NON-INTERVENTIONAL (NI) STUDY FINAL REPORT

Study Information

Title	A Descriptive Study of Potential Sight-Threatening Events and Severe Visual Loss Following Exposure to XALKORI® (Crizotinib)
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Active substance	L01XE16/Crizotinib
Medicinal product	XALKORI®
Research question and objectives	This study aimed 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	Council for International Organizations of Medical Sciences
CRC	Clinical and Research Collaboration
CTCAE	Common Terminology Criteria for Adverse Events
DCA	Data Capture Aid
DSU	Drug Safety Unit
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPFV	First Patient First Visit
HGFR	Hepatocyte Growth Factor Receptor
IEC	Independent Ethics Committee
IIR/ISR	Investigator-initiated Research/Investigator-sponsored Research
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mesenchymal Epithelial Transition
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NI	Non-interventional
NSCLC	Non-small Cell Lung Cancer
OCT	Optical Coherence Tomography
PAS	Post-authorisation Study
PASS	Post-authorisation Safety Study
PMR	Post-marketing Requirement
PSTE	Potential Sight-threatening Event
PT	Preferred Term
PV	Pharmacovigilance
QC	Quality Control
QT	Q Wave/T Wave
RON	Recepteur d'Origine Nantais
ROS1	c-ROS oncogene 1

Abbreviation	Definition
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedures
SVL	Severe Visual Loss
US	United States
USPI	United States Package Insert

3. INVESTIGATORS

Principal Investigators of the Protocol

Name, Degree(s)	Title	Affiliation
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Keith Wilner, PhD	Executive Director, Clinical Development, Global Oncology	Pfizer Inc.

4. OTHER RESPONSIBLE PARTIES

None.

5. MILESTONES

Milestone	Planned date	Actual date
Start of data collection	31 Mar 2016	31 Mar 2016
Registration in the EU PAS register	30 Mar 2016	30 Mar 2016
Annual interim report 1	Oct 2016	28 Oct 2016
Annual interim report 2	Oct 2017	26 Oct 2017
Annual interim report 3	Oct 2018	31 Oct 2018
Annual interim report 4	Oct 2019	31 Oct 2019
Annual interim report 5	Oct 2020	28 Oct 2020
End of data collection	31 Mar 2021	31 Mar 2021
Final study report	Dec 2021	--

6. 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 mesenchymal epithelial transition (MET)/hepatocyte growth factor receptor (HGFR), c-ROS oncogene 1 (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.[1] 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.[1] In Study ADVL0912 of 121 patients who were ≤21 years of age treated with crizotinib, 26 patients with ALCL were included and vision disorders were reported in 65% of these patients.[1] The most frequent 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.[2] 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.

7. RESEARCH QUESTION AND OBJECTIVES

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

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendment Number	Date	Substantial or Administrative Amendment	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
1	28-APR-2017	Substantial	1. PASS information (cover page)	1. Added EU PAS registration number	1. The study was registered at EU PAS register.
			2. Section 5	2. Updated relevant regulatory information related to approval history for crizotinib	2. Crizotinib has been approved in more countries for ALK-positive advanced NSCLC and for ROS1positive advanced NSCLC in the US and EU since the original protocol.
			3. Section 7	3. Updated data collection procedures for new crizotinib Investigator Initiated Research (IIR) and Clinical and Research Collaboration (CRC) clinical trials	3. To improve the quality of data collection, new crizotinib IIR and CRC clinical trials in which a FPFV occurs after June 30, 2017 during the study period will follow the same data collection procedures

Table 1. Amendments to the Protocol

Amendment Number	Date	Substantial or Administrative Amendment	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				in which a First Patient First Visit (FPFV) occurs after June 30, 2017 during the study period; updated the list of variables to be collected in this study and the data analysis section; added a new section for the external adjudication committee	as Pfizer sponsored crizotinib clinical trials. In addition, the list of variables to be collected in this study and the data analysis section were updated, and a new section was added to describe the external adjudication committee that was formed to determine whether reported cases indicative of PSTE/SVL are PSTE/SVL cases based on pre-defined clinical criteria.
			4. Section 8.1 5. Entire document	4. Updated patient privacy and consent language 5. Editorial changes	4. To conform to local laws and regulations, protocol language regarding consent and privacy was updated. 5. Editorial changes made throughout document to enhance clarity.

9. RESEARCH METHODS

9.1. 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.

9.2. Setting

This study collected data on AEs and SAEs indicative of SVL or PSTE received from the following sources:

- Pfizer-sponsored ongoing and new crizotinib clinical trials.
- Non-Pfizer-sponsored ongoing and new crizotinib clinical trials.

  - Investigator-sponsored Research [ISR] clinical trials (previously denoted as Investigator-initiated Research [IIR] in the protocol).
  - Clinical and Research Collaboration [CRC] clinical trials.
- Pfizer-sponsored ongoing and new crizotinib NI primary data collection studies.
- Post-marketing spontaneous reports.
- Other solicited data sources.
  - Compassionate use programs.
  - Customer Engagement Program [CEP]).

9.3. Patients

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.

9.4. Variables

Cases indicative of SVL in Pfizer-sponsored or non-Pfizer-sponsored clinical trials were identified by 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 based on CTCAE are blindness (20/200 or worse) in the affected eye. Cases indicative of SVL in NI Primary Data Collection studies, spontaneous reports, and other solicited data sources were identified by the following preferred terms (PTs) (Medical Dictionary for Regulatory Activities [MedDRA] v.23.0) that correspond with Grade 3 or Grade 4 events on CTCAE: Blindness, 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.

Cases indicative of PSTE in Pfizer-sponsored crizotinib clinical trials and non-Pfizer-sponsored ISR and CRC clinical trials with a FPFV that occurred after 30 June 2017 included 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 other non-Pfizer-sponsored crizotinib trials with a FPFV that occurred up to 30 June 2017, Pfizer-sponsored ongoing and new NI Primary Data

Collection studies, post-marketing spontaneous reports, and other solicited data sources, the following PTs were used to capture cases indicative of PSTE: Retinal detachment, Retinal edema, Maculopathy, Iritis, Uveitis, and Visual field tests abnormal.

Variables collected in this study and their descriptions are shown in Table 2.

Table 2. Variables and Roles

Variable	Role
Age	Demographic
Gender	Demographic
Race	Demographic
Crizotinib	Exposure
SVL cases based on preferred terms	Outcome
PSTE cases based on preferred terms	Outcome
SVL based on adjudication	Outcome
PSTE based on adjudication	Outcome
Treatment for PSTE/SVL	Outcome
Grade for PSTE	Outcome
Grade for SVL	Outcome
Medical history	Risk factor
Exposure to potential ocular toxicity medications	Risk factor
Brain metastases	Risk factor
Brain magnetic resonance images (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
Ocular surgery	Ocular history/Risk factor
Best corrected distance visual acuity	Ophthalmic exam/Outcome
Pupil size	Ophthalmic exam/Outcome
Pupil reaction to light	Ophthalmic exam/Outcome
Slit lamp examination	Ophthalmic exam/Outcome
Intraocular pressure	Ophthalmic exam/Outcome
Optic atrophy	Ophthalmic exam/Outcome

Table 2. Variables and Roles

Variable	Role
Optic nerve edema	Ophthalmic exam/Outcome
Retinal hemorrhages	Ophthalmic exam/Outcome
Macular edema	Ophthalmic exam/Outcome
Retinal holes or detachment	Ophthalmic exam/Outcome
Retinal photographs	Ophthalmic exam/Outcome
Visual field test	Ophthalmic exam/Outcome
Defects in the visual field test	Ophthalmic exam/Outcome
Optical coherence tomography (OCT)	Ophthalmic exam/Outcome
Medications with potential ocular toxicity	Concomitant medications/Risk factor
Elevated intracranial pressure	Co-morbidities/Risk factor
Carotid doppler	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 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, IIR/ISR and CRC clinical trials).
- Post-marketing spontaneous reports.
- Other solicited data sources (eg, compassionate use programs, CEP).

Data for this study were collected through the routine data collection practices of AE reporting from these data sources, with enhanced data collection as described below.

To assure collection of the variables noted in Table 2, particularly ocular history and ophthalmologic examination findings, the following tools were used:

- A PSTE/SVL Follow-up Form was used by the investigators in Pfizer-sponsored ongoing and new crizotinib clinical trials, Pfizer-sponsored ongoing and new crizotinib NI Prospective Primary Data Collection studies (eg, prospective cohort studies), and in non-Pfizer-sponsored ongoing and new crizotinib ISR and CRC

clinical trials, specifically in ISR and CRC clinical trials in which a FPFV occurred after 30 June 2017 during the study period.

- A PSTE/SVL Data Capture Aid (DCA) was used by local Pfizer Drug Safety Unit (DSU) staff for collecting additional data on PSTE or SVL for Pfizer-sponsored ongoing and new NI other Primary Data Collection studies (eg, cross-sectional surveys), post-marketing spontaneous reports, other solicited data sources, and non-Pfizer-sponsored ongoing crizotinib clinical trials, specifically non-Pfizer-sponsored ongoing crizotinib clinical trials in which the FPFV occurred up to 30 June 2017.

9.6. Bias

As an enhanced PV study that relies on the evaluation, quantity and quality of reported AEs and SAEs, the main biases include underreporting and information bias stemming from incomplete information needed to fully evaluate the events of interest. A patient treated with crizotinib may have had potential risk factors for PSTE or SVL such as presence of brain metastases, relevant ocular history, significant past medical history (eg, diabetes mellitus), or may have been treated with medicines that have ocular toxicities. These data may not have been available, especially from sources with expected low data quality (eg, spontaneous reports). Additionally, underreporting was expected from spontaneous reports; therefore, the cases indicative of PSTE or SVL reported in this study may not provide a complete understanding of the potential risk factors and sequelae of these events.

9.7. Study Size

All AE or SAE reports indicative of PSTE or SVL in patients treated with crizotinib in Pfizer-sponsored ongoing and new crizotinib clinical trials, Pfizer-sponsored ongoing and new NI Primary Data Collection studies, non-Pfizer-sponsored ongoing and new crizotinib trials, post-marketing spontaneous reports and other solicited data sources during the study period were included in the study. As a descriptive study, there were no a priori hypotheses specified; therefore, sample size calculations were not applicable.

