NON-INTERVENTIONAL (NI) STUDY FINAL REPORT ABSTRACT

Title: A Descriptive Study of Potential Sight Threatening Event and Severe Visual Loss Following Exposure to XALKORI® (Crizotinib)

Date of Abstract: 04 November 2021

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Key words: Crizotinib, non-small cell lung cancer, severe visual loss (SVL), potential sight-threatening event (PSTE)

Rationale and background: Crizotinib (XALKORI®) is a selective small-molecule inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase (RTK) and its oncogenic variants (ie, ALK fusion events and selected ALK mutations). Crizotinib is also an inhibitor of MET/hepatocyte growth factor receptor (HGFR), ROS1, and recepteur d'origine Nantais (RON) RTKs.

Crizotinib first received marketing approval in the United States (US) in 2011 for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ALK-positive as detected by a Food and Drug Administration (FDA)-approved test.

Crizotinib also received approval in the European Union (EU) in 2012 for the treatment of adults with previously treated and subsequently for previously untreated ALK-positive advanced NSCLC. Crizotinib has additionally received approvals for the treatment of ALK-positive advanced NSCLC in more than 90 countries worldwide. Crizotinib received approval for a second indication of ROS1-positive advanced NSCLC in the US and EU in March 2016 and August 2016, respectively, and has additionally received approvals for the treatment of ROS1-positive advanced NSCLC in more than 75 countries worldwide. In the US, crizotinib was approved in January 2021 for the treatment of pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma that is ALK-positive.

As per the current XALKORI US Package Insert (USPI) dated January 2021, the most serious adverse reactions in patients with ALK positive or ROS1 positive advanced NSCLC are hepatotoxicity, interstitial lung disease/pneumonitis, and QT interval prolongation. The most frequent adverse reactions (≥25%) in decreasing frequency seen in crizotinib clinical trials are vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness and neuropathy. In patients 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. In Study ADVL0912 of 121 patients who were ≤21 years of age treated with XALKORI, 26 patients with ALCL were included and vision disorders were reported in 65% of these patients. The most common visual symptoms were blurred vision and visual impairment.

A number of factors may predispose patients with lung cancer to develop severe visual loss (SVL). First, patients with lung cancer are often treated with 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. Second, approximately 20% of patients with lung cancer develop brain metastases. Treatment modalities for brain metastases 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 (as is NSCLC) and these conditions may also predispose patients to SVL.

Some Grade 2 ocular adverse events (AEs) may be initially noticed and considered minor by physicians or patients but may lead to significant visual loss. Therefore, it is important to assess these potential sight-threatening events (PSTE).

To better understand SVL and PSTE, this descriptive study aimed 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 a Post-Marketing Requirement (PMR 2956-1) issued by the US FDA. This US PMR required the conduct of an Enhanced Pharmacovigilance (PV) Study to evaluate the risk factors for and outcomes of SVL, as well as PSTE, following exposure to crizotinib.

As planned, this Final Study Report includes all AE/serious adverse event (SAE) reports indicative of SVL and PSTE from 31 March 2016 to 31 March 2021.

Research question and objectives: The objective of the study was to evaluate the frequency of risk factors for and sequelae of SVL and PSTE following exposure to crizotinib.

Study design: This was a 5-year descriptive, NI, enhanced PV, global study of adult patients treated with crizotinib. The study observation period was from 31 March 2016 to 31 March 2021.

Setting: This study collected data on AEs and SAEs indicative of SVL or PSTE received from Pfizer-sponsored ongoing and new crizotinib clinical trials, non-Pfizer-sponsored ongoing and new crizotinib clinical trials (ie, Investigator-Sponsored Research [ISR] clinical trials, previously denoted as Investigator-Initiated Research [IIR] in the protocol, and Clinical and Research Collaboration [CRC] clinical trials), Pfizer-sponsored ongoing and new crizotinib NI primary data collection studies, post-marketing spontaneous reports, and other solicited data sources (eg, compassionate use programs, solicited Customer Engagement Program [CEP]).

Patients and study size, including dropouts: To be eligible for this NI study, patients must have been treated with crizotinib and had at least 1 AE/SAE report indicative of SVL or PSTE received from data sources between 31 March 2016 and 31 March 2021. All reports indicative of SVL or PSTE in patients who had been treated with crizotinib were included, regardless of the indication for use of crizotinib. There were no exclusion criteria for the study.

Variables and data sources: Variables collected in this study included patient demographics, crizotinib exposure, treatment for SVL and PSTE, risk factors, ocular history, concomitant medications, co-morbidities, ophthalmic examinations, and sequelae of PSTE and SVL. The following data sources were used: Pfizer-sponsored ongoing and new crizotinib clinical trials, Pfizer-sponsored ongoing and new crizotinib NI Primary Data Collection studies, non-Pfizer-sponsored ongoing and new crizotinib clinical trials (ie, ISR and CRC clinical trials), post-marketing spontaneous reports, and other solicited data sources (eg, compassionate use programs, CEP).

An external expert adjudication committee, comprised of experts in research and clinical ophthalmology, provided additional scientific integrity to the study by determining whether cases reported with AEs potentially indicative of SVL or PSTE were likely to be true cases of SVL or PSTE.

Results: Cumulatively, 50 cases indicative of SVL or PSTE were received between 31 March 2016 and 31 March 2021. (An additional 8 cases were received prior to 31 March 2016 and therefore were not included in any analyses but were included as an addendum to the First Annual Interim Report.) Thus, 50 cases were adjudicated by the adjudication committee. Of these 50 cases, 46 were AE/SAE reports potentially indicative of SVL and 4 were AE/SAE reports potentially indicative of PSTE. Of the 46 cumulative reported cases potentially indicative of SVL, 5 cases were adjudicated as likely to be SVL,

10 cases as likely to be PSTE, 1 report was adjudicated to be a non-case, and there was insufficient information for 30 cases. Adjudication of the 4 reported cases indicative of PSTE found all 4 cases as likely to be PSTE. In total, there have been 14 cumulative adjudicated PSTE cases, 5 cumulative adjudicated SVL cases, 1 non-case, and 30 cases with insufficient information.

Of the 5 cumulative adjudicated SVL cases, 2 were from spontaneous reports, 2 were from a Pfizer-sponsored clinical trial, and 1 was reported from a non-Pfizer-sponsored clinical trial. The presenting characteristics of the SVL were unilateral for 2 cases, bilateral for 1 case, and unspecified for 2 cases. All 5 cases were reported as serious. Of these 5 cumulative adjudicated SVL cases, the causal relationship to crizotinib was assessed as not related by the treating physician for 2 cases and unknown for 3 cases. Three cases were reported to have a sudden onset while 2 cases were reported with unknown onset time. Two cases experienced other symptoms (cerebral infarction and headache left side, one case each) associated with the reported SVL, 1 case did not experience other symptoms, and it was unknown whether the other 2 cases experienced other symptoms.

Of the 14 cumulative adjudicated PSTE cases, 11 were from spontaneous reports and 3 reports were from a non-Pfizer-sponsored clinical trial. The presenting characteristics of the PSTEs were bilateral for 3 cases, unilateral for 1 case, and unspecified for 10 cases. Three cases were non-serious, 10 cases were serious, and for 1 case the level of seriousness was unknown. The causal relationship to crizotinib was assessed by the treating physician as related for 1 case, not related for 4 cases, and unknown for 9 cases. The onset time of the PSTE was sudden for 1 case and unknown for the remaining 13 cases. Five cases experienced other symptoms (candida infection of eye, flashing lights, nausea, visual disturbances, optic neuritis, 1 case each) associated with the PSTE, 1 case did not experience other symptoms, and it was unknown whether 8 cases experienced other symptoms.

Among the 5 adjudicated SVL cases, PTs were Blindness (n=1), Blindness cortical (n=1), Blindness unilateral (n=1), Cerebral infarction (n=1), Headache (n=1), Optic atrophy (n=1), and Retinal detachment (n=1). Among the 14 adjudicated PSTE cases, PTs were Amaurosis (n=2), Uveitis (n=2), Retinal detachment (n=2), Blindness (n=2), Candida infection (n=1), Flashing lights (n=1), Nausea (n=1), Neuritis optic (n=1), Optic neuropathy (n=1), Retinopathy (n=1), Vision blurred (n=1), Visual disturbance not otherwise specified (n=1), Visual disturbances (n=1), Visual field defect (n=1), Visual field tests abnormal (n=1), Papilledema (n=1), and Visual impairment (n=1).

Discussion: Of 50 reported cases, there were 46 AE/SAE reports potentially indicative of SVL, 4 were AE/SAE reports potentially indicative of PSTE. Of the 46 cumulative reported cases potentially indicative of SVL, 5 cases were adjudicated as likely to be SVL and 10 cases as likely to be PSTE. Adjudication of the 4 reported cases indicative of PSTE found all 4 cases as likely to be PSTE. Cumulatively, there were a total of 19 adjudicated cases: 5 SVL cases and 14 PSTE cases. This limited number of cases does not allow for a meaningful evaluation of risk factors for and sequelae of SVL and PSTE cases following exposure to crizotinib.

Associated risk factors for SVL/PSTE were noted among the cases, which included a prior history of ocular disease (cataracts, macular edema and retinal detachment). In terms of general medical history, diabetes, hypertension, hyperlipidemia, and transient ischemic attack/stroke were observed. In addition, 3 of the 5 adjudicated SVL and 2 of the 14 adjudicated PSTE cases had prior history of brain metastases. However, given the low numbers of cases and limited information, no firm conclusions can be made.

The results of this study are not generalizable because of the limited number of adjudicated cases of SVL or PSTE during the study period.

A major limitation of this study is the large amount of data missing or incomplete on the cases. This is expected as 42 of the 50 (84.0%) reported cases potentially indicative of SVL or PSTE were received from the spontaneous reporting system.

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Document Approval Record

Document Name:	A8081062 NI Study Report Final Abstract
Document Title:	A8081062

Signed By:	Date(GMT)	Signing Capacity
De Bernardi, Barbara	15-Nov-2021 14:39:43	EUQPPV Approval
Rubino, Heather	15-Nov-2021 16:20:30	Manager Approval