NON-INTERVENTIONAL (NI) STUDY FIRST ANNUAL INTERIM REPORT

Study Information

Title	A Descriptive Study of Potential Sight Threatening Event and Severe Visual Loss Following Exposure to XALKORI® (crizotinib)
Protocol number	A8081062
Version identifier of the first annual interim study report	1.0
Date of last version of the first annual interim study report	19 October 2016
EU Post Authorization Study (PAS) register number	ENCEPP/SDPP/12963
Active substance	L01XE16/Crizotinib
Medicinal product	XALKORI®
Research question and objectives	This study aims to evaluate the frequency of risk factors for and sequelae of potential sight-threatening events and severe visual loss among patients being treated with crizotinib.
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1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALK	Anaplastic lymphoma kinase
CEP	Customer Engagement Program
CIOMS	The Council for International Organizations of Medical Sciences
CMET	c-Mesenchymal epithelial growth factor
CRC	Clinical and Research Collaboration
CTCAE	Common Terminology Criteria for Adverse Events
DCA	Data capture aid
DSU	Drug safety unit
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
HGFR	Hepatocyte growth factor receptor
IIR	Investigator Initiated Research
ISPE	The International Society for Pharmacoepidemiology
NI	Non-interventional
NSCLC	Non-small cell lung cancer
PASS	Post-authorization safety study
PMR	Postmarketing requirement
PSTE	Potential sight threatening event

PT	Preferred terms
RON	Recepteur d'Origine Nantais
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SOP	Standard operating procedures
SVL	Severe visual loss
UBC	United BioSource Corporation
US	United States
USPI	United States Product Insert

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Kui Huang, PhD, MPH	Senior Director, Epidemiology, Worldwide Safety & Regulatory	Pfizer, Inc.
Elizabeth Kim, MD	Senior Director, Safety Strategy Risk Management, Worldwide Safety & Regulatory	Pfizer, Inc.
Keith Wilner, PhD	Executive Director, Clinical Development, Global Oncology	Pfizer, Inc.

4. OTHER RESPONSIBLE PARTIES

None

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	31 Mar 2016	31 Mar 2016	
End of data collection	31 Mar 2021		
Registration in the EU PAS register	30 Mar 2016	30 Mar 2016	
Annual interim report 1	Oct 2016		
Annual interim report 2	Oct 2017		
Annual interim report 3	Oct 2018		
Annual interim report 4	Oct 2019		
Annual interim report 5	Oct 2020		
Final study report	Dec 2021		

6. RATIONALE AND BACKGROUND

Crizotinib is a selective small-molecule inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase (RTK) and its oncogenic variants (i.e., ALK fusion events and selected ALK mutations). Crizotinib is also an inhibitor of the hepatocyte growth factor receptor (Hepatocyte growth factor receptor [HGFR] and c-Mesenchymal epithelial growth factor [cMET]), ROS1, and Recepteur d'Origine Nantais (RON) RTKs. Crizotinib was first approved in the United States (US) in 2011 for the treatment of patients with ALK-positive locally advanced or metastatic non-small cell lung cancer (NSCLC). To date, crizotinib has received approval for the treatment of patients with ALK-positive advanced NSCLC in over 85 countries including the European Union (EU) and Japan. In addition, in the US, crizotinib was approved for the treatment of patients with metastatic NSCLC whose tumors are ROS1-positive in March 2016. In the EU, crizotinib was approved for the treatment of adults with ROS1-positive advanced NSCLC in August 2016.

As per the current XALKORI United States Product Insert (USPI) dated April 2016, the most serious adverse reactions in patients with ALK-positive or ROS1-positive advanced NSCLC include hepatotoxicity, interstitial lung disease/pneumonitis, and QT interval prolongation. The most common adverse reactions (≥25%) seen in crizotinib clinical trials were vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness, and neuropathy. In addition, across clinical trials (n=1719), there were 13 patients (0.8%) with a Grade 3 visual impairment and 4 patients (0.2%) with a Grade 4 visual impairment.[1]

A number of factors may predispose patients with lung cancer to develop conditions affecting vision. First, patients with lung cancer often have treatments such as cytotoxic chemotherapy, which is associated with ocular toxicities. Cisplatin and carboplatin, commonly used therapies in lung cancer, have been shown to cause toxicities such as optic neuritis, transient cortical blindness, and maculopathy (Schmid et al, 2006).[2] Second, approximately 20% of patients with lung cancer develop brain metastases. Treatment modalities include radiotherapy and stereotactic brain surgery, which can lead to complications such as optic neuropathy, retinopathy, and cortical blindness. Finally, general medical conditions such as hypertension, diabetes, and age-related macular degeneration are prevalent in the elderly population and these may also predispose patients to conditions affecting vision.

