To study the quality of life of the patients during treatment.
- To study the safety profile of the drug, especially for potentially serious adverse events (prolonged QTc interval, bradycardia, skin photosensitivity, vision disorders, oedema, elevated liver enzymes and neutropenia).

- ROS1 Treatment Sub-study:

Primary Objective: To study the efficacy of treatment with crizotinib in patients with advanced/metastatic NSCLC with ROS1 translocation in terms of progression-free survival (PFS).

Secondary Objectives:

- To describe the clinical characteristics of these patients.
- To evaluate the efficacy of treatment with crizotinib in these patients in terms of ORR, DOR and DOT.
- To evaluate the survival of these patients in terms of OS.

- To study the safety profile of the drug, especially for potentially serious adverse events (prolonged QTc interval, bradycardia, skin photosensitivity, vision disorders, oedema, elevated liver enzymes and neutropenia).

9. RESEARCH METHODS

9.1 Study design

This is a multicentre, observational post-authorisation study with retrospective and/or prospective follow-up for the ALK population and a retrospective multicentre study for the ROS1 population.

All the evaluations described in this protocol are carried out as part of routine clinical practice or standard practice guidelines for the patient population and the specialty of the healthcare professional in the countries where this non-interventional study is conducted.

9.2 Scope

The study will be carried out on patients with advanced/metastatic non-small cell lung cancer (NSCLC). Patients with this condition will be included in the following sub-studies of the study:

- ALK Incidence sub-study: All patients with advanced/metastatic NSCLC diagnosed at the hospital will be registered. Subsequently, those who are to undergo ALK translocation molecular testing will be included in the incidence sub-study.

All patients who meet the inclusion criteria and none of the exclusion criteria may be enrolled in this sub-study for as long as the recruitment period of the treatment sub-study remains open to reach its sample size. As such, in this first sub-study, the number of patients to be enrolled is not predetermined.

- ALK Treatment Sub-study: Patients with advanced/metastatic NSCLC with confirmed ALK-positive translocation and who have been treated or are going to be with crizotinib. Within this population, data on the treatment of patients who are to receive crizotinib will be collected according to routine clinical practice.

An estimated 100 patients with advanced/metastatic ALK+ NSCLC being treated with crizotinib as routine clinical practice will be included in the treatment sub-study (retrospective inclusion from January 2014 of approximately 50% of patients is allowed, plus prospective inclusion of approximately the other 50%). The quality of life study will only be carried out on patients enrolled prospectively.

It is planned to conduct the study in 20-30 sites across Spain in order to recruit the planned number of study patients; around 100 patients with advanced/metastatic NSCLC per site are expected, with approximately 3 ALK-positive patients according to the estimated incidence.

The study will start at each site after the agreement with the site is signed and all study documentation and information on the procedures and objectives of the study are received by the person appointed by the sponsor.

Recruitment will be competitive among all participating sites and will be open for simultaneous inclusion for both sub-studies of the ALK study.

All NSCLC patients on whom ALK molecular testing is to be performed prospectively will be considered assessable for the incidence sub-study.

For the ALK treatment sub-study, a patient will be considered assessable if they have confirmed ALK translocation and provided they have received at least one dose of crizotinib.

In order to have a representative sample of patients being treated with crizotinib for the quality-of-life study, the treatment sub-study is expected to include approximately 50% of the patients retrospectively by site.

- ROS1 Treatment Sub-study: Patients with advanced/metastatic NSCLC with confirmed ROS1-positive translocation and who have been treated with crizotinib. Within this population, data on the treatment of patients who have received crizotinib according to routine clinical practice will be collected.

It is estimated that 50 patients will be included in this sub-study, all ROS1+ with advanced/metastatic NSCLC, who have received treatment with crizotinib as per routine clinical practice (patients who started treatment with crizotinib on or after 8 February 2017, the market launch date of crizotinib in Spain for the ROS1 indication, will be included retrospectively, from the opening of the site).

The study is expected to be conducted in approximately 50 sites across Spain in order to include the planned number of study patients. This sample number is equivalent to the inclusion of at least 1 ROS1+ patient per site, considering the low incidence of the disease of 1-2% of all patients with non-small cell lung cancer.

The study will start at each site after the agreement with the site is signed and all study documentation and information on the procedures and objectives of the study are received by the person appointed by the sponsor.

Recruitment will be competitive among all participating sites.

For the ROS1 treatment sub-study, a patient will be considered assessable if they have confirmed ROS1 translocation and provided they have received at least one dose of crizotinib.

9.2.1 Inclusion criteria

In general, all patients must meet all the inclusion criteria below to be eligible for inclusion in the study:

1. Diagnosis of advanced/metastatic non-small cell lung cancer
2. Patients over 18 years of age

For the ALK incidence sub-study, in addition:

1. Patients who are going to undergo molecular testing in order to establish ALK translocation will be included

For the ALK treatment sub-study, patients must meet the following additional criteria:

1. Confirmation of NSCLC with ALK-positive translocation
2. Be eligible to receive treatment with crizotinib according to routine clinical practice
3. Patients should have a predetermined minimum amount of data recorded in their medical records.

Where patients are included prospectively, evidence of an informed consent form personally signed and dated stating that the patient (or their legal representative) has been informed of all relevant aspects of the study.

For the ROS1 treatment sub-study:

1. Confirmation of NSCLC with ROS1-positive translocation
2. Have been eligible to receive treatment with crizotinib according to routine clinical practice since the market launch of the ROS1 indication in Spain on 8 February 2017 until the opening of the site.
3. Patients should have a predetermined minimum amount of data recorded in their medical records.

9.2.2 Exclusion criteria:

Any patient who does not meet any of the inclusion criteria defined in the previous section, according to the sub-study in which they are to be included.