9.8. Data Transformation

Data collected in this study were transferred on a regular basis through secure email from Pfizer's global safety database to UBC for data entry and analysis. Data were stored on a secure database hosted by UBC and maintained by trained data managers, ensuring compliance with local or national regulations.

9.9. Adjudication Committee

An external expert adjudication committee, comprised of experts in research and clinical ophthalmology, provided additional scientific integrity for the study by determining whether cases reported with AEs potentially indicative of PSTE or SVL are likely to be true cases of PSTE or SVL. The composition of this committee and the process by which it adjudicated cases based on pre-defined clinical criteria are specified in the Adjudication Committee Charter (Appendix 8.2). The adjudicated results were stored on the same secure database

described in Section 9.8 and are presented in the reports, beginning with the Second Annual Interim Report and ending with this Final Study Report.

9.10. Statistical Methods

9.10.1. Main Summary Measures

No statistical hypothesis or sample sizes were specified in the protocol or SAP for this study and all analyses were descriptive. Descriptive statistics were used for continuous variables (number of observations [n], mean, standard deviation, minimum, median, and maximum) and for categorical variables (counts and percentages).

9.10.2. Analysis Populations

9.10.2.1. Full Analysis Set

The Full Analysis Set (FAS) consisted of AE or SAE reports indicative of PSTE or SVL in patients treated with crizotinib in Pfizer-sponsored ongoing and new crizotinib clinical trials, non-Pfizer-sponsored ongoing and new crizotinib trials, Pfizer-sponsored ongoing and new NI Prospective Primary Data Collection studies, post-marketing spontaneous reports, and other solicited data sources during the study period.

9.10.2.2. Safety Analysis Set

The Safety Analysis Set only included adjudicated PSTE or SVL cases.

9.10.3. 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 or the PSTE/SVL DCA are presented using 3 different analysis levels: Patient, Event, and Eye, as appropriate. Three different analysis levels were used because a patient may have had multiple events in 1 or both eyes.

The Patient Level is comprised of all unique patients for whom 1 or multiple PSTE or SVLs were reported. This analysis unit was used for the description of demographic characteristics.

The Event Level is defined as all adjudicated PSTEs or SVLs reported as part of this study. Since there were no patients with multiple adjudicated events, the Event Level and the Patient Level were the same.

The Eye Level is defined as the affected eye. For this analysis, a patient with both eyes affected was counted twice. This analysis unit was used for all analyses referring to the ocular history and the ocular examinations. For patients with only 1 eye affected, the contra-lateral eye was summarized as “unaffected eye.”

The affected eye was derived from the following data points in the PSTE/SVL Follow-up Form and the DCA, which were available for the right and the left eye:

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

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

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

If an eye was identified as affected by any of the above 3 questions, the eye was counted as an affected eye. If an eye was not identified as an affected eye and at least 1 question was answered by "NA," or if data on all 3 questions was missing, the eye was not counted as an affected eye.

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

9.10.4. Missing Values

Missing values for the safety endpoints or the other endpoints were not inputted. However, partial date values were imputed as specified in the Statistical Analysis Plan (SAP).

9.10.5. Sensitivity Analyses

None.

9.10.6. Amendments to the Statistical Analysis Plan

The amended statistical analysis plan version 2.0 was completed and dated 27 June 2017. The following changes were made to the statistical analysis plan (version 1.0, dated 23 June 2016) based on the final amended protocol version 2.0 dated 28 April 2017:

1. An external adjudication committee was formed to determine whether reported cases indicative of PSTE or SVL are likely to be true cases of PSTE or SVL based on pre-defined clinical criteria. As a result, the vast majority of the analyses will be based on the adjudicated PSTE or SVL cases (ie, the reported cases indicative of PSTE or SVL classified by the adjudication committee as likely to be PSTE or SVL) in place of the analyses based on reported cases indicative of PSTE or SVL in the previous version of the SAP.

2. Analysis sets were re-defined as adjudicated likely PSTE or SVL cases in consideration of the adjudication committee.

3. To allow for meaningful interpretation of data, a sample size criterion of at least 5 cumulative cases of adjudicated PSTE or SVL was pre-specified for performing any summary analyses.

9.11. 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 and programming Quality Control (QC) plan, appropriate documentation of data cleaning and validity for created variables, and description of available data.

10. PROTECTION OF HUMAN PATIENTS

10.1. Subject Information and Consent

The information used in this study was anonymized (ie, the information per se does not identify any patient and cannot be used to re identify the patients with the available information) before the study was conducted. Therefore, no study specific consent form was required for this study.

10.2. Independent Ethics Committee (IEC)/ Institutional Review Board (IRB)

IEC/IRB review and approval were not required for this study.

10.3. Ethical Conduct of the Study

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 issued by the International Society for Pharmacoepidemiology and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment.

11. RESULTS

11.1. Participants

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 (Table 3). 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 (Table 3). 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. The presentation of the remaining results will focus on the 19 cumulative adjudicated cases.

A detailed report for all adjudicated cases (Council for International Organizations of Medical Sciences [CIOMS] forms) is included in Appendix 8.1.

Table 3. Reported Cases Indicative of PSTE or SVL and Classification of the Reported Cases by the Adjudication Committee – Full Analysis Set, Event Level

		Reported Cases Indicative of PSTE or SVL		
		PSTE (N=4) n (%)	SVL (N=46) n (%)	Total (N=50) n (%)
Adjudicated outcome	PSTE	4 (100.0)	10 (21.7)	14 (28.0)
	SVL	0	5 (10.9)	5 (10.0)
	Insufficient Information	0	30 (65.2)	30 (60.0)
	Non-case	0	1 (2.2)	1 (2.0)
	Total	4 (100.0)	46 (100.0)	50 (100.0)

Note: The FAS consists of AE or SAE reports indicative of PSTE or SVL in patients treated with crizotinib from study data sources.
AE = adverse event; FAS = full analysis set; N, n = number of PSTE or SVL events; PSTE = potential sight-threatening event; SAE = serious adverse event; SVL = severe visual loss.
Source: Section 14: Table 1.

11.2. Descriptive Data

11.2.1. Demographic and Clinical Characteristics of All Adjudicated Cases (Safety Analysis Set)

11.2.1.1. Demographics

Of the 5 cumulative adjudicated SVL cases, the median age was 52.5 years (range: 19-71); 3 were male, 1 was female, and gender was unknown for 1 patient. One patient was Black, 1 patient was Hispanic, 1 patient was Asian, and race was unknown for 2 patients (Section 14: Table 3). Of the 14 cumulative adjudicated PSTE cases, the median age was 65.0 years (range: 18-77); 6 patients were male, 7 were female, and gender was unknown for 1 patient. Two patients were White, 2 patients were Asian, and race was unknown for 10 patients.

11.2.1.2. Overview of Cumulative Adjudicated SVL and PSTE Cases

The following adjudicated SVL and PSTE cases were included in previous interim reports from 2016 to 2020:

- In the 2016 interim report (31 March 2016 – 01 July 2016) and prior to the introduction of the adjudication process, there was 1 spontaneously reported case by a consumer of an event that could have been indicative of SVL or PSTE, but there was very limited information and the event was not consistent with the clinical presentation of SVL.
- In the 2017 interim report (31 March 2016 – 01 July 2017), cumulatively, there were 2 adjudicated cases of SVL, no cases of PSTE, and 7 cases with insufficient information; 1/2 (50.0%) of the adjudicated cases were from spontaneous reports.
- In the 2018 interim report (31 March 2016 – 01 July 2018), cumulatively, there were 3 adjudicated cases of SVL, 6 cases of PSTE, and 21 cases with insufficient information; 6/9 (67.0%) of adjudicated cases were from spontaneous reports.
- In the 2019 interim report (31 March 2016 – 01 July 2019), cumulatively, there were 5 adjudicated cases of SVL, 11 cases of PSTE, and 26 cases with insufficient information; 11/16 (67.5%) of adjudicated cases were from spontaneous reports.
- In the 2020 interim report (31 March 2016 – 01 July 2020), cumulatively, there were 5 adjudicated cases of SVL, 13 cases of PSTE, and 28 cases with insufficient information; 12/18 (66.7%) of adjudicated cases were from spontaneous reports

Table 4 provides an overview of the 5 cumulative adjudicated cases of SVL, the 14 cumulative adjudicated cases of PSTE, and the total number of reported cases. Note that the number of cases is equal to the number of events and will hereafter be referred to as cases.

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.

Table 4. Overview of PSTE or SVL in All Patients in the Study – Full Analysis Set, Event Level

	Total Outcomes				
	Adjudicated PSTE (N=14)	**Adjudicated SVL (N=5)**	**Insufficient Information (N=30)**	**Non-cases (N=1)**	**Total (N=50)**
Numbers of PSTE or SVLs	14 (100.0)	5 (100.0)	30 (100.0)	1 (100.0)	50 (100.0)
Characteristic of the PSTE or SVL					
Unilateral	1 (7.1)	2 (40.0)	1 (3.3)	0	4 (8.0)
Bilateral	3 (21.4)	1 (20.0)	0	0	4 (8.0)
Unspecified	10 (71.4)	2 (40.0)	29 (96.7)	1 (100.0)	42 (84.0)
Type of data source					
Spontaneous report	11 (78.6)	2 (40.0)	28 (93.3)	1 (100.0)	42 (84.0)
Literature	0	0	0	0	0
Unpublished Manuscripts, Unpublished Abstracts, or Meeting reports	0	0	0	0	0
Regulatory Authorities	0	0	0	0	0
Other Company including License Party	0	0	0	0	0
Other Registry Reports	0	0	0	0	0
Other	11 (78.6)	2 (40.0)	28 (93.3)	1 (100.0)	42 (84.0)
Pfizer-sponsored clinical trial	0	2 (40.0)	0	0	2 (4.0)
Non-Pfizer-sponsored clinical trial	3 (21.4)	1 (20.0)	1 (3.3)	0	5 (10.0)
Pfizer-sponsored prospective primary data collection noninterventional study	0	0	0	0	0
Other solicited data sources	0	0	1 (3.3)	0	1 (2.0)
Seriousness (maximum grade)					
Non-serious	3 (21.4)	0	13 (43.3)	1 (100.0)	17 (34.0)
Serious	10 (71.4)	5 (100.0)	14 (46.7)	0	29 (58.0)
Unknown	1 (7.1)	0	3 (10.0)	0	4 (8.0)

Table 4. Overview of PSTE or SVL in All Patients in the Study – Full Analysis Set, Event Level