Some Grade 2 ocular adverse events (AEs) may be initially noted by physicians or patients, but have the potential to lead to significant visual loss, i.e., Grade 3 or 4 events. Therefore, it is important to assess those potential sight threatening events (PSTE).

To better understand severe visual loss (SVL) and PSTE, this descriptive study aims to assess the frequency of risk factors for and sequelae of SVL and PSTE among patients being treated with crizotinib.

This non-interventional (NI) study is a Post-Authorization Safety Study (PASS) and is a postmarketing requirement (PMR) issued by the US Food and Drug Administration (FDA). The US PMR requires the conduct of an Enhanced Pharmacovigilance Study to evaluate the

risk factors for and outcomes of SVL, as well as PSTE, following exposure to XALKORI (crizotinib).

7. RESEARCH QUESTION AND OBJECTIVES

The objective of the study is to evaluate the frequency of risk factors for and sequelae of SVL and PSTE following exposure to crizotinib.

8. AMENDMENTS AND UPDATES

None

9. RESEARCH METHODS

9.1. Study design

This is a NI study.

9.2. Setting

This descriptive NI study collects data on SVL and PSTE between March 31, 2016 and March 31, 2021 from SAE reports from Pfizer-sponsored ongoing crizotinib clinical trials and non-Pfizer sponsored ongoing crizotinib clinical trials (e.g., Investigator Initiated Research [IIRs], Clinical and Research Collaborations [CRCs] and co-development trials), from AE or SAE reports from Pfizer-sponsored ongoing crizotinib NI Prospective Primary Data Collection studies, postmarketing spontaneous reports, and from other solicited data sources (e.g., compassionate use programs, solicited Customer Engagement Program [CEP]) in patients being treated with crizotinib.

The AE/SAE reports for SVL and PSTE events that occurred prior to the start of the study period, i.e., from September 14, 2015 to March 30, 2016, are included as an addendum to this First Annual Interim Report (reference: FDA General Advice Letter dated December 8, 2015) (see Annex 1, Addendum to First Annual Interim Report). These cases will not be included in any subsequent annual interim report or the final study report.

9.3. Patients

To be eligible for this study, patients need to be treated with crizotinib and have AE/SAE reports of SVL and PSTE received from study data sources described in Section 9.5 between March 31, 2016 and March 31, 2021. All AE/SAE reports of SVL and PSTE in patients that have been treated with crizotinib are to be included, regardless of the indication for use of crizotinib. There are no exclusion criteria for the study. This First Annual Interim Report includes all AE/SAE reports of SVL and PSTE from March 31, 2016 to July 1, 2016.

9.4. Preferred terms and variables

An SVL event in clinical trials is defined as Grade 3 or Grade 4 eye disorders based on Common Terminology Criteria for Adverse Events (CTCAE). According to CTCAE version 4.03, Grade 3 eye disorders include symptomatic retinopathy with marked decrease in visual

acuity (worse than 20/40) or disabling (limited self-care activities of daily living). Grade 4 eye disorders on CTCAE are blindness (20/200 or worse) in the affected eye.

An SVL event in Pfizer-sponsored NI Prospective Primary Data Collection studies and spontaneous reports and other solicited data sources is identified by the following PTs (MedDRA v.18.0) that correspond with the following Grade 3 or Grade 4 events on CTCAE: Blindness cortical, Blindness day, Blindness transient, Blindness unilateral, Amaurosis, Amaurosis fugax, Night blindness, Sudden visual loss, Optic neuropathy, Optic ischemic neuropathy, Optic nerve disorder, Retinopathy, Toxic optic neuropathy, Visual cortex atrophy, Visual pathway disorder, Optic atrophy, Hemianopia, Hemianopia heteronymous, Hemianopia homonymous, Quadrantanopia, Tunnel vision, and Visual field defect.

A PSTE in Pfizer-sponsored ongoing crizotinib clinical trials includes all identified Grade 2 eye disorders as listed above (except Visual field defect) and other Grade 2 eye disorders of Retinal detachment, Retinal edema, Maculopathy, Iritis, Uveitis, and Visual field tests abnormal. For non-Pfizer sponsored ongoing crizotinib trials, NI Primary Data Collection studies, spontaneous reports, and other solicited data sources, the following PTs were used to capture PSTE: Retinal detachment, Retinal edema, Maculopathy, Iritis, Uveitis, and Visual field tests abnormal.