9.3 Variables

The initial objective is to determine the actual incidence of ALK-positive tumours, for which all patients with advanced/metastatic NSCLC diagnosed in a specified period of time at the participating sites will be described prospectively. A full description of these patients will be compiled to determine the clinical profile of ALK-positive patients, and the treatments administered will be described retrospectively and/or prospectively. In addition, the quality of life of patients prospectively included in the ALK treatment sub-study will be evaluated through completion of a quality-of-life questionnaire over the course of the treatment.

Similarly, for ROS1-positive patients, a complete description of their clinical characteristics will be compiled, and the treatments administered will be described retrospectively.

Variables to analyse:

- Patient characteristics: age, gender, smoking status, Eastern Cooperative Oncology Group (ECOG) Quality of Life score, previous relevant medical history.
- Tumour characteristics: origin and type of sample, histological subtype (adenocarcinoma, epidermoid, etc.), Tumour staging system. T, tumour size, N, spread to lymph nodes, M, metastasis (TNM), molecular alterations, location of metastases.
- Treatment-related: different lines of treatment, adverse effects, treatment response, survival.
- Quality of life measured by the EORTC "QLQ-C30" and "QLQ-LC13" questionnaires.

By analysing the collected variables, the following aspects will be assessed:

- Incidence of patients with advanced/metastatic NSCLC and ALK-positive translocation among the patients included in the study, defined as % of ALK-positive patients out of the total number of patients with advanced/metastatic NSCLC.

- Progression-free survival (PFS): defined as the period between the first day of treatment and the first day that progressive disease (PD) is observed according to RECIST criteria (Version 1.1), or *death*. Patients who have not had an event at the time of the study data analysis will be censored at the date of the last available follow-up.

- Objective Response Rate (ORR): defined as the proportion of subjects who achieve complete response (CR) or partial response (PR). Additionally, the patients with stable disease (SD) will be evaluated. The subjects will be evaluated in accordance with RECIST criteria (Version 1.1).

- Duration of response (DOR): in patients with PR or CR, it will be defined as the period from the day the response is documented to the first day that disease progression is observed.

- Overall survival (OS): defined as the period from the first day of treatment until *death* or censored up to the last date on which it was known that the subject was alive.

- Safety: The safety of crizotinib will be evaluated by reporting the incidence of all adverse effects and their seriousness.

- ALK patient quality of life: measured by patient completion of the EORTC "QLQ-C30" and "QLQ-LC13" questionnaires over the course of the treatment visits (this evaluation only applies to patients prospectively enrolled in the treatment sub-study).

9.4 Source documents

The investigator will, at all times, be fully responsible for the accuracy and authenticity of all clinical and laboratory data included in the CRFs.

Patient-related source documents will consist of the medical records of each patient and tests performed in relation to their disease (e.g. computed axial tomography (CT scan), electrocardiogram (ECG), laboratory tests, etc.), which will be kept at the study site. The information recorded on the CRFs should be consistent with the data in the medical records.

For the quality of life assessment in the treatment sub-study, the "QLQ-C30" and "QLQ-LC13" questionnaires, which are to be filled out by the patient and kept by the investigator together with the study documentation, will be used as the source document.

9.5 Sample size

As this is a descriptive and exploratory study, the sample size is not based on any statistical assumption.

The population has been estimated based on known data on the incidence of advanced/metastatic ALK+ and ROS1+ NSCLC and with the aim of recruiting subjects over a three-year period for ALK, as described in the study schedule,
as well as to collect data retrospectively, until the opening of the site, from patients who started treatment with crizotinib on or after 8 February 2017, the marketing launch date of crizotinib in Spain for the ROS1 indication.

9.6. Data processing

The investigator will collect data from the enrolled patients in an electronic Case Report Form specifically designed for this study.

The patient number we provide is a serial number that cannot be used to identify the patient.
The information is stored in an SAS database. The investigators will record their data through the online CRF created for this purpose, which they access by entering their email and unique password. Access will not be granted without these credentials. The principal investigator (and the members of the collaborating team specified by him or her) will be given the study's website address with the corresponding access to the electronic case report form (eCRF), providing them with a link where they must create the password to access the system. The access codes to the eCRF are personal and non-transferable, and their safekeeping is one of the responsibilities that the investigator assumes as a participant in this study.
A Data Management Plan (DMP) will be drafted, and once approved by the study coordinator, the "Queries" will be programmed in the electronic case report form so that when the investigator saves the data, he/she is informed of any queries regarding the data.

All changes made by the investigators during the collection of data will be stored in a table specially designed for this purpose, indicating the user, date, modified field, the old value and the new value.

9.6.1 Case Report Forms (CRFs) /*Data Collection Tools* (DCTs) / Electronic data recording

As used in this protocol, the term eCRF refers to both a printed document and an electronic data record, or both, depending on the data collection method used in the study.

An eCRF is required and must be completed for each enrolled patient. Completed original eCRFs shall remain the exclusive property of Pfizer and will not be made available to third parties without the written permission of Pfizer, except to authorised representatives of Pfizer or the appropriate regulatory authorities. The investigator will ensure that the eCRFs are kept securely at the study site in *encrypted* and *password-protected* electronic format to prevent access by unauthorised third parties.

The investigator is ultimately responsible for the collection and reporting of all clinical, safety and laboratory data recorded on the eCRFs and on any other data collection print-outs (source documents) and will ensure that the data are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporary), durable and available when needed. The eCRFs must be signed by the investigator or an authorised member of the team to attest that the eCRF data are true. All corrections made to annotations in eCRFs or source documents must be dated, initialed and explained (if necessary), and may not conceal the original annotation.

In most cases, the source documents will be the hospital's or doctor's medical records. In these cases, the data recorded in the eCRF must match the data in those records.

In some cases, the eCRF can also serve as a source document. In such cases, a document that clearly identifies the data recorded in the eCRF and for which the eCRF will serve as the source document must be kept at both the investigator's site and Pfizer's facilities.