	Total Outcomes				
	Adjudicated PSTE (N=14)	Adjudicated SVL (N=5)	Insufficient Information (N=30)	Non-cases (N=1)	Total (N=50)
Reported causal relationship of the PSTE or SVL to crizotinib					
Related	1 (7.1)	0	2 (6.7)	0	3 (6.0)
Not related	4 (28.6)	2 (40.0)	0	0	6 (12.0)
Unknown	9 (64.3)	3 (60.0)	28 (93.3)	1 (100.0)	41 (82.0)
Onset of the PSTE or SVL					
Suddenly	1 (7.1)	3 (60.0)	0	0	4 (8.0)
Gradually	0	0	0	0	0
Other	0	0	0	0	0
Unknown	13 (92.9)	2 (40.0)	30 (100.0)	1 (100.0)	46 (92.0)
Any other symptoms associated with PSTE or SVL					
Yes	5 (35.7)	2 (40.0)	10 (33.3)	0	17 (34.0)
No	1 (7.1)	1 (20.0)	2 (6.7)	0	4 (8.0)
Unknown	8 (57.1)	2 (40.0)	18 (60.0)	1 (100.0)	29 (58.0)

Note: For the outcome of bilateral PSTE or SVLs, the worse outcome of both eyes is tabulated. The outcomes from best to worse are: resolved - resolved with sequelae - ongoing. The outcome will only be summarized as 'Unknown' if the outcome of both eyes is unknown. For bilateral PSTE or SVLs, the onset is counted as suddenly if the onset of at least one eye is reported as suddenly and counted as 'Other' if both eyes are reported as 'Other'. Bilateral PSTE or SVLs are counted only once in this table. The Full Analysis Set (FAS) consists of AE or SAE reports indicative of PSTE or SVL in patients with crizotinib from study data sources. Percentages are calculated based on the number of PSTE or SVL events or a subset of PSTE or SVL events as appropriate.
N, n = number of PSTE or SVL events; PSTE = potential sight-threatening event; SVL = severe visual loss.
Source: Section 14: Table 2.

11.2.1.3. Risk Factors

11.2.1.3.1. Ocular History

Among the 5 adjudicated SVL cases, a history of ocular disease prior to the SVL occurrence was reported in the affected eye in 3 cases and in the unaffected eye in 1 case, including 2 cases of cataracts in the affected eye, 1 case of macular edema in the affected eye, 1 case of retinal holes in the unaffected eye, and 1 case of retinal detachment in the affected eye (Section 14: Table 5). There was no ocular history reported for the remaining SVL case.

A history of ocular disease prior to the occurrence of 13 of the 14 cumulative adjudicated PSTEs was unknown; for the remaining 1 PSTE case, there was no history of any ocular disease (Section 14: Table 6).

11.2.1.3.2. Medical History and Prior Exposure to Treatment with Ocular Toxicity

The medical history of the adjudicated SVL or PSTE cases included diabetes (2 SVL and 1 PSTE cases), hypertension (1 SVL and 3 PSTE cases), hyperlipidemia (1 SVL case), and transient ischemic attack/stroke (1 PSTE case) (Section 14: Table 8). No cases were known to have elevated intracranial pressure prior to the occurrence of SVL or PSTE

(Section 14: Table 10). All but 2 cases had no relevant clinical examinations or investigations (ie, carotid Doppler, erythrocyte sedimentation rate, c-reactive protein) within 1 year prior to the occurrence of the SVL or PSTE event. For the remaining 2 cases (1 SVL and 1 PSTE), c-reactive protein was measured at least once; 1 was determined to be not clinically significant and the other's significance was unknown (Section 14: Table 11). No cases were reported to have carotid Doppler or erythrocyte sedimentation rate performed within 1 year subsequent to the occurrence of the SVL or PSTE (Section 14: Table 12). Two patients (1 SVL and 1 PSTE) had c-reactive protein measured at least once within 1 year subsequent to the occurrence of SVL or PSTE, and the results were not clinically significant for the SVL case (0.2 mg/dL) and the significance was unknown for the PSTE case (4.2 mg/dL) (Section 14: Table 12).

No adjudicated cases of SVL had a prior history of exposure to medications associated with ocular toxicity (Section 14: Table 7). There was 1 adjudicated PSTE case in which the patient took a medication with potential ocular toxicity prior to the onset of the PSTE. This medication, recorded as "Other," was binimetinib 30 mg twice daily taken from 07 to 08 March 2018 (data on file).

11.2.1.3.3. Brain Metastases

Three of the 5 adjudicated SVL cases were reported to have brain metastases prior to SVL and 2 of the 14 adjudicated PSTE cases prior to a PSTE. For 1 SVL case, the brain metastases involved the optic nerve, visual pathway, or occipital lobe; in 1 SVL case there was no observed involvement of the optic nerve, visual pathway, or occipital lobe; and involvement of these areas was unknown for the other 3 cases (1 SVL and 2 PSTE). Time from diagnosis of brain metastases until onset was known for 1 SVL case, which was 3.49 months. Time from diagnosis of brain metastases and time from last brain surgery until onset were unknown for the other 2 SVL and 2 PSTE cases. Two SVL cases had no stereotactic surgery or other surgery for brain metastases and surgery status was unknown for 1 SVL and 2 PSTE cases. One SVL case had radiotherapy at a total mean dose of 233.0 gray units and at 6.45 months prior to the onset of the SVL event; 1 SVL case did not receive radiotherapy and in 1 SVL case radiotherapy treatment was unknown, and for these 2 cases, dose and time relative to event onset were unknown. One case with a PSTE had radiotherapy at an unknown total dose and at an unknown time relative to the onset of the PSTE event (Section 14: Table 9).

11.2.1.3.4. Ophthalmologic Examinations Prior to Occurrence of SVL or PSTE

Two of the 5 adjudicated SVL cases had no ophthalmologic examination and 1 adjudicated SVL case had 1 ophthalmologic examination within 1 year prior to the start of crizotinib treatment. Information about ophthalmologic examinations within 1 year prior to the start of crizotinib was unknown for 2 cases. One SVL case had 1 ophthalmologic examination between the start of crizotinib and the onset of the SVL event, 2 cases had no ophthalmologic examinations, and for 2 cases information was unknown. Subsequent to the SVL events, 3 cases each had at least 1 ophthalmologic examination and for 2 cases information was unknown. For 1 case, time from last ophthalmologic examination until the onset of SVL was

8 days, and for 3 cases, median time from onset of the SVL until the first ophthalmologic examination was 7 days (min, max: 2, 86). For 1 SVL case, there were significant findings in the ophthalmologic examination 1 year prior to the start of crizotinib treatment. No SVL cases had confirmed significant findings in the ophthalmologic examination between the start of crizotinib treatment and onset of a SVL (Section 14: Table 17).

Of the 14 adjudicated PSTE cases, 1 had an ophthalmologic examination within 1 year prior to the start of crizotinib treatment; information about ophthalmologic examinations within 1 year prior to the start of crizotinib was unknown for the remaining 13 cases. One PSTE case had no ophthalmologic examination between the start of crizotinib and the onset of the PSTE event and for 13 cases information was unknown. Subsequent to the PSTE events, 2 cases each had at least 1 ophthalmologic examination and for 12 cases, information was unknown. For 1 case, time from last ophthalmologic examination until the onset of PSTE was 407 days, and for 2 cases, median time from onset of the PSTE until the first ophthalmologic examination was 45.5 days (min, max: 1, 90). For 1 PSTE case, there were no significant findings in the ophthalmologic examination 1 year prior to the start of crizotinib treatment. No PSTE cases had confirmed significant findings in the ophthalmologic examination between the start of crizotinib treatment and onset of a PSTE (Section 14: Table 17).

11.2.2. Crizotinib Exposure

Crizotinib dosing information was reported for 4 of the 5 adjudicated SVL cases. The median time from the first exposure to crizotinib until the onset of a SVL event was 77 days (min, max: 41, 152). The median cumulative days of treatment with crizotinib prior to onset of SVL was 76.5 days (min, max: 41, 152). The median total cumulative dose of crizotinib prior to onset of SVL was 25125 mg (min, max: 20500, 76000). The median total daily dose of crizotinib prior to the onset of SVL was 500 mg (min, max: 250, 500) (Table 5).

Crizotinib dosing information was reported for 9 of the 14 adjudicated PSTE cases. The median time from the first exposure to crizotinib until onset of a PSTE was 8 days (min, max: 1, 1068). The remaining dosing information was available for 7 of the 14 adjudicated PSTE cases. The median duration of exposure prior to onset of a PSTE was 4 days (min, max: 1, 671). The median total cumulative dose of crizotinib prior to onset of a PSTE was 2000 mg (min, max: 250, 335500). The median total daily dose of crizotinib prior to the onset of a PSTE was 500 mg (min, max: 250, 500).

Table 5. Exposure to Crizotinib Prior to the Onset of the PSTE or SVL of All Adjudicated PSTE or SVL Patients in the Study (Safety Analysis Set, Event Level)

Parameter	PSTE (N=14)	SVL (N=5)	PSTE+SVL (N=19)
Time from first exposure to crizotinib until onset of the PSTE or SVL (days)			
N	9	4	13
Mean	241.3	86.8	193.8
SD	391.89	51.99	329.51
Median	8.0	77.0	41.0
Min, Max	1, 1068	41, 152	1, 1068
Number of cumulative days being treated with crizotinib prior to the onset of the PSTE or SVL (days)			
N	7	4	11
Mean	155.6	86.5	130.5
SD	271.57	52.23	215.14
Median	4.0	76.5	41.0
Min, Max	1, 671	41, 152	1, 671
Total cumulative dose of crizotinib prior to onset of the PSTE or SVL (mg)			
N	7	4	11
Mean	70942.9	36687.5	58486.4
SD	129756.45	26314.90	102997.45
Median	2000.0	25125.0	20500.0
Min, Max	250, 335500	20500, 76000	250, 335500
Total daily dose of crizotinib immediately prior to onset of the PSTE or SVL (mg)			
N	7	4	11
Mean	392.9	437.5	409.1
SD	133.63	125.00	126.13
Median	500.0	500.0	500.0
Min, Max	250, 500	250, 500	250, 500

Table 5. Exposure to Crizotinib Prior to the Onset of the PSTE or SVL of All Adjudicated PSTE or SVL Patients in the Study (Safety Analysis Set, Event Level)

Parameter	PSTE (N=14)	SVL (N=5)	PSTE+SVL (N=19)
Average daily dose of crizotinib prior to onset of the PSTE or SVL (mg)			
N	7	4	11
Mean	411.8	437.5	421.2
SD	118.55	125.00	115.27
Median	500.0	500.0	500.0
Min, Max	250, 500	250, 500	250, 500

Note: Time from first exposure until onset of PSTE or SVL is calculated as date of onset of PSTE or SVL - date of first exposure to crizotinib +1 day. The number of cumulative days being treated with crizotinib is defined as the sum of days the patient who experienced the PSTE or SVL has been treated with any dose of crizotinib between the treatment start date with crizotinib and the onset date of the PSTE or SVL event. The total cumulative dose prior to the onset of the PSTE or SVL is calculated as the cumulative dose a patient with the PSTE or SVL was exposed to from the date of the first exposure to crizotinib until (and including) the date of the onset of the PSTE or SVL. The total daily dose immediately prior to the onset of the PSTE or SVL is defined as the total daily dose the patient who experienced a PSTE or SVL was taking the day before the onset of the PSTE or SVL. The average daily dose is defined as the cumulative dose of crizotinib prior to the onset of the PSTE or SVL divided by the cumulative number of days treated with crizotinib. PSTE or SVL events where both eyes are affected are counted only once. The safety analysis set includes adjudicated PSTE or SVL cases only.
N = number of PSTE/SVL events, SD = standard deviation, min=minimum, max = maximum. PSTE = potential sight-threatening event; SVL = severe visual loss.
Source: Section 14: Table 13.