Variables collected in this study and their descriptions are as follows:

Variable	**Description**
• Age	Demographic
• Gender	Demographic
• Race	Demographic
• Treatment with crizotinib	Exposure
• Treatment for PSTE/SVL	Treatment
• Medical history	Risk factor
• Brain metastases	Risk factor
• Brain MRI and images	Examination
• Brain radiation therapy	Risk factor
• Macular degeneration	Ocular history/Risk factor
• Glaucoma	Ocular history/Risk factor
• Diabetic retinopathy	Ocular history/Risk factor
• Cataracts	Ocular history/Risk factor
• Trauma to the eye	Ocular history/Risk factor
• Optic atrophy	Ocular history/Risk factor
• Optic nerve edema	Ocular history/Risk factor
• Retinal hemorrhages	Ocular history/Risk factor
• Vitreous hemorrhage	Ocular history/Risk factor
• Macular edema	Ocular history/Risk factor
• Retinal holes	Ocular history/Risk factor
• Retinal detachment	Ocular history/Risk factor
• Iritis	Ocular history/Risk factor

Variable	Description
• Uveitis	Ocular history/Risk factor
• Ocular surgery	Ocular history/Risk factor
• Best corrected distance visual acuity	Ophthalmic exam
• Pupil size	Ophthalmic exam
• Pupils' reaction to light	Ophthalmic exam
• Slit lamp examination	Ophthalmic exam
• Intraocular pressure	Ophthalmic exam
• Retinal photographs	Ophthalmic exam
• Visual Field test	Ophthalmic exam
• Defects in the Visual Field test	Ophthalmic exam
• Optical Coherence Tomography (OCT)	Ophthalmic exam
• Medications known for ocular toxicity	Concomitant medications/Risk factor
• Elevated intracranial pressure	Co-morbidities/Risk factor
• Carotid Doppler	Exam/Co-morbidities/Risk factor
• Erythrocyte Sedimentation rate	Co-morbidities/Risk factor
• C-reactive protein	Co-morbidities/Risk factor

9.5. Data sources and measurement

Data sources for this study included:

- Pfizer-sponsored ongoing crizotinib clinical trials,
- Pfizer-sponsored ongoing crizotinib NI Prospective Primary Data Collection studies,
- non-Pfizer sponsored ongoing crizotinib clinical trials (e.g., IIRs, CRCs, co-development trials),
- Post-marketing spontaneous reports,
- Other solicited data sources (e.g., compassionate use programs, CEP).

Data for this study are collected through the routine data collection practices of AE reporting from these data sources.

To assure collection of the variables noted above, particularly ocular history and ophthalmologic examination findings, the following tools are used:

- a PSTE/SVL Follow-up Form is used by the investigators in Pfizer sponsored ongoing crizotinib clinical trials and in NI Prospective Primary Data Collection studies, and

- a PSTE/SVL Data Capture Aid (DCA) is used by local Pfizer Drug Safety Unit (DSU) staff for collecting additional data for SVL and PSTE for non-Pfizer sponsored ongoing crizotinib clinical trials, Pfizer-sponsored NI other Primary Data Collection studies, and postmarketing spontaneous reports and other solicited data sources.

9.6. Bias

Potential sources of bias in this study usually present a challenge to observational studies using existing data sources. Sources of bias specific to the use of secondary data important in the context of this study include information bias due to confounding factors and missing or incomplete data. For example, a patient treated with crizotinib may have had potential risk factors for SVL and PSTE such as presence of brain metastases, relevant ocular history, significant past medical history (e.g., diabetes mellitus), or may have been treated with medicines that have ocular toxicities, but these data may not have been available, especially from sources with expected low data quality (e.g., spontaneous reports). Additionally, this study uses predetermined PTs to capture SVL and PSTEs but a Verbatim Term or Lowest Level Term in the report that is not meant to denote SVL and PSTEs may be coded to a predetermined PT.

9.7. Study size

All AE or SAE reports for SVL and PSTE received from patients treated with crizotinib in Pfizer-sponsored ongoing crizotinib clinical trials, other ongoing crizotinib trials, Pfizer-sponsored ongoing NI Prospective Primary Data Collection studies, postmarketing spontaneous reports, and other solicited data sources during the study period are included in all analyses.

9.8. Data transfer

Data collected in this study are transferred on a regular basis through secure email from Pfizer's global safety database to United BioSource Corporation (UBC) for analysis. They are stored on a secure database hosted by UBC and maintained by trained data managers, ensuring compliance with local or national regulations. SAS® software is used for statistical analyses in this study.

9.9. Statistical methods

9.9.1. Main summary measures

All data presented in the interim reports and final report will be summarized using descriptive statistics. Descriptive statistics will be used for continuous variables (number of observations (n), mean, standard deviation, minimum, median, and maximum) and for categorical variables (counts and percentages).

An overview of all reported SVL and PSTE will be provided on the patient unit using frequency counts and percentages. All reported SVL and PSTE based on the PT will be presented on the patient unit by means of frequency counts and percentages.

9.9.2. Main statistical methods

The frequency of risk factors (medical history, past ocular history, and concomitant medications) and outcomes of SVL and PSTE collected on the PSTE/SVL Follow-up Form and the PSTE/SVL DCA will be presented using 3 different analysis units: patient, event, and eye as appropriate. Three different analysis units will be used because a patient may have multiple events and have one or both eyes affected.

The patient analysis unit is all unique patients for whom one or multiple SVL events or PSTEs were reported.

The event level is defined as all SVL events and PSTE reported as part of this study. For this analysis, a patient with 2 reported events is counted twice. This analysis unit will be used for parameters collected on patient level that may change over time (e.g., intracranial pressure, presence of brain metastases). If the vast majority of patients having AE or SAE reports of SVL or PSTE are single event, the event level analysis may not be conducted. Instead, a patient level analysis may be performed.

The eye analysis unit is defined as the affected eye. For this analysis, a patient with both eyes affected will be counted twice to the affected eye group. For patients where only one eye was affected, the contra-lateral eye will be summarized as "unaffected eye." This analysis unit will be used for all analyses referring to the ocular history and the ocular examinations.

The affected eye will be derived from the following data points in the PSTE/SVL Follow-up Form or the PSTE/SVL DCA:

- Onset date: If the question "Do you know when the Potential Sight Threatening Event/Severe Visual Loss event occurred?" is answered with "Yes," or "No," but a start date is given to the right or left eye, it will be assumed that the eye is affected. If the question was answered with "Not applicable (NA)," it was assumed that the eye was not affected.

- End date: If the question "Is Potential Sight Threatening Event/Severe Visual Loss ongoing?" is answered with any response to the right or left eye other than "NA," it will be assumed that the eye is affected.

- Onset of the SVL or PSTE: If the question "How did the onset of Potential Sight Threatening Event/Severe Visual Loss occur?" is answered with "Suddenly," "Gradually," or "Other," to the right or left eye, it will be assumed that the eye is affected.

If an eye is identified as affected by any of the above 3 questions, the eye will be counted as an affected eye. If an eye is not identified as an affected eye by any of the 3 questions above, or if data on all 3 questions is missing when there are some data for the other eye, the eye will not be counted as an affected eye.

If the data points in all 3 questions are completely missing for both eyes, the eye will be classified as "Missing."

9.9.3. Missing values

There is no substitution of missing values. However, partial date values are imputed as specified in the statistical analysis plan.

9.9.4. Sensitivity analyses

None

9.9.5. Amendments to the statistical analysis plan

None

9.10. Quality control

UBC was responsible for following their standard operating procedures (SOPs) as well as Pfizer's SOPs whenever appropriate to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, and description of available data.

9.11. Protection of human patients

All parties were to ensure protection of patient personal data and not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by law. In case of data transfer, Pfizer maintained high standards of confidentiality and protection of patient personal data.

A study specific informed consent was not required for this study. In addition, the informed consent was already obtained from Pfizer-sponsored ongoing crizotinib clinical trials, non-Pfizer sponsored ongoing crizotinib clinical trials, Pfizer-sponsored NI Prospective Primary Data Collection studies, and spontaneous reporting related activities and other solicited data sources.

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and followed generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment.

10. RESULTS

10.1. Participant

Overall, one report of an SVL event was received during this interim reporting period between March 31, 2016 and July 1, 2016, and this was from a spontaneous report.

10.2. Descriptive data

The one reported case was received on April 1, 2016 for Mfr Control No. 2016192327 as a report from a Pfizer Sponsored program entitled "XALKORI patient engagement." A contactable consumer reported a male patient started to receive crizotinib in January 2014 at an unknown dose for ROS1-positive advanced NSCLC. The patient's medical history and concomitant medications were not reported. On an unknown date, the patient reported fatigue and vision loss/difficulty. Symptoms had subsided by the time of reporting and the patient reported "minimal incidence" since that time. The action taken and the outcome of the events were unknown. No further information was received. A detailed report for this case (CIOMS) is included in Annex 1, Appendix 1 for First Annual Interim Report.

10.3. Outcome data

Not applicable, since only 1 reported case of a PT that could be indicative of SVL or PSTE was received during the First Annual Interim Report period.

10.4. Main results

Not applicable since only 1 reported case of a PT that could be indicative of SVL or PSTE was received during the First Annual Interim Report period.

10.5. Other analysis

Not applicable since only 1 reported case of a PT that could be indicative of SVL or PSTE was received during the First Annual Interim Report period.

10.6. Adverse events / adverse reactions

Data sources for this study include Pfizer sponsored ongoing crizotinib clinical trials, non-Pfizer sponsored ongoing crizotinib clinical trials (e.g., IIRs, CRCs), Pfizer-sponsored ongoing crizotinib NI Primary Data Collection studies, and post-marketing spontaneous reports. Regulatory reporting of AEs/adverse reactions based on data source occurs per standard practice. Severe visual loss events and PSTE described in this study have met regulatory reporting requirements as applicable based on their initial source (i.e., SAE reporting of clinical trials, SAE/AE reporting of NI studies, or spontaneous reporting).

11. DISCUSSION

11.1. Key results

This First Annual Interim Report was based on 1 reported case of a PT that could be indicative of SVL from March 31, 2016 to July 1, 2016. The reported case was received via a spontaneous report and was reported as Verbatim term "vision loss/difficulty" which was coded to PT Blindness. This case had very limited information about the event with unknown or not reported medical history and concomitant medications. The duration of treatment with crizotinib prior to the onset of the reported PT that could be indicative of SVL, the final outcome of the event, and the ophthalmologic examinations after the occurrence was unknown. Although follow-up was attempted per Pfizer's SOPs, it was not possible because the consumer refused to be contacted.

11.2. Limitations

There are two major limitations in this First Annual Interim Report. First, the description of the AE/SAEs (Verbatim term) may be coded in the MedDRA system to a PT on the list of predetermined SVL and PSTE as defined in the study protocol, even if the reporters do not consider cases to be an SVL or PSTE. Second, a large amount of data was missing or incomplete on the only 1 SVL report, as expected with reporting via the spontaneous reporting system.

After reviewing the reported SVL case, Pfizer's Ocular Safety council concluded that based on the available information, it was difficult to assess the reported SVL case and classify it as a true SVL event due to lack of information on relevant medical history and ophthalmologic examinations after the occurrence of reported SVL events. The council suggested an external expert committee review and adjudicate all reported SVL cases received during the study period (i.e., between March 31, 2016 and March 30, 2021). Therefore, an external expert committee will be established to review and adjudicate all SVL cases before each subsequent annual interim report submission.

11.3. Interpretation

The results presented in this First Annual Interim Report were based on 1 report of a PT that could be indicative of SVL received between March 31, 2016 and July 1, 2016, and the report was received via a spontaneous report that had very limited case details. Because the case narrative reported "fatigue, vision loss/difficulty" and that the symptoms had "subsided," the Pfizer Ocular Safety Council suggested that this is not consistent with the clinical presentation of SVL. The data reported in this First Annual Interim Report do not identify any specific risk factors for and sequelae of SVL and PSTE following exposure to crizotinib.

11.4. Generalizability

The results of this First Annual Interim Report are not generalizable because only 1 reported case of SVL was received during the interim report period.

12. OTHER INFORMATION

Not Applicable

13. CONCLUSIONS

There was 1 reported case which was received via a spontaneous report. From the limited information provided, it appeared that this event may have been transient in nature and was not consistent with the clinical presentation of SVL. As no medical history or concomitant medications were provided by the reporter, there is insufficient information to identify potential risk factors for the event. The ophthalmologic safety profile of crizotinib has not changed as a result of data obtained during the reporting period for this First Annual Interim Report.

14. REFERENCES

1. XALKORI (crizotinib) United States Package Insert (version 4/2016) http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo

2. Schmid KE1, Kornek GV, Scheithauer W, Binder S. Update on ocular complications of systemic cancer chemotherapy. Surv Ophthalmol. 2006 Jan-Feb;51(1):19-40.

15. LIST OF SOURCE TABLES AND FIGURES

None

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Appendix 1 for First Annual Interim Report

Addendum to First Annual Interim Report

Appendix 1 for Addendum

Document Approval Record

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