9.6.2 Records storage

To facilitate evaluations and/or inspections/audits by regulatory authorities or Pfizer, the investigator agrees to retain records, including the identity of all participating patients (information to link the records, for example, the eCRF, to the hospital records), all original signed informed consent documents, copies of all eCRFs, safety notification forms, source documents, detailed records of provision of treatment, and adequate documentation of relevant correspondence (e.g. letters, meeting minutes or phone call reports). The records should be kept by the investigator in accordance with local regulations or as specified in the clinical study agreement, whichever is the longer of the two. The investigator must ensure that the records are kept securely throughout the retention period.

If for any reason the investigator is unable to keep the study records for the stipulated period (e.g., retirement or transfer), he or she must notify Pfizer in advance. The study records should be transferred to a delegate person acceptable to Pfizer, such as another investigator or other institution, or to an independent third party provided by Pfizer.

The investigator records should be kept for a minimum of 15 years after study completion or discontinuation, or longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7 Data analysis

For the ALK incidence sub-analysis, in order to study the incidence of patients with advanced/metastatic and ALK-positive NSCLC, the incidence rates for the total N of patients enrolled in the study will be used. The characteristics of patients with advanced NSCLC enrolled in the study, who will undergo ALK and ROS1 testing, will be studied using absolute and relative frequencies for qualitative variables and the main measures of centralisation and dispersion for quantitative variables. To find statistically significant differences in the characteristics of the population of patients with positive and negative ALK, Pearson's chi-squared statistical test (or Fisher's exact test for a 2 x 2 contingency table or the likelihood ratio test, if necessary) will be used for qualitative variables, and Student’s t-test, the one-way analysis of variance (ANOVA) or its non-parametric equivalents, Mann-Whitney U, Kruskal-Wallis H for quantitative variables.

For the treatment sub-studies and to evaluate the efficacy and safety of treatment with crizotinib in patients with advanced/metastatic and ALK/ROS1-positive NSCLC, the Kaplan Meier estimator for the survival function will be used to study patients’ PFS, DOR and OS. The ORR will be studied by presenting absolute and relative frequencies. The quality of life of ALK patients will be studied with the QLQ-C30 and QLQ-LC13 questionnaires; mean, standard deviation and confidence intervals will be used if they follow a normal distribution or median, minimum, maximum and interquartile range if they do not follow Gaussian distribution. The Wilcoxon test will be used to analyse the association between visits in patients’ quality of life.

The log-rank test will be used to compare the survival functions. The incidence rate of specific adverse effects will be described in the total population.

The assumptions of normality and homoscedasticity of the variables for the use of parametric tests will be studied.

An interim analysis of the ALK data will be performed when approximately half of the patients have been enrolled in the treatment sub-study.

The detailed methodology for the statistical analysis of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans described in the protocol; any significant change in the definitions or analyses of the study's variables will be reflected in an amendment to the protocol.

9.8 Quality control

As this is a post-authorisation study, the same procedures will be followed by the investigator as in routine clinical practice.

However, the investigators are responsible for ensuring compliance with the protocol and Good Clinical Practice (GCP) guidelines.

Study sites might be subject to face-to-face or remote monitoring by the person appointed by the sponsor, and inspection by the Independent Ethics Committee (IEC) and/or quality assurance audits conducted by the relevant regulatory authorities and the study sponsor.

- **Monitoring**

Face-to-face monitoring will take place in 10% of sites with patients enrolled in the treatment sub-study. The electronic case report form will be reviewed at all other sites. The sponsor will appoint the person responsible for monitoring the study.

9.9 Limitations of the research methods

As this is an exploratory study and an analysis of ALK incidence with a population that has been little studied to date, it is difficult to estimate the time and the number of patients that may be recruited for the ALK incidence sub-study.

9.10 Further aspects

- **Observation period**

The estimated date of inclusion of the first patient will be February 2016.

During the observation period, data from patients who may be included will be recorded in the case report form. The follow-up period within the study of each patient enrolled in the study will be at least 6 months.

The end of the study at all participating sites is defined as the data collection from the last time point in the study. As one of the endpoints of the study is survival, it is anticipated that the last data collection point will be the last survival follow-up (i.e. the most recent date on which it was known that the patient was alive or the date of death) before the cut-off date for closing the database for the final clinical study report.

- **Description of the treatment and definition of exposure**

No treatment data is included in the ALK incidence sub-study.

In the treatment sub-studies, patients can be recruited retrospectively and prospectively for ALK and only retrospectively for ROS1.

For retrospective patient inclusion, patients will have already received crizotinib prior to enrolment in the treatment study, so this decision is independent of the current protocol.

In the ALK treatment sub-study, there will be no interference with the investigator's decision on the most appropriate treatment for the patient, since what determines the treatment in these patients is whether or not they test positive for ALK translocation. Routine clinical practice and the investigator's decision on the best option available for the patient will prevail at all times.

Data will be collected from those patients who are going to receive or have received crizotinib according to routine clinical practice.

The decision to treat a patient with crizotinib will be prior to and irrespective of the patient's participation in the study according to the clinical judgement and routine clinical practice of the doctor responsible for the patient. That is, the patient will receive the same treatment whether or not they participate in the study.

- **Study procedures:**

In the ALK incidence sub-study, all patients will be included prospectively in order to estimate the true incidence of ALK translocation in the study population.

In the ALK treatment sub-study, patients may be included prospectively and retrospectively (patients who undergo molecular testing from January 2014).

In the ROS1 treatment sub-study, retrospective inclusion of the data of patients who started treatment with crizotinib on or after 8 February 2017, the marketing launch date of crizotinib in Spain for the ROS1 indication, will be allowed, until the opening of the site.

During the screening visit, the inclusion/exclusion criteria will be reviewed and patients enrolled prospectively will have to sign the ICF before inclusion in the study.

The study has one Patient Information Sheet/Informed Consent Form for patients enrolled in the ALK incidence phase and another version for patients included prospectively in the treatment phase (please find attached to the protocol).

For the retrospective inclusion of patients in the treatment sub-study, since it is not necessary to interview the subject and the recording of patient data is guaranteed to be anonymous and dissociated, informed consent is not required, in accordance with order SAS/3470/2009 of 16 December on observational post-authorisation studies.

The information requested in the visits referred to in the document will be recorded in the electronic case report form (attached as Appendix I of this protocol), together with the data available in the medical records.

- ALK Incidence Sub-study:

- Review and confirmation of meeting the inclusion criteria and none of the exclusion criteria for the study, explaining the procedures and purpose of the study to the patient, and requesting the signing of the ICF if willing to participate in the study.

- Data on medical history and demographic characteristics and diagnosis of NSCLC.

- ALK Treatment Sub-study:

-Baseline Visit:

Review and confirmation of meeting the inclusion criteria and none of the exclusion criteria for the study.

Explaining the procedures and purpose of the study to the patient, and requesting patients included prospectively to sign the ICF.

Disease history:

- Patient's medical records
- Details of the disease justifying treatment with crizotinib
- Details of previous treatments for the disease, if any.

- Completion by the patient of the study's ALK quality-of-life tests (QLQ-C30 and QLQ-LC13) (for patients included prospectively).

- Quality-of-life assessment visits for ALK patients: the patient will be given the quality-of-life questionnaire, which must be completed at the treatment follow-up visits according to routine clinical practice, at least at the baseline visit prior to starting treatment, at the treatment assessment visit after receiving the first cycle, at the assessment visit three months after the start of treatment (coinciding with the tumour assessment) and at treatment discontinuation.

- Final visit: (The following information will be extracted from all visits during treatment with crizotinib):

- Response to treatment with crizotinib
- Worst toxicity during treatment with crizotinib (the investigator should follow pharmacovigilance requirements and responsibilities as described in section 10 of the protocol, on Management and Communication of Adverse Effects, throughout the study)
- Information on dose reductions and discontinuations
- Reason for terminating treatment with crizotinib
- Information on survival and progression dates, if any
- Completion by the patient of the quality-of-life questionnaire (for patients included prospectively)
- Further treatment(s) received, if any

- Treatment sub-study for ROS1.

  No initial, follow-up or final visits shall be necessary.

10. PROTECTION OF STUDY SUBJECTS

The study will be conducted in accordance with routine clinical practice, as described in the protocol, *Good Clinical Practice* guidelines, the International Conference on Harmonisation and the applicable local laws and requirements (Order SAS/3470/2009 of 16 December).

10.1 Patient information

All parties will comply with all applicable laws, including those relating to the implementation of organisational and technical measures to ensure the protection of patients' personal data. Such measures will include the omission of the patient's name or other directly identifiable data in reports, publications or other means of dissemination, except when required by current legislation.

Personal data will be kept at the study site in encrypted electronic and/or paper and password-protected format or in a locked room to ensure that only authorised study personnel have access. The study site will apply the appropriate technical and organisational measures to guarantee the recovery of personal data in the event of a disaster. In the event of a possible breach in personal data security, the study site will be responsible for determining whether a personal data security breach has actually occurred and, if so, for reporting the incident as required by law.

To protect the rights and freedoms of natural persons in relation to the processing of personal data, when study data are collected for transfer to Pfizer and other authorised parties, patient names will be removed and replaced by a specific unique numeric code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorised parties will be identified by this unique, patient-specific code. The research site will maintain a confidential list of the patients who have participated in the study in which the numerical code of each patient is linked to their real identity. For data transfer, Pfizer will maintain a high degree of confidentiality and protection of patients' personal data in accordance with the clinical study agreement and applicable privacy laws.

10.2 Patient consent

The informed consent documents and any patient recruitment materials must comply with local legal and regulatory requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer and approved by the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) prior to use, and be available for inspection.

The investigator must ensure that all prospective study patients, or their legal representative, are fully informed of the nature and objectives of the study, the disclosure of study-related data and the potential risks associated with participation, including risks associated with the processing of the patient's personal data. The investigator must also ensure that all prospective study patients, or their legal representative, are fully informed of their right to access and correct their personal data and to withdraw their consent to the processing of their personal data.

Whenever the consent of the patient's *legal representative* is obtained, the consent (agreement of conformity) of the patient must be obtained later, when the patient is capable of granting it, as determined by the IRB/IEC. If the investigator determines that a patient's decision-making power is so limited that he or she cannot be reasonably consulted, then, as permitted by the IRB/IEC and in accordance with local legal and regulatory requirements, the patient's assent may be waived, recording in the original documentation the reason why the assent was not obtained. If the study patient does not give his or her own consent, the original documents should record the reason (e.g., minor, adult with impaired decision-making capacity), how the investigator determined that the person signing the consent was his or her representative legal, the relationship of the signer of the consent to the study patient (e.g., parent, spouse) and whether the consent of the patient or waiver of the need for this document was obtained. If assent has been obtained verbally, it must be documented in the original documents.

The patient data collected in the CRF must be dissociated and anonymously recorded by being assigned a code (patient number), so that only the investigator is able to associate these data with an identified or identifiable person.

For prospective patient inclusion, the investigator, or the person designated by the investigator, will obtain the written informed consent of each patient or their legal representative before carrying out any specific study activity. The investigator will keep the original of all consent documents signed by patients.

The study has one Patient Information Sheet/Informed Consent Form for patients enrolled in the ALK incidence phase and another version for patients included prospectively in the treatment phase of ALK patients (please find attached to the protocol).

In the ALK treatment sub-study, patients may be included prospectively and/or retrospectively.

For patients included retrospectively, according to Order SAS/3470/2009 of 16 December on observational post-authorisation studies: "In studies that require subjects to be interviewed or in those in which, using other sources of information, it is not possible to use a secure dissociation procedure that ensures that the information contains no data of a personal nature, subjects must be asked to give their informed consent, which must be granted in writing, in accordance with current regulations". Therefore, these patients are not required to sign the Informed Consent Form.

The investigator, or his or her designated person, will obtain written informed consent from each prospective patient or his or her legal representative before performing any study-specific activity. The investigator will keep all the original consent documents signed by patients.

10.3 Patient withdrawal

Patients may leave the study at any time of their own volition, or they may be withdrawn at any time at the discretion of the investigator or the sponsor for safety, behaviour or administrative reasons. In either case, every effort should be made to document the patient's progress, if possible. The investigator should ask about the reason for the withdrawal and conduct patient follow-up in relation to any unresolved adverse event.

If the patient leaves the study and also withdraws his/her consent for future dissemination of information, no further assessment should be made and no further data collected. The sponsor may retain and continue to use all data collected before the withdrawal of consent.

10.4. Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

It is the responsibility of the investigator to obtain prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents (e.g., recruitment materials), as applicable, from the IRB/IEC. All correspondence with the IRB/IEC must be retained by the investigator. Copies of the approvals from the IRB/IEC must be sent to Pfizer.

10.5 Ethical considerations of the study

Thorough, continuous quality control is required to guarantee the accuracy and scientific rigour of the data obtained, maintaining uniform data collection conditions.

The study will be conducted in accordance with the protocol, *Good Clinical Practice* guidelines, the International Conference on Harmonisation and applicable local laws and requirements.

Additionally, the study will be governed by the basic ethical principles contained in the Declaration of Helsinki.

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigour, and will follow the generally accepted research practices described in Good Clinical Practice Guidelines.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

REQUIREMENTS

The following table summarises the requirements for the recording of safety events in the case report form (CRF) and the reporting of safety events to the Department of Drug Safety at Pfizer, using the "Non-interventional Study (NIS) Adverse Event Monitoring (AEM) Report Form".

These requirements are set out for three types of event: (1) Serious Adverse Events (SAEs); (2) Non-serious Adverse Events (AEs) (as appropriate); and (3) Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast-feeding, medication errors, overdose, incorrect use of the drug, extravasation, loss of efficacy and occupational exposure. These events are defined in the "Definitions of safety events" section.

Safety event	**Recorded in the Case Report Form**	**Reported on the NIS AEM Report Form to the Department of Drug Safety at Pfizer within 24 hours of becoming aware of it**
SAE (Serious Adverse Event)	All	All
AE (Non-serious Adverse Event)	All	- Grade 3-4 Oedema - Grade 3-4 Photosensitivity (skin reaction) - Grade 3-4 Neutropenia - Grade 3-4 Visual disorders - Grade 3-4 Bradycardia, or any grade of symptomatic bradycardia - Grade 3-4 prolonged QTc interval or any grade of symptomatic prolonged QTc interval - Grade 3-4 Elevated liver enzymes
Scenarios involving exposure to a drug during the study, including exposure during pregnancy, exposure during breast-feeding, medication error, overdose, incorrect use of the drug, extravasation, lack of efficacy and occupational exposure	All (regardless of whether they are associated with an AE), **except occupational exposure**	All (regardless of whether they are associated with an AE) Note: Any associated AE is reported along with the exposure scenario

For each AE, the investigator must obtain adequate information to both determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE (see the "Serious Adverse Events" section below).

The safety events listed in the above table must be reported to Pfizer within 24 hours of the investigator becoming aware of the event **regardless of whether or not the investigator determines that it is related** to crizotinib. In particular, if the SAE has resulted in death or is life-threatening, it must be reported to Pfizer immediately, regardless of the amount of information available on the event. This period must also apply to the new additional information (follow-up) on previously reported safety events. In the unlikely event that the investigator does not immediately detect a safety event, he/she must report it within 24 hours of becoming aware of it and document the day and time he/she became aware of it for the first time.

For safety events that are considered serious or that are identified in the right-hand column of the above table, which should be reported to Pfizer within 24 hours of becoming aware of them, the investigator is required to obtain and provide Pfizer with any additional information within 24 hours. Pfizer may also require that an investigator expeditiously obtains specific follow-up information. This information is more detailed than the information collected in the CRF. In general, it should include a description of the adverse event in sufficient detail to allow a full medical evaluation of the case and an independent assessment of the possible causality. Any relevant information related to the event should be provided, such as medication and comorbidities. In the event of the death of a patient, a summary of the available post-mortem findings must be sent as soon as possible to Pfizer or its designated representative.

Reporting period

For each patient, the reporting period of the safety event begins at the time the patient receives the first dose of crizotinib or signs the informed consent if he/she has already been exposed to crizotinib, and lasts until the end of the study's observation period, which should cover at least 28 calendar days after the last administration of the study drug; a report must be sent to the Department of Drug Safety at Pfizer (or its designated representative) if any of the types of safety event listed in the above table occur during this period. In this study, for patients included retrospectively without signing the ICF, the reporting period will begin at the time of the first dose and continue until 28 calendar days after administration of the last dose. If a patient receives a study drug on the last day of the observation period, the reporting period should be extended to 28 calendar days after the end of the observation period. The date of informed consent is often the same as the recruitment date. In some situations, there may be a delay between the informed consent date and the recruitment date. In these situations, if a patient gives their informed consent but is never included in the study (e.g. the patient changes his/her mind about taking part, screening failure, etc.), the reporting period ends on the date on which it is decided not to recruit the patient.

If the investigator is aware of an SAE occurring any time after completion of the study and believes that the SAE is related to crizotinib, the SAE should also be reported to the Pfizer Department of Drug Safety.

Causality Assessment

The investigator is obliged to assess and record the causal link. For all AEs, the investigator should obtain sufficient information to determine the causality of each adverse event. For crizotinib-related AEs, the investigator is required to follow up until the event and/or its sequelae are resolved, or stabilised at an acceptable level from the investigator's point of view, and Pfizer agrees with that assessment.

The purpose of the investigator's causality assessment is to determine whether there is a reasonable possibility that crizotinib caused or contributed to an adverse event. If the final determination of causality by the investigator is "unknown" and he/she is unable to determine whether crizotinib caused the event, it must be reported within 24 hours.

If the investigator cannot determine the aetiology of the event but has determined that crizotinib was not the cause, this should be recorded in the CRF and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse Events

An AE is any unwanted medical episode that happens to a patient who has received a drug. The event does not necessarily have a causal link with the treatment.

Below are some examples of adverse events:

- Abnormal test results (see below for the circumstances under which an abnormal test result is an adverse event);
- Clinically significant signs and symptoms;
- Changes in the physical examination findings;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;
- Drug dependence.

In addition, for medications, such events may include signs and symptoms arising from:

- Drug overdose;
- Drug discontinuation;
- Incorrect use of the drug;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast-feeding;
- Medication error;
- Occupational exposure;

Abnormal test results

The criteria for determining whether an abnormal result of an objective test should be reported as an adverse event are:

- The test result is associated with accompanying symptoms; and/or
- The test result requires additional diagnostic tests or medical or surgical intervention; and/or
- The test result leads to modification of the study dosage or withdrawal from the study, requires a major additional concomitant drug treatment or another kind of treatment; and/or
- The investigator or the sponsor consider the test result to be an adverse event.

Simply repeating a test with an abnormal result in the absence of the above conditions does not constitute an adverse event. It is not necessary to report as adverse events any abnormal test results that are found to be erroneous.

Serious adverse events

A serious adverse event is any undesirable medical episode in a patient who has received a drug or nutritional product (including paediatric formulations) of any dose that:

- Causes death;
- Is life-threatening;
- Requires hospitalisation of the patient or prolongation of existing hospitalisation (see below for the circumstances that do not constitute an adverse event);
- Causes persistent or significant disability/incapacity (significant disruption of the ability to perform the functions necessary to lead a normal life);
- Causes a congenital anomaly or birth defect.

The progression of the cancer being studied (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is death during the study or during the reporting period. Hospitalisation due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignant tumour is fatal during the study or in the reporting period, the death-causing episode should be recorded as a grade 5 serious adverse event.

Medical and scientific judgement should be applied to determine whether a particular episode is a medically significant adverse event. An adverse event may be medically significant without being immediately life-threatening or causing death or hospitalisation. However, if it is determined that the adverse event may endanger the patient and/or may require intervention to prevent one of the other outcomes included in the above definitions, the adverse event should be reported as serious.

These events comprise, for example, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia or seizures that do not require hospitalisation, or development of drug dependency or abuse.

Suspected transmission of an infectious, pathogenic or non-pathogenic agent through a Pfizer product is considered serious. The event may be suspected due to clinical symptoms or laboratory results indicating an infection in a patient exposed to a Pfizer product. The terms 'suspected transmission' and 'transmission' are considered synonymous. These cases are considered unexpected and are managed as serious and expeditious by the pharmacovigilance staff. These cases are also considered for reporting as product defects, if deemed appropriate.

Hospitalisation

Hospitalisation is defined as any initial admission (even if less than 24 hours) to a medical facility or any extension of hospitalisation if already admitted. Transfer within the hospital to an acute care or intensive care unit (e.g. from a psychiatric ward to a medical ward, from a medical ward to the coronary care unit, from a neurology ward to a tuberculosis unit) is also deemed to be an admission. Going to A&E does not necessarily constitute hospitalisation; however, an event that causes the patient to go to A&E should be evaluated to determine its medical relevance.

Hospitalisations in the absence of a medical adverse event are not considered an adverse event *per se* and do not need to be reported. For example, the following reports of hospitalisation without adverse events do not need to be reported:

- Social hospitalisation (for example, if the patient has nowhere to spend the night)
- Administrative hospitalisation (for example, for an annual check-up)
- Optional hospitalisation not precipitated by an adverse event (for example, for elective cosmetic surgery)
- Hospitalisation for observation without a medical adverse event
- Hospitalisation for the treatment of a pre-existing condition not associated with the development of a new adverse event or exacerbation of a pre-existing condition (e.g. investigation of pre-existing laboratory test abnormalities)
- Hospitalisation described in the protocol during the study (e.g. for a procedure required by the study protocol)

Situations that require reporting to the Department of Drug Safety at Pfizer within 24 hours

Situations involving exposure during pregnancy, exposure during breast-feeding, medication error, overdose, incorrect use of the drug, extravasation, lack of efficacy and occupational exposure are described below.

Exposure during pregnancy

Exposure during pregnancy (EDP) takes place if:

1. A woman becomes pregnant or discovers that she is pregnant while receiving crizotinib or having been directly exposed (whether in treatment or through environmental exposure) to crizotinib; or if the woman becomes pregnant or discovers she is pregnant after stopping or having been directly exposed to crizotinib (maternal exposure);

An example of environmental exposure would be a case involving the direct contact of a pregnant woman with a Pfizer product (e.g. a nurse reports that she is pregnant and has been exposed to chemotherapy agents).

2. A man has been exposed, whether in treatment or through environmental exposure, to crizotinib before or around the time of conception and/or exposed during the pregnancy of the partner (paternal exposure).

As a general rule, exposure during pregnancy, prospective and retrospective of any kind, is reportable regardless of whether it involves an AE, and the procedures for reporting SAEs should be followed.

If a participant in a study or their partner becomes pregnant or it is discovered that she is pregnant while undergoing treatment with crizotinib, this information should be reported to Pfizer using the NIS AEM Report Form and EDP Supplemental Form, regardless of whether there is an associated adverse event.

Furthermore, information relating to environmental exposure to crizotinib in a pregnant woman (e.g. she reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be reported using the NIS AEM Report Form and EDP Supplemental Form. This must be done regardless of whether there has been an AE.

The information reported must include the due date (see abortion information below).

Follow-up should be performed to obtain general information on the pregnancy. In addition, for all EDP reports where the outcome of the pregnancy is unknown, the case should be followed up to obtain information on the outcome. The pregnancy will be followed up to the end or until termination (e.g. induced abortion) and Pfizer notified of the outcome. This information will be provided as follow-up to the initial EDP report. In the event of birth, the structural integrity of the newborn can be assessed at the time of birth. In the event of abortion, the reasons for the termination should be specified and, if clinically possible, the structural integrity of the foetus should be evaluated by visual inspection (unless there are previous conclusive laboratory findings that denote congenital anomalies and these findings are reported).

If the pregnancy outcome meets the SAE criteria (e.g. ectopic pregnancy, spontaneous abortion, intrauterine foetal death, neonatal death or congenital anomaly [in a child born alive, post-abortion foetus, intrauterine foetal death or neonatal death]), the procedures for reporting SAEs must be followed.

Additional information on the outcome of the pregnancy that should be reported as SAEs:

- Spontaneous abortion includes miscarriages and missed abortions.
- Neonatal deaths that occur within one month of birth should be reported as SAEs, regardless of causality. Deaths that occur after the first month must also be reported as SAEs when the investigator qualifies them as related or possibly related to exposure to the investigational medicinal product.

Additional information about exposure during pregnancy can be requested. The need for increased follow-up of the outcome of the birth will be determined on an individual basis (e.g. monitoring of premature infants to identify developmental delay).

In the case of paternal exposure, the study participant will be provided with a "Pregnant Partner Release of Information Form" to give to their partner. It must be recorded that this document was provided to the participant to give to their partner.

Exposure during breast-feeding

Cases of exposure during breast-feeding must be reported regardless of the presence of an associated AE. A report of exposure during breast-feeding will not be generated when a Pfizer drug specifically approved for use in breast-feeding women (e.g. vitamins) is administered in accordance with its authorised use. However, if the child has an AE associated with the administration of the drug, the AE must be reported along with the exposure during breast-feeding.

Medication error

A medication error is an unintended mistake in the prescription, dispensing or administration of a drug that may cause or lead to inappropriate use of the medication or patient harm when the medication is under the control of the healthcare professional, the patient or the consumer. These events may be related to professional practice, products, healthcare procedures and systems, including: prescription; order form; package leaflet; packaging and nomenclature; composition; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Potential medication errors, whether or not linked directly to a patient (e.g. unintentional/incorrect administration, which may be an accidental off-label use or prescription of the product by the healthcare professional or the patient/consumer)
- Confusion related to fictitious names (e.g. trade name, brands)

The investigator must notify Pfizer of the following medication errors, regardless of the occurrence of an associated AE/SAE:

- Medication errors in which the patient has been exposed to the drug, whether or not the error is accompanied by an AE.
- Medication errors that do not involve a patient directly (e.g. potential medication errors). When a medication error does not involve a patient being exposed to the drug, the following minimum reporting criteria are required:
    - An identifiable reporter;
    - A suspect drug;

- The medication error.

Overdose, Incorrect use of the Drug, Extravasation

Reports of overdose, incorrect use of the drug and extravasation associated with using a Pfizer product should be reported to Pfizer by the investigator regardless of the presence of an associated AE/SAE.

Lack of efficacy

Reports of lack of efficacy of a Pfizer product must be reported to Pfizer by the investigator regardless of the presence of an associated AE/SAE or the indication of the Pfizer product.

Occupational exposure

Reports of occupational exposure to a Pfizer product must be reported to Pfizer by the investigator regardless of the presence of an associated AE/SAE.

11.1 Single safety reference document

The latest approved version of the Summary of Product Characteristics of the medicinal product will be used as the single safety reference document during the study, which will be used by the Department of Drug Safety at Pfizer to evaluate any safety event reported to Pfizer by the Investigator during the course of the study.

The single safety reference document should be used by the investigator as prescribing guidelines.

12. PUBLICATION OF RESULTS

All information obtained as a result of this study will be considered confidential.

The Scientific Coordinator of the study, together with the sponsor, will undertake to disclose the results through the usual scientific channels.

The authors listed in the publication of the study results must meet the following requirements:

•Substantial contribution to the proposal and design of the study or to the collection, analysis and interpretation of the study data AND

•Involvement or contribution in writing and/or reviewing the publications with regard to the intellectual content AND

•Contribution to the final approval of the published version AND

•Agreement to act responsibly in all aspects of the publication of the data to ensure that issues pertaining to the accuracy or integrity of any part of the work are investigated and appropriately addressed.

In the event that a ban or restriction (e.g. temporary suspension) is imposed by a competent authority in any part of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer must be immediately informed.

The investigator will also inform Pfizer immediately of any urgent safety measures taken by him/her to protect the study patients from any danger, as well as any violation of the protocol of which the investigator is aware.

13. REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Disponible en: http://globocan.iarc.fr. [Último acceso: noviembre 2013].

2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012 Jan-Feb;62(1):10-29. doi: 10.3322/caac.20138. Epub 2012 Jan 4.

3. Malvezzi M, Bertuccio P, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2012. Ann Oncol. 2012 Apr;23(4):1044-52.doi: 10.1093/annonc/mds024. Epub 2012 Feb 28

4. NCCN Clinical Practices Guidelines in Oncology – Middle East and North Africa (MENA) Edition v3 2014. NCCN.org.

5. Gettinger S, Lynch T.Clin Chest Med. 2011 Dec;32(4):839-51. A decade of advances in treatment for advanced non-small cell lung cancer. doi: 0.1016/j.ccm.2011.08.017. Review.

6. Ettinger DS, Akerley W, Bepler G, Blum MG, Chang A, Cheney RT, Chirieac LR, D'Amico TA, Demmy TL, Ganti AK, Govindan R, Grannis FW Jr, Jahan T, Jahanzeb M, Johnson DH, Kessinger A, Komaki R, Kong FM, Kris MG, Krug LM, Le QT, Lennes IT, Martins R, O'Malley J, Osarogiagbon RU, Otterson GA, Patel JD, Pisters KM, Reckamp K, Riely GJ, Rohren E, Simon GR, Swanson SJ, Wood DE, Yang SC; NCCN Non-Small Cell Lung Cancer Panel Members. Non-small cell lung cancer. J Natl Compr Canc Netw. 2010 Jul;8(7):740-801.

7. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, Fujiwara S, Watanabe H, Kurashina K, Hatanaka H, Bando M, Ohno S, Ishikawa Y, Aburatani H, Niki T, Sohara Y, Sugiyama Y, Mano H. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007 Aug 2;448(7153):561-6.

8. Scagliotti G, Stahel RA, Rosell R, Thatcher N, Soria JC. ALK translocation and crizotinib in non-small cell lung cancer: an evolving paradigm in oncology drug development. Eur J Cancer. 2012 May;48(7):961-73. doi: 10.1016/j.ejca.2012.02.001. Epub 2012 Mar 6.

9. Takeuchi K, Choi YL, Togashi Y, Soda M, Hatano S, Inamura K, et al. KIF5B-ALK, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for ALK-positive lung cancer. Clin Cancer Res. 2009;15:3143-9.

10. Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB, Heist RS, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol. 2009;27:4247-53

11. Ou SH. Drug Des Devel Ther. Crizotinib: a novel and first-in-class multitargeted tyrosine kinase inhibitor for the treatment of anaplastic lymphoma kinase rearranged non-small cell lung cancer and beyond. 2011;5:471-85. doi: 10.2147/DDDT.S19045. Epub 2011 Nov 23. Review.

12. Ficha técnica de XALKORI®.- http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/002489/WC500134759.pdf.

13. Federico Cappuzzoa,∗, Denis Moro-Sibilotb, Oliver Gautschic, Ekaterini Boleti d, Enriqueta Felip e, Harry J.M. Groenf, Paul Germonprég, Peter Meldgaardh, Edurne Arriolai, Nicola Steelej, Jesme Foxk, Patrick Schnelll, Arne Engelsbergm, Jürgen Wolfn. Management of crizotinib therapy for ALK-rearranged non-small cell lung carcinoma: An expert consensus. Lung Cancer 87 (2015) 89–95.

14. Benjamin J Solomon , Dong-Wan Kim , Yi-Long Wu , Kazuhiko Nakagawa , Tarek Mekhail , Enriqueta Felip , Federico Cappuzzo , Jolanda Paolini , Tiziana Usari , Yiyun Tang , Keith D Wilner , Fiona Blackhall , Tony S Mok Final Overall Survival Analysis From a Study Comparing First-Line Crizotinib Versus Chemotherapy in ALK-Mutation-Positive Non-Small-Cell Lung Cancer. J Clin Oncol 36(22), 2251-2258.

15. Lin J, Shaw A. Recent Advances in Targeting ROS1 in Lung CancerJ Thorac Oncol. 2017 Nov; 12(11): 1611–1625.

16. Sociedad Española de Oncología Médica SEOM Las cifras del cáncer en España. Recuperado de: https://seom.org/dmcancer/wp-content/uploads/2019/Informe-SEOM-cifras-cancer-2019.pdf

17. A T Shaw , G J Riely , Y-J Bang , D-W Kim , D R Camidge , B J Solomon , M Varella-Garcia , A J Iafrate , G I Shapiro , T Usari , S C Wang , K D Wilner , J W Clark , S-H I Ou. Crizotinib in ROS1-rearranged Advanced Non-Small-Cell Lung Cancer (NSCLC): Updated Results, Including Overall Survival, From PROFILE 1001. Ann Oncol 30 (7), 1121-1126
18. Mariano Provencio; Enric Carcereny, Delvys Rodriguez-Abreu, Rafael Lopez-Castro, María Guirado, Carlos Camps, et al. Lung Cancer in Spain: Information from the Thoracic Tumors Registry (TTR study). Transl Lung Cancer Res 2019, S(4): 461-47.
19. P Garrido , E Conde , J de Castro , J J Gómez-Román , E Felip , L Pijuan , D Isla , J Sanz , L Paz-Ares , F López-Ríos Updated Guidelines for Predictive Biomarker Testing in Advanced Non-Small-Cell Lung Cancer: A National Consensus of the Spanish Society of Pathology and the Spanish Society of Medical Oncology. Clin Transl Oncol 2019 Oct 9.

14. LIST OF TABLES

Not applicable.

15. LIST OF CHARTS

Not applicable

APPENDIX 1. LIST OF INDEPENDENT DOCUMENTS

Number	Document reference code	Date	Title
Appendix 1	N/A	N/A	List of Appendices to the Protocol
Appendix 2	Pt. create new version		Case Report Form
Appendix 3	CT24-WI-ESP01-RF03	1 January 2014	Commitment of the Coordinating Investigators
Appendix 4	N/A	4 November 2015	Agreement of the central IEC
Appendix 5	CT24-WI-ESP01-RF18	01-Jul-2014	Patient Information Sheet and Informed Consent Form

Appendix 6	N/A	V.2.0 March 2020	Schedule of Payments/Financial Report
Appendix 7	N/A	N/A	Crizotinib SmPC
Appendix 8	N/A	V. 5.0 August 2016	AEs Report Form
Appendix 9	N/A	V.2.0 March 2020	Expected study sites
Appendix 10	V. 3.0 Spanish	N/A	QLQ-C30 Quality-of-Life Questionnaire
Appendix 11	N/A	N/A	QLQ-LC13 Quality-of-Life Questionnaire