11.3. Outcome Data

11.3.1. Outcome of Adjudicated SVL and PSTE Cases

Table 6 provides the outcomes of the 5 adjudicated cases of SVL and the 14 adjudicated cases of PSTE.

All 5 adjudicated SVL cases were serious. As of the date of the last available information, 4 SVL cases were ongoing and the status of 1 case was unknown. Two cases received treatment for SVL, 1 case did not receive treatment, and for 2 cases the treatment status was unknown. Two cases were reported as not related to crizotinib and for 3 cases the relationship was unknown. There were no SVL cases that were reported as related to crizotinib.

Of the 14 adjudicated PSTE cases, 10 cases were serious, 3 were non-serious, and the seriousness was unknown for 1 case. Two cases received treatment for PSTE, 1 case didn't receive treatment, and for 11 cases, the treatment status was unknown. Of the 10 serious cases, 4 were ongoing at the time of the data cut-off date, 3 resolved without sequelae, and 3 had an unknown outcome. There was 1 PSTE case considered related to crizotinib and the status of this case was ongoing at the time of data cut-off.

Table 6. Outcomes of Adjudicated PSTE or SVL of All Patients in the Study – Full Analysis Set, Event Level

	Adjudicated PSTE (N=14)	Adjudicated SVL (N=5)
Outcome, n (%)		
Resolved without sequelae	3 (21.4)	0
Resolved with sequelae	0	0
Ongoing	7 (50.0)	4 (80.0)
Unknown	4 (28.6)	1 (20.0)
Outcome of serious events, n (%)	**(N=10)**	**(N=5)**
Resolved without sequelae	3 (30.0)	0
Resolved with sequelae	0	0
Ongoing	4 (40.0)	4 (80.0)
Unknown	3 (30.0)	1 (20.0)
Outcome of the PSTE or SVLs related to crizotinib, n (%)[1]	**(N=1)**	**(N=0)**
Resolved without sequelae	0	0
Resolved with sequelae	0	0
Ongoing	1 (100.0)	0
Unknown	0	0
Outcome of the serious PSTE or SVLs, related to crizotinib, n (%)[1]	**(N=0)**	**(N=0)**
Resolved without sequelae	0	0
Resolved with sequelae	0	0
Ongoing	0	0
Unknown	0	0
Treatment of the PSTE or SVLs, n (%)		
Yes	2 (14.3)	2 (40.0)
No	1 (7.1)	1 (20.0)
Unknown	11 (78.6)	2 (40.0)

Note: For the outcome of bilateral PSTE or SVLs, the worse outcome of both eyes is tabulated. The outcomes from best to worse are: resolved - resolved with sequelae - ongoing. The outcome will only be summarized as 'Unknown' if the outcome of both eyes is unknown. For bilateral PSTE or SVLs, the onset is counted as suddenly if the onset of at least 1 eye is reported as suddenly and counted as 'Other' if both eyes are reported as 'Other'. Bilateral PSTE or SVLs are counted only once in this table. The FAS consists of AE or SAE reports indicative of PSTE or SVL in patients with crizotinib from study data sources. Percentages are calculated based on the number of PSTE or SVL events or a subset of PSTE or SVL events as appropriate;
FAS = full analysis set; N, n = number of PSTE or SVL events; PSTE = potential sight-threatening event; SVL = severe visual loss.

[1] Cases with an unknown relationship to crizotinib are not included in this section.
Source: Section 14: Table 2.

11.3.2. Ophthalmologic Examination and Treatment Subsequent to an SVL/PSTE

After the onset of SVL, 2 of the 5 adjudicated cases had slit lamp examination with no abnormalities found in the anterior chamber; 1 case had no slit lamp examination performed and for 2 cases the examination status was unknown (Section 14: Table 30). After the onset of PSTE, the status of slit lamp examinations was unknown for all 14 cases.

Two patients with an adjudicated SVL event and 1 patient with an adjudicated PSTE had a visual field test performed. Defects in the visual field test were noted in 1 SVL patient (hemianiopsia) and 1 PSTE patient (flicker perimetry decreased) (Section 14: Table 34).

No PSTE cases had other ophthalmologic examinations performed subsequent to the SVL/PSTE (reaction of pupils, pupil size, intraocular pressure [Section 14: Table 29], or optical coherence tomography [Section 14: Table 35]). For retinal examinations and retinal photographs subsequent to the SVL/PSTE (Section 14: Table 39), no cases had a recorded examination.

11.3.3. SVL/PSTE Adjudicated Events Reported by Preferred Term

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) (Section 14: Table 15).

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) (Section 14: Table 16).

11.4. Summary of Results

Overall, 50 cases indicative SVL or PSTE were received between 31 March 2016 and 31 March 2021 and 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 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. Thus, in total there have been 14 cumulative adjudicated PSTE cases, 5 cumulative adjudicated SVL cases, 1 non-case, and 30 cases with insufficient information.

Demographic characteristics were generally similar between SVL and PSTE cases, with the exception of age for which the median age of SVL cases was 52.5 years and 65.0 years for the PSTE cases. The 50 cases potentially indicative of SVL/PSTE were reported via spontaneous reports (n=42), Pfizer-sponsored clinical trials (n=2), non-Pfizer-sponsored clinical trials (n=5), and other solicited data sources (n=1).

All 5 adjudicated SVL cases were serious: 4 cases were ongoing and the status of 1 case was unknown. Two cases received treatment for SVL, 1 case did not receive treatment, and for 2 cases the treatment status was unknown. Two SVL cases were reported as not related to crizotinib and for 3 cases the relationship was unknown; there were no SVL cases that were reported as related to crizotinib. Of the 14 adjudicated PSTE cases, 10 cases were serious, 3 were non-serious, and the seriousness was unknown for 1 case. Two cases received

treatment for PSTE, 1 case did not receive treatment, and for 11 cases, the treatment status was unknown. Of the 10 serious cases, 4 were ongoing at the time of the data cut-off date, 3 resolved without sequelae, and 3 had an unknown outcome. There was 1 PSTE case considered related to crizotinib and the status of this case was ongoing at the time of data cut-off for the study. Three of the 5 SVL cases and 1 of the 14 PSTE cases had a sudden onset, while onset times were unknown for the remaining cases.

Among the 5 adjudicated SVL cases, a history of ocular disease prior to the SVL occurrence was reported in the affected eye in 3 cases and in the unaffected eye in 1 case, including 2 cases of cataracts in the affected eye, 1 case of macular edema in the affected eye, 1 case of retinal holes in the unaffected eye, and 1 case of retinal detachment in the affected eye. Ocular history was not reported for the remaining SVL case. A history of ocular disease prior to the occurrence of 13 adjudicated PSTEs was unknown; for the remaining 1 PSTE case, there was no history of any ocular disease. The medical history of the adjudicated SVL or PSTE cases was remarkable for diabetes (2 SVL and 1 PSTE cases), hypertension (1 SVL and 3 PSTE cases), hyperlipidemia (1 SVL case), and transient ischemic attack/stroke (1 PSTE case). No cases were known to have elevated intracranial pressure prior to the occurrence of SVL or PSTE. Three SVL cases were reported to have brain metastases prior to an SVL and 2 PSTE cases prior to a PSTE. The brain metastases involved the optic nerve, visual pathway, or occipital lobe for 1 SVL case, did not involve the optic nerve, visual pathway, or occipital lobe for 1 SVL case, and involvement was unknown for the other 3 cases.

Crizotinib dosing information was reported for 4 of the 5 adjudicated SVL cases. The median time from the first exposure to crizotinib until the onset of a SVL event was 77 days (min, max: 41, 152). The median cumulative days being treated with crizotinib prior to onset of a SVL was 76.5 days (min, max: 41, 152). The median total cumulative dose of crizotinib prior to onset of a SVL was 25125 mg (min, max: 20500, 76000). The median daily dose of crizotinib prior to the onset of a SVL was 500 mg (min, max: 250, 500). Crizotinib dosing information was reported for 9 of the 14 adjudicated PSTE cases. The median time from the first exposure to crizotinib until onset of a PSTE was 8 days (min, max: 1, 1068). The remaining dosing information was available for 7 of the 14 cases. The median duration of exposure prior to onset of a PSTE was 4 days (min, max: 1, 671). The median total cumulative dose of crizotinib prior to onset of a PSTE was 2000 mg (min, max: 250, 335500). The median daily dose of crizotinib prior to the onset of a PSTE was 500 mg (min, max: 250, 500).

After the onset of SVL, 2 of the 5 adjudicated cases had slit lamp examination with no abnormalities found in the anterior chamber; 1 case had no slit lamp examination performed and for 2 cases the examination status was unknown. After the onset of PSTE, the status of slit lamp examinations was unknown for all 14 cases. Two of the 5 patients with an adjudicated SVL event and 1 patient with an adjudicated PSTE had a visual field test performed. Defects in the visual field test were noted in 1 SVL patient (hemianiopsia) and 1 PSTE patient (flicker perimetry decreased).

11.5. Other Analysis

Pfizer has summarized the actions that were taken with crizotinib in response to the 5 SVL and 14 PSTE occurrences. It is noted that due to treatment interventions and changes in therapy, no clear cases of dechallenge/rechallenge were identified.

11.5.1. Adjudicated SVL Cases

- **2016504933 – Blindness unilateral Grade 3 – Italy – Non-Pfizer-sponsored clinical trial**
  A 19-year-old male started crizotinib 250 mg BID for lymphoma in an investigator-initiated research study. Approximately 1 month after starting crizotinib, the patient had loss of vision in the left eye. Brain metastases with involvement of hypophysis was reported and cause of vision loss was determined to be disease progression as per the investigator. Crizotinib was continued and the dose was not changed in response to the event.

- **2017080628 – Vision loss Grade 4 – Saudi Arabia – Spontaneous report**
  A 47-year-old male who was previously treated with chemotherapy for squamous cell NSCLC and had a history of diabetic retinopathy and seizures was treated with crizotinib 250 mg BID. Approximately 6 months after starting crizotinib, the patient was reported to have decreased vision in the right eye with Grade 4 vision loss and Grade 3 neutropenia. Examinations reported multiple brain metastases, bone metastases with spinal cord compression, and diabetic retinopathy. It was reported that crizotinib was permanently withdrawn at an unknown date.

- **2018175366 – Cortical blindness – Japan – Pfizer-sponsored clinical trial**
  A 71-year-old male with a history of diabetes and hyperlipidemia started treatment with crizotinib for NSCLC. Approximately 6 weeks after starting treatment, the patient was noted to be mildly disoriented and had loss of sight. Brain MRI showed bilateral infarction of the occipital and temporal lobes. Crizotinib was withdrawn. The patient was treated for cerebral infarction. Cardiac ventricular hypokinesia and hyperlipidemia were reported by the investigator as likely causative of the cerebral infarction. Cerebral infarction was reported as the cause of the vision loss. The patient was not restarted on crizotinib in the clinical trial.

- **2019009906 – Retinal detachment – Mexico – Pfizer-sponsored clinical trial**
  A 58-year-old female with a history of brain metastases and brain radiation was started on crizotinib treatment for NSCLC. Approximately 3 months after starting crizotinib, the patient was diagnosed with a rhegmatogenous retinal detachment in the right eye and lesions predisposing to detachment (retinal holes) in the left eye. Crizotinib was temporarily withdrawn and patient received surgery in the right eye and laser treatment in the left eye. The treating physician concluded that the retinal detachment was not related to crizotinib and the study drug was restarted. No recurrence was reported.

- **2019090641 – Atrophy optic nerve – Egypt – Spontaneous report**
  The information received from this spontaneous report is extremely limited. A patient (age not reported) experienced "decrease in visual acuity" and "optic nerve atrophy." It was reported that crizotinib was permanently withdrawn on an unspecified date.

11.5.2. Adjudicated PSTE cases

- **2015283231- Retinal detachment – Korea – Non-Pfizer-sponsored clinical trial**
  A 62-year-old male with a history of diabetes mellitus was treated with crizotinib for over one year when he was diagnosed with Grade 3 rhegmatogenous retinal detachment of the left eye that was treated with surgery. Crizotinib was temporarily withdrawn for 3 days after the retinal detachment and restarted. The patient continued on crizotinib for approximately 2 more years.

- **2017335339 – Amaurosis – Germany – Spontaneous report**
  A 65-year-old male with history of arteriosclerosis and hypertension was treated with crizotinib for NSCLC. Approximately one to two weeks later, the patient had surgery in a prone position and was diagnosed with amaurosis after the surgery. Crizotinib was permanently discontinued.

- **2017357856 – Amaurosis – Germany – Spontaneous report**
  (Note: this case is likely a duplicate of Case 2017335339 but additional details are provided.) A 65-year-old male was treated with crizotinib for NSCLC. Approximately 1-2 weeks later, the patient had surgery on the spinal column in a prone position and was diagnosed with amaurosis. Crizotinib was permanently discontinued.

- **2017414790 – Panuveitis – United Kingdom – Spontaneous report**
  A 57-year-old female was treated with crizotinib for NSCLC with cerebral metastases. Approximately 11 months later, the patient developed panuveitis due to a Candida infection. It was reported that crizotinib was temporarily withdrawn but the time when drug was restarted was not reported.

- **20174711044 – Panuveitis – United Kingdom – Spontaneous report**
  A 70-year-old female was treated with crizotinib for NSCLC for approximately 3 years when panuveitis from Staphylococcus was diagnosed after a knee replacement surgery. Crizotinib was temporarily discontinued and restarted at an unspecified date.

- **2017512615 – Visual field test abnormal – Japan – Spontaneous report**
  This spontaneous report had very limited information. A patient of unspecified age was treated with crizotinib for ROS1-positive NSCLC when the patient developed an abnormal visual field test at an unspecified time. Crizotinib was continued and dose was unchanged.

- **2018103887 – Chorioretinopathy – United Kingdom – Non-Pfizer-sponsored clinical trial**
  A 67-year-old female started crizotinib and binimetinib for colorectal cancer in an investigator-initiated research study. One day after receiving the study drugs, the patient was diagnosed with bilateral central serous retinopathy. Both crizotinib and binimetinib were permanently discontinued.

- **2018261777 – Retinal detachment – France – Spontaneous report**
  This spontaneous report had very limited information. A 46-year-old male was treated with crizotinib for approximately 1 year. The patient was diagnosed with a retinal detachment on an unspecified dated. The action in response to the event for crizotinib was unknown.

- **201803191 – Visual field defect – Japan – Non-Pfizer-sponsored Clinical trial**
  A 72-year-old male was enrolled in a non-Pfizer study with crizotinib for treatment of NSCLC. On the first day of starting treatment, it was reported that the patient had an abnormal visual field. The patient continued on crizotinib after the adverse event.

- **2019029595 – Visual field defect – Japan – Spontaneous report**
  An 18-year-old female was treated with crizotinib for anaplastic large cell lymphoma. Three days after starting treatment, the patient reported visual disturbance. The patient was diagnosed with a visual field defect related to brain metastasis. No change in crizotinib dosing was reported related to the visual adverse event, but crizotinib was discontinued approximately 1 month after starting treatment due to increased bilirubin.

- **2019077353 – Optic neuropathy – Ireland – Spontaneous report**
  This spontaneous report had very limited information. A female patient of an unspecified age was diagnosed with optic neuropathy of the right eye at an unspecified time after starting crizotinib for NSCLC. Crizotinib was permanently discontinued.

- **2019118992 – Optic neuropathy – Ireland – Spontaneous report**
  (Note: This case is likely a duplicate of 2019077353 but more details are provided.) A female patient of an unspecified age with history of brain surgery and radiotherapy was treated with crizotinib. Treatment also included ceritinib and chemotherapy. Glioblastoma multiforme was also diagnosed at an unspecified date. Cerebral metastasis was reported. Right optic neuropathy was diagnosed at an unspecified date. Crizotinib and ceritinib were permanently withdrawn on an unspecified date.

- **2019461104 – Blindness – United States – Spontaneous report**
  A 77-year-old female with history of hypertension and stroke started crizotinib for ROS1-positive NSCLC. The patient reported that she developed a visual field defect and brain swelling at unspecified dates. Crizotinib was permanently discontinued.

- **2020395575 – Blindness – France – Spontaneous report**
  A 61-year-old male started crizotinib in May 2018 for lung adenocarcinoma. The patient experienced papilledema in July 2019 (outcome: not resolved), visual disturbance NOS in July 2019 (outcome: not resolved), optic neuritis on 30 May 2020 (outcome: not resolved), and blindness in March 2020 (outcome: recovering). Crizotinib was permanently discontinued.

11.6. Adverse Events

Regulatory reporting of AEs based on data sources occurred per standard practice. SVL and PSTE events described in this study have met regulatory reporting requirements as applicable based on their initial source (ie, SAE reporting of clinical trials, SAE/AE reporting of NI studies, or spontaneous reporting).

12. DISCUSSION AND CONCLUSION

12.1. Key Results

Cumulatively, 50 cases indicative of SVL or PSTE were received between 31 March 2016 and 31 March 2021, all of which 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 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.

All 5 adjudicated SVL and 10 of 14 adjudicated PSTE cases were reported as serious. Two SVL cases were reported as not related to crizotinib and for 3 cases the relationship was unknown; there were no SVL cases that were reported as related to crizotinib. The likely etiologies for the 5 SVL cases were: 1) brain metastases, 2) brain metastases, diabetic retinopathy, 3) bilateral infarction of the occipital and temporal lobes, 4) rhegmatogenous retinal detachment with retinal holes, and 5) data too limited to assess etiology of optic atrophy. One PSTE case was considered related to crizotinib by the treating physician, 4 cases were reported to be not related, and the relationship was unknown for 9 cases. Three of the 5 SVL cases and 1 of the 14 PSTE cases had a sudden onset, while onset times were unknown for the remaining cases.

Of the 5 adjudicated SVL cases (all serious), 4 were ongoing, and the status of 1 case was unknown. Two SVL cases received treatment, 1 case did not receive treatment, and for 2 cases the treatment was unknown. Of the 14 adjudicated PSTE cases, 3 PSTE cases resolved without sequelae, 7 cases were ongoing, and outcome was unknown for 4 cases. Of the 10 serious PSTE cases, 4 were ongoing at the time of the data cut-off date, 3 resolved without sequelae, and 3 had an unknown outcome.

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.

12.2. Limitations

As an enhanced PV study that relies on reported AE and SAE data, the major limitations include underreporting and incomplete information for a large proportion of cases, which limits the ability to fully evaluate the reports. A large amount of data was missing or incomplete (~50%) from 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.

12.3. Interpretation

The results presented in this final report are based on 5 adjudicated cases of SVL and 14 adjudicated cases of PSTE received between 31 March 2016 and 31 March 2021. This small number of cases with limited information does not allow for a meaningful evaluation of risk factors of SVL and PSTE cases following exposure to crizotinib.

12.4. Generalizability

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

12.5. Conclusion

Upon evaluation of the independently adjudicated reports of SVL and PSTE crizotinib cases in this study, ocular risk factors for SVL/PSTE or pre-existing history of ocular disease could be identified in a large proportion of SVL cases. Of the 14 PSTE cases, the ocular history was unknown in 13 cases and 1 case had no history. Based on the overall assessment of the low number of cases, many of which had limited information, no new safety signals were identified and the ophthalmologic safety risk profile of crizotinib remains unchanged.

13. REFERENCES

1. XALKORI (crizotinib) United States Package Insert (version 1/2021). https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202570s030lbl.pdf.

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

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Appendix 5. Sample Case Report Form / Data Collection Tool

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Table 1
Reported Cases Indicative of Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) and Classification of the Reported Cases by the Adjudication Committee
(Full Analysis Set, Event Level)

		Reported Cases indicative of PSTE or SVL		
		PSTE (N=4) n (%)	**SVL (N=46) n (%)**	**Total (N=50) n (%)**
Adjudicated outcome	PSTE	4 (100.0)	10 (21.7)	14 (28.0)
	SVL	0	5 (10.9)	5 (10.0)
	Insufficient Information	0	30 (65.2)	30 (60.0)
	Non-case	0	1 (2.2)	1 (2.0)
	Total	4 (100.0)	46 (100.0)	50 (100.0)

Note: The Full Analysis Set (FAS) consists of AE or SAE reports indicative of PSTE or SVL in patients treated with crizotinib from study data sources. There were 8 patients with an event of severe visual loss from September 14, 2015 to March 30, 2016 (period from PMR 2956-1 effective date to day before the date of study start). These events occurred prior to the start of the study, so these data were included as an addendum to the first annual interim report, but were not included in any cumulative reports or data analyses. Therefore, these 8 patients are not included in this summary table. N, n = Number of PSTE or SVL events. PSTE = Potential sight threatening event; SVL = Severe visual loss; AE = Adverse Event; SAE = Serious Adverse Event.

Table 2
Overview of Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Patients in the Study
(Full Analysis Set, Event Level)

	Total Outcomes				
	Adjudicated PSTE (N=14)	Adjudicated SVL (N=5)	Insufficient Information (N=30)	Non-cases (N=1)	Total (N=50)
Number of PSTE or SVLs	14 (100.0)	5 (100.0)	30 (100.0)	1 (100.0)	50 (100.0)
Characteristic of the PSTE or SVL					
Unilateral	1 (7.1)	2 (40.0)	1 (3.3)	0	4 (8.0)
Bilateral	3 (21.4)	1 (20.0)	0	0	4 (8.0)
Unspecified	10 (71.4)	2 (40.0)	29 (96.7)	1 (100.0)	42 (84.0)

Note: For the outcome of bilateral PSTE or SVLs, the worse outcome of both eyes is tabulated. The outcomes from best to worse are: resolved - resolved with sequelae - ongoing. The outcome will only be summarized as 'Unknown' if the outcome of both eyes is unknown. For bilateral PSTE or SVLs, the onset is counted as suddenly if the onset of at least one eye is reported as suddenly and counted as 'Other' if both eyes are reported as 'Other'. Bilateral PSTE or SVLs are counted only once in this table. The Full Analysis Set (FAS) consists of AE or SAE reports indicative of PSTE or SVL in patients with crizotinib from study data sources. Percentages are calculated based on the number of PSTE or SVL events or a subset of PSTE or SVL events as appropriate. There were 8 patients with an event of severe visual loss from September 14, 2015 to March 30, 2016 (period from PMR 2956-1 effective date to day before the date of study start). These events occurred prior to the start of the study, so these data were included as an addendum to the first annual interim report, but were not included in any cumulative reports or data analyses. Therefore, these 8 patients are not included in this summary table.

N, n = Number of PSTE or SVL events. PSTE = Potential sight threatening event; SVL = Severe visual loss

[a] Includes Patients 5555-0013 (Grade 1, Vision abnormal), 5555-0019 (Grade 1, Vision field defect), 5555-0012 (Grade 3, Transient vision loss), and 5555-0021 (Grade 4, Amaurosis), whose events were not classified as serious or non-serious.

Table 2
Overview of Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Patients in the Study
(Full Analysis Set, Event Level)

	Total Outcomes				
	Adjudicated PSTE (N=14)	**Adjudicated SVL (N=5)**	**Insufficient Information (N=30)**	**Non-cases (N=1)**	**Total (N=50)**
Type of data source					
Spontaneous report	11 (78.6)	2 (40.0)	28 (93.3)	1 (100.0)	42 (84.0)
Literature	0	0	0	0	0
Unpublished Manuscripts, Unpublished Abstracts, or Meeting reports	0	0	0	0	0
Regulatory Authorities	0	0	0	0	0
Other Company including License Party	0	0	0	0	0
Other Registry Reports	0	0	0	0	0
Other	11 (78.6)	2 (40.0)	28 (93.3)	1 (100.0)	42 (84.0)
Pfizer sponsored clinical trial	0	2 (40.0)	0	0	2 (4.0)
Non-Pfizer sponsored clinical trial	3 (21.4)	1 (20.0)	1 (3.3)	0	5 (10.0)

Note: For the outcome of bilateral PSTE or SVLs, the worse outcome of both eyes is tabulated. The outcomes from best to worse are: resolved - resolved with sequelae - ongoing. The outcome will only be summarized as 'Unknown' if the outcome of both eyes is unknown. For bilateral PSTE or SVLs, the onset is counted as suddenly if the onset of at least one eye is reported as suddenly and counted as 'Other' if both eyes are reported as 'Other'. Bilateral PSTE or SVLs are counted only once in this table. The Full Analysis Set (FAS) consists of AE or SAE reports indicative of PSTE or SVL in patients with crizotinib from study data sources. Percentages are calculated based on the number of PSTE or SVL events or a subset of PSTE or SVL events as appropriate. There were 8 patients with an event of severe visual loss from September 14, 2015 to March 30, 2016 (period from PMR 2956-1 effective date to day before the date of study start). These events occurred prior to the start of the study, so these data were included as an addendum to the first annual interim report, but were not included in any cumulative reports or data analyses. Therefore, these 8 patients are not included in this summary table.

N, n = Number of PSTE or SVL events. PSTE = Potential sight threatening event; SVL = Severe visual loss

[a] Includes Patients 5555-0013 (Grade 1, Vision abnormal), 5555-0019 (Grade 1, Vision field defect), 5555-0012 (Grade 3, Transient vision loss), and 5555-0021 (Grade 4, Amaurosis), whose events were not classified as serious or non-serious.

Table 2
Overview of Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Patients in the Study
(Full Analysis Set, Event Level)

	Total Outcomes				
	Adjudicated PSTE (N=14)	**Adjudicated SVL (N=5)**	**Insufficient Information (N=30)**	**Non-cases (N=1)**	**Total (N=50)**
Pfizer sponsored prospective primary data collection non-interventional study	0	0	0	0	0
Other solicited data sources	0	0	1 (3.3)	0	1 (2.0)
Serious or non-serious event					
Non-serious	3 (21.4)	0	13 (43.3)	1 (100.0)	17 (34.0)
Serious	10 (71.4)	5 (100.0)	14 (46.7)	0	29 (58.0)
Unknown[a]	1 (7.1)	0	3 (10.0)	0	4 (8.0)

Note: For the outcome of bilateral PSTE or SVLs, the worse outcome of both eyes is tabulated. The outcomes from best to worse are: resolved - resolved with sequelae - ongoing. The outcome will only be summarized as 'Unknown' if the outcome of both eyes is unknown. For bilateral PSTE or SVLs, the onset is counted as suddenly if the onset of at least one eye is reported as suddenly and counted as 'Other' if both eyes are reported as 'Other'. Bilateral PSTE or SVLs are counted only once in this table. The Full Analysis Set (FAS) consists of AE or SAE reports indicative of PSTE or SVL in patients with crizotinib from study data sources. Percentages are calculated based on the number of PSTE or SVL events or a subset of PSTE or SVL events as appropriate. There were 8 patients with an event of severe visual loss from September 14, 2015 to March 30, 2016 (period from PMR 2956-1 effective date to day before the date of study start). These events occurred prior to the start of the study, so these data were included as an addendum to the first annual interim report, but were not included in any cumulative reports or data analyses. Therefore, these 8 patients are not included in this summary table.

N, n = Number of PSTE or SVL events. PSTE = Potential sight threatening event; SVL = Severe visual loss

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Table 2
Overview of Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Patients in the Study
(Full Analysis Set, Event Level)

	Total Outcomes				
	Adjudicated PSTE (N=14)	Adjudicated SVL (N=5)	Insufficient Information (N=30)	Non-cases (N=1)	Total (N=50)
Outcome					
Resolved without sequelae	3 (21.4)	0	3 (10.0)	0	6 (12.0)
Resolved with sequelae	0	0	0	0	0
Ongoing	7 (50.0)	4 (80.0)	6 (20.0)	0	17 (34.0)
Unknown	4 (28.6)	1 (20.0)	21 (70.0)	1 (100.0)	27 (54.0)
Outcome of serious events	**(N=10)**	**(N=5)**	**(N=14)**	**(N=0)**	**(N=29)**
Resolved without sequelae	3 (30.0)	0	1 (7.1)	0	4 (13.8)
Resolved with sequelae	0	0	0	0	0
Ongoing	4 (40.0)	4 (80.0)	2 (14.3)	0	10 (34.5)
Unknown	3 (30.0)	1 (20.0)	11 (78.6)	0	15 (51.7)

Note: For the outcome of bilateral PSTE or SVLs, the worse outcome of both eyes is tabulated. The outcomes from best to worse are: resolved - resolved with sequelae - ongoing. The outcome will only be summarized as 'Unknown' if the outcome of both eyes is unknown. For bilateral PSTE or SVLs, the onset is counted as suddenly if the onset of at least one eye is reported as suddenly and counted as 'Other' if both eyes are reported as 'Other'. Bilateral PSTE or SVLs are counted only once in this table. The Full Analysis Set (FAS) consists of AE or SAE reports indicative of PSTE or SVL in patients with crizotinib from study data sources. Percentages are calculated based on the number of PSTE or SVL events or a subset of PSTE or SVL events as appropriate. There were 8 patients with an event of severe visual loss from September 14, 2015 to March 30, 2016 (period from PMR 2956-1 effective date to day before the date of study start). These events occurred prior to the start of the study, so these data were included as an addendum to the first annual interim report, but were not included in any cumulative reports or data analyses. Therefore, these 8 patients are not included in this summary table.

N, n = Number of PSTE or SVL events. PSTE = Potential sight threatening event; SVL = Severe visual loss

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Table 2
Overview of Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Patients in the Study
(Full Analysis Set, Event Level)

	Total Outcomes				
	Adjudicated PSTE (N=14)	**Adjudicated SVL (N=5)**	**Insufficient Information (N=30)**	**Non-cases (N=1)**	**Total (N=50)**
Reported causal relationship of the PSTE or SVL to crizotinib					
Related	1 (7.1)	0	2 (6.7)	0	3 (6.0)
Not related	4 (28.6)	2 (40.0)	0	0	6 (12.0)
Unknown	9 (64.3)	3 (60.0)	28 (93.3)	1 (100.0)	41 (82.0)
Outcome of the PSTE or SVLs related to crizotinib	**(N=1)**	**(N=0)**	**(N=2)**	**(N=0)**	**(N=3)**
Resolved without sequelae	0	0	0	0	0
Resolved with sequelae	0	0	0	0	0
Ongoing	1 (100.0)	0	1 (50.0)	0	2 (66.7)
Unknown	0	0	1 (50.0)	0	1 (33.3)

Note: For the outcome of bilateral PSTE or SVLs, the worse outcome of both eyes is tabulated. The outcomes from best to worse are: resolved - resolved with sequelae - ongoing. The outcome will only be summarized as 'Unknown' if the outcome of both eyes is unknown. For bilateral PSTE or SVLs, the onset is counted as suddenly if the onset of at least one eye is reported as suddenly and counted as 'Other' if both eyes are reported as 'Other'. Bilateral PSTE or SVLs are counted only once in this table. The Full Analysis Set (FAS) consists of AE or SAE reports indicative of PSTE or SVL in patients with crizotinib from study data sources. Percentages are calculated based on the number of PSTE or SVL events or a subset of PSTE or SVL events as appropriate. There were 8 patients with an event of severe visual loss from September 14, 2015 to March 30, 2016 (period from PMR 2956-1 effective date to day before the date of study start). These events occurred prior to the start of the study, so these data were included as an addendum to the first annual interim report, but were not included in any cumulative reports or data analyses. Therefore, these 8 patients are not included in this summary table.

N, n = Number of PSTE or SVL events. PSTE = Potential sight threatening event; SVL = Severe visual loss

[a] Includes Patients 5555-0013 (Grade 1, Vision abnormal), 5555-0019 (Grade 1, Vision field defect), 5555-0012 (Grade 3, Transient vision loss), and 5555-0021 (Grade 4, Amaurosis), whose events were not classified as serious or non-serious.

Table 2
Overview of Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Patients in the Study
(Full Analysis Set, Event Level)

	Total Outcomes				
	Adjudicated PSTE (N=14)	Adjudicated SVL (N=5)	Insufficient Information (N=30)	Non-cases (N=1)	Total (N=50)
Outcome of the serious PSTE or SVLs, related to crizotinib	**(N=0)**	**(N=0)**	**(N=1)**	**(N=0)**	**(N=1)**
Resolved without sequelae	0	0	0	0	0
Resolved with sequelae	0	0	0	0	0
Ongoing	0	0	0	0	0
Unknown	0	0	1 (100.0)	0	1 (100.0)
Treatment of the PSTE or SVLs					
Yes	2 (14.3)	2 (40.0)	0	0	4 (8.0)
No	1 (7.1)	1 (20.0)	1 (3.3)	0	3 (6.0)
Unknown	11 (78.6)	2 (40.0)	29 (96.7)	1 (100.0)	43 (86.0)

Note: For the outcome of bilateral PSTE or SVLs, the worse outcome of both eyes is tabulated. The outcomes from best to worse are: resolved - resolved with sequelae - ongoing. The outcome will only be summarized as 'Unknown' if the outcome of both eyes is unknown. For bilateral PSTE or SVLs, the onset is counted as suddenly if the onset of at least one eye is reported as suddenly and counted as 'Other' if both eyes are reported as 'Other'. Bilateral PSTE or SVLs are counted only once in this table. The Full Analysis Set (FAS) consists of AE or SAE reports indicative of PSTE or SVL in patients with crizotinib from study data sources. Percentages are calculated based on the number of PSTE or SVL events or a subset of PSTE or SVL events as appropriate. There were 8 patients with an event of severe visual loss from September 14, 2015 to March 30, 2016 (period from PMR 2956-1 effective date to day before the date of study start). These events occurred prior to the start of the study, so these data were included as an addendum to the first annual interim report, but were not included in any cumulative reports or data analyses. Therefore, these 8 patients are not included in this summary table.

N, n = Number of PSTE or SVL events. PSTE = Potential sight threatening event; SVL = Severe visual loss

[a] Includes Patients 5555-0013 (Grade 1, Vision abnormal), 5555-0019 (Grade 1, Vision field defect), 5555-0012 (Grade 3, Transient vision loss), and 5555-0021 (Grade 4, Amaurosis), whose events were not classified as serious or non-serious.

Table 2
Overview of Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Patients in the Study
(Full Analysis Set, Event Level)

	Total Outcomes				
	Adjudicated PSTE (N=14)	Adjudicated SVL (N=5)	Insufficient Information (N=30)	Non-cases (N=1)	Total (N=50)
Onset of the PSTE or SVL					
Suddenly	1 (7.1)	3 (60.0)	0	0	4 (8.0)
Gradually	0	0	0	0	0
Other	0	0	0	0	0
Unknown	13 (92.9)	2 (40.0)	30 (100.0)	1 (100.0)	46 (92.0)
Any other symptoms associated with PSTE or SVL					
Yes	5 (35.7)	2 (40.0)	10 (33.3)	0	17 (34.0)
No	1 (7.1)	1 (20.0)	2 (6.7)	0	4 (8.0)
Unknown	8 (57.1)	2 (40.0)	18 (60.0)	1 (100.0)	29 (58.0)

Note: For the outcome of bilateral PSTE or SVLs, the worse outcome of both eyes is tabulated. The outcomes from best to worse are: resolved - resolved with sequelae - ongoing. The outcome will only be summarized as 'Unknown' if the outcome of both eyes is unknown. For bilateral PSTE or SVLs, the onset is counted as suddenly if the onset of at least one eye is reported as suddenly and counted as 'Other' if both eyes are reported as 'Other'. Bilateral PSTE or SVLs are counted only once in this table. The Full Analysis Set (FAS) consists of AE or SAE reports indicative of PSTE or SVL in patients with crizotinib from study data sources. Percentages are calculated based on the number of PSTE or SVL events or a subset of PSTE or SVL events as appropriate. There were 8 patients with an event of severe visual loss from September 14, 2015 to March 30, 2016 (period from PMR 2956-1 effective date to day before the date of study start). These events occurred prior to the start of the study, so these data were included as an addendum to the first annual interim report, but were not included in any cumulative reports or data analyses. Therefore, these 8 patients are not included in this summary table.

N, n = Number of PSTE or SVL events. PSTE = Potential sight threatening event; SVL = Severe visual loss

[a] Includes Patients 5555-0013 (Grade 1, Vision abnormal), 5555-0019 (Grade 1, Vision field defect), 5555-0012 (Grade 3, Transient vision loss), and 5555-0021 (Grade 4, Amaurosis), whose events were not classified as serious or non-serious.

Table 3
Demographic Characteristics of All Adjudicated Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) Patients in the Study (Safety Analysis Set, Patient Level)

	Total Adjudicated PSTE or SVL		
Parameter	**PSTE (N=14)**	**SVL (N=5)**	**Total (N=19)**
Age (years)			
n	11	4	15
Mean	60.0	48.8	57.0
SD	16.14	22.13	17.82
Median	65.0	52.5	62.0
Min, Max	18, 77	19, 71	18, 77
Age group, n (%)			
<65 years	5 (35.7)	3 (60.0)	8 (42.1)
65 - 74 years	5 (35.7)	1 (20.0)	6 (31.6)
75 or older	1 (7.1)	0	1 (5.3)
Unknown	3 (21.4)	1 (20.0)	4 (21.1)
Gender, n (%)			
Male	6 (42.9)	3 (60.0)	9 (47.4)
Female	7 (50.0)	1 (20.0)	8 (42.1)
Unknown	1 (7.1)	1 (20.0)	2 (10.5)

Note: Percentages are based on the number of patients with PSTE or SVL events. Patients with more than one PSTE or SVL event are counted only once in this table. For patients with multiple PSTE or SVL events, the age at the first event is used for summary statistics. The safety analysis set includes adjudicated PSTE or SVL cases only.
N, n = Number of patients, SD = standard deviation, min=minimum, max=maximum, PSTE = Potential sight threatening event, SVL = Severe visual loss.

Table 3
Demographic Characteristics of All Adjudicated Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) Patients in the Study (Safety Analysis Set, Patient Level)

	Total Adjudicated PSTE or SVL		
Parameter	**PSTE (N=14)**	**SVL (N=5)**	**Total (N=19)**
Race, n (%)			
White	2 (14.3)	0	2 (10.5)
Black	0	1 (20.0)	1 (5.3)
Hispanic	0	1 (20.0)	1 (5.3)
Asian	2 (14.3)	1 (20.0)	3 (15.8)
Japanese	0	1 (20.0)	1 (5.3)
Chinese	0	0	0
Korean	1 (7.1)	0	1 (5.3)
Other Asian	0	0	0
Unknown	1 (7.1)	0	1 (5.3)
Other	0	0	0
Unknown	10 (71.4)	2 (40.0)	12 (63.2)

Note: Percentages are based on the number of patients with PSTE or SVL events. Patients with more than one PSTE or SVL event are counted only once in this table. For patients with multiple PSTE or SVL events, the age at the first event is used for summary statistics. The safety analysis set includes adjudicated PSTE or SVL cases only.
N, n = Number of patients, SD = standard deviation, min=minimum, max=maximum, PSTE = Potential sight threatening event, SVL = Severe visual loss.

Table 4
Ocular History Prior to the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) among Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Eye Level)

	Total Adjudicated PSTE or SVL		
Parameter, n (%)	**Affected eye (N=11)**	**Unaffected eye (N=3)**	**Unspecified eye (N=24)**
Macular Degeneration			
Yes	0	0	0
No	4 (36.4)	2 (66.7)	0
Unknown	7 (63.6)	1 (33.3)	24 (100.0)
Glaucoma			
Yes	0	0	0
No	4 (36.4)	2 (66.7)	0
Unknown	7 (63.6)	1 (33.3)	24 (100.0)
Diabetic Retinopathy			
Yes	0	0	0
No	4 (36.4)	2 (66.7)	0
Unknown	7 (63.6)	1 (33.3)	24 (100.0)

Note: If the affected eye is unspecified, both eyes are presented as unspecified eyes. For events where both eyes are affected, the ocular history of both eyes are counted as affected eyes. The history of at least one of the above ocular diseases is counted as 'Unknown' if at least one ocular disease is reported as 'unknown' and no ocular disease is reported as 'Yes'. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected or unspecified eyes, as appropriate.

N, n = Number of affected, unaffected or unspecified eyes, as appropriate. PSTE = Potential sight threatening event; SVL = Severe visual loss.

Table 4
Ocular History Prior to the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) among Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Eye Level)

	Total Adjudicated PSTE or SVL		
Parameter, n (%)	**Affected eye (N=11)**	**Unaffected eye (N=3)**	**Unspecified eye (N=24)**
Cataracts			
Yes	2 (18.2)	0	0
No	2 (18.2)	2 (66.7)	0
Unknown	7 (63.6)	1 (33.3)	24 (100.0)
Trauma to the eyes			
Yes	0	0	0
No	4 (36.4)	2 (66.7)	0
Unknown	7 (63.6)	1 (33.3)	24 (100.0)
Optic atrophy			
Yes	0	0	0
No	4 (36.4)	2 (66.7)	0
Unknown	7 (63.6)	1 (33.3)	24 (100.0)

Note: If the affected eye is unspecified, both eyes are presented as unspecified eyes. For events where both eyes are affected, the ocular history of both eyes are counted as affected eyes. The history of at least one of the above ocular diseases is counted as 'Unknown' if at least one ocular disease is reported as 'unknown' and no ocular disease is reported as 'Yes'. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected or unspecified eyes, as appropriate.

N, n = Number of affected, unaffected or unspecified eyes, as appropriate. PSTE = Potential sight threatening event; SVL = Severe visual loss.

Table 4
Ocular History Prior to the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) among Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Eye Level)

	Total Adjudicated PSTE or SVL		
Parameter, n (%)	**Affected eye (N=11)**	**Unaffected eye (N=3)**	**Unspecified eye (N=24)**
Optic nerve edema			
Yes	0	0	0
No	4 (36.4)	2 (66.7)	0
Unknown	7 (63.6)	1 (33.3)	24 (100.0)
Retinal hemorrhages			
Yes	0	0	0
No	4 (36.4)	2 (66.7)	0
Unknown	7 (63.6)	1 (33.3)	24 (100.0)
Vitreous hemorrhage			
Yes	0	0	0
No	4 (36.4)	2 (66.7)	0
Unknown	7 (63.6)	1 (33.3)	24 (100.0)

Note: If the affected eye is unspecified, both eyes are presented as unspecified eyes. For events where both eyes are affected, the ocular history of both eyes are counted as affected eyes. The history of at least one of the above ocular diseases is counted as 'Unknown' if at least one ocular disease is reported as 'unknown' and no ocular disease is reported as 'Yes'. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected or unspecified eyes, as appropriate.
N, n = Number of affected, unaffected or unspecified eyes, as appropriate. PSTE = Potential sight threatening event; SVL = Severe visual loss.

Table 4
Ocular History Prior to the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) among Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Eye Level)

	Total Adjudicated PSTE or SVL		
Parameter, n (%)	**Affected eye (N=11)**	**Unaffected eye (N=3)**	**Unspecified eye (N=24)**
Macular edema			
Yes	1 (9.1)	0	0
No	3 (27.3)	2 (66.7)	0
Unknown	7 (63.6)	1 (33.3)	24 (100.0)
Retinal holes			
Yes	0	1 (33.3)	0
No	4 (36.4)	2 (66.7)	0
Unknown	7 (63.6)	0	24 (100.0)
Retinal detachment			
Yes	1 (9.1)	0	0
No	4 (36.4)	2 (66.7)	0
Unknown	6 (54.5)	1 (33.3)	24 (100.0)

Note: If the affected eye is unspecified, both eyes are presented as unspecified eyes. For events where both eyes are affected, the ocular history of both eyes are counted as affected eyes. The history of at least one of the above ocular diseases is counted as 'Unknown' if at least one ocular disease is reported as 'unknown' and no ocular disease is reported as 'Yes'. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected or unspecified eyes, as appropriate.

N, n = Number of affected, unaffected or unspecified eyes, as appropriate. PSTE = Potential sight threatening event; SVL = Severe visual loss.

Table 4
Ocular History Prior to the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) among Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Eye Level)

	Total Adjudicated PSTE or SVL		
Parameter, n (%)	**Affected eye (N=11)**	**Unaffected eye (N=3)**	**Unspecified eye (N=24)**
Iritis			
Yes	0	0	0
No	4 (36.4)	2 (66.7)	0
Unknown	7 (63.6)	1 (33.3)	24 (100.0)
Uveitis			
Yes	0	0	0
No	4 (36.4)	2 (66.7)	0
Unknown	7 (63.6)	1 (33.3)	24 (100.0)
History of at least one of the above ocular diseases			
Yes	3 (27.3)	1 (33.3)	0
No	2 (18.2)	2 (66.7)	0
Unknown	6 (54.5)	0	24 (100.0)

Note: If the affected eye is unspecified, both eyes are presented as unspecified eyes. For events where both eyes are affected, the ocular history of both eyes are counted as affected eyes. The history of at least one of the above ocular diseases is counted as 'Unknown' if at least one ocular disease is reported as 'unknown' and no ocular disease is reported as 'Yes'. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected or unspecified eyes, as appropriate.

N, n = Number of affected, unaffected or unspecified eyes, as appropriate. PSTE = Potential sight threatening event; SVL = Severe visual loss.

Table 5
Ocular History Prior to the Occurrence of the Severe Visual Loss (SVL) among Adjudicated SVL Patients in the Study
(Safety Analysis Set, Eye Level)

	Adjudicated SVL		
Parameter, n (%)	**Affected eye (N=4)**	**Unaffected eye (N=2)**	**Unspecified eye (N=4)**
Macular Degeneration			
Yes	0	0	0
No	3 (75.0)	1 (50.0)	0
Unknown	1 (25.0)	1 (50.0)	4 (100.0)
Glaucoma			
Yes	0	0	0
No	3 (75.0)	1 (50.0)	0
Unknown	1 (25.0)	1 (50.0)	4 (100.0)
Diabetic Retinopathy			
Yes	0	0	0
No	3 (75.0)	1 (50.0)	0
Unknown	1 (25.0)	1 (50.0)	4 (100.0)
Cataracts			
Yes	2 (50.0)	0	0
No	1 (25.0)	1 (50.0)	0
Unknown	1 (25.0)	1 (50.0)	4 (100.0)

Note: If the affected eye is unspecified, both eyes are presented as unspecified eyes. For events where both eyes are affected, the ocular history of both eyes are counted as affected eyes. The history of at least one of the above ocular diseases is counted as 'Unknown' if at least one ocular disease is reported as 'unknown' and no ocular disease is reported as 'Yes'. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected or unspecified eyes, as appropriate.
N, n = Number of affected, unaffected or unspecified eyes, as appropriate. SVL = Severe visual loss.

Table 5
Ocular History Prior to the Occurrence of the Severe Visual Loss (SVL) among Adjudicated SVL Patients in the Study
(Safety Analysis Set, Eye Level)

	Adjudicated SVL		
Parameter, n (%)	**Affected eye (N=4)**	**Unaffected eye (N=2)**	**Unspecified eye (N=4)**
Trauma to the eyes			
Yes	0	0	0
No	3 (75.0)	1 (50.0)	0
Unknown	1 (25.0)	1 (50.0)	4 (100.0)
Optic atrophy			
Yes	0	0	0
No	3 (75.0)	1 (50.0)	0
Unknown	1 (25.0)	1 (50.0)	4 (100.0)
Optic nerve edema			
Yes	0	0	0
No	3 (75.0)	1 (50.0)	0
Unknown	1 (25.0)	1 (50.0)	4 (100.0)
Retinal hemorrhages			
Yes	0	0	0
No	3 (75.0)	1 (50.0)	0
Unknown	1 (25.0)	1 (50.0)	4 (100.0)

Note: If the affected eye is unspecified, both eyes are presented as unspecified eyes. For events where both eyes are affected, the ocular history of both eyes are counted as affected eyes. The history of at least one of the above ocular diseases is counted as 'Unknown' if at least one ocular disease is reported as 'unknown' and no ocular disease is reported as 'Yes'. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected or unspecified eyes, as appropriate.
N, n = Number of affected, unaffected or unspecified eyes, as appropriate. SVL = Severe visual loss.

Table 5
Ocular History Prior to the Occurrence of the Severe Visual Loss (SVL) among Adjudicated SVL Patients in the Study
(Safety Analysis Set, Eye Level)

	Adjudicated SVL		
Parameter, n (%)	**Affected eye (N=4)**	**Unaffected eye (N=2)**	**Unspecified eye (N=4)**
Vitreous hemorrhage			
Yes	0	0	0
No	3 (75.0)	1 (50.0)	0
Unknown	1 (25.0)	1 (50.0)	4 (100.0)
Macular edema			
Yes	1 (25.0)	0	0
No	2 (50.0)	1 (50.0)	0
Unknown	1 (25.0)	1 (50.0)	4 (100.0)
Retinal holes			
Yes	0	1 (50.0)	0
No	3 (75.0)	1 (50.0)	0
Unknown	1 (25.0)	0	4 (100.0)
Retinal detachment			
Yes	1 (25.0)	0	0
No	3 (75.0)	1 (50.0)	0
Unknown	0	1 (50.0)	4 (100.0)

Note: If the affected eye is unspecified, both eyes are presented as unspecified eyes. For events where both eyes are affected, the ocular history of both eyes are counted as affected eyes. The history of at least one of the above ocular diseases is counted as 'Unknown' if at least one ocular disease is reported as 'unknown' and no ocular disease is reported as 'Yes'. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected or unspecified eyes, as appropriate.
N, n = Number of affected, unaffected or unspecified eyes, as appropriate. SVL = Severe visual loss.

Table 5
Ocular History Prior to the Occurrence of the Severe Visual Loss (SVL) among Adjudicated SVL Patients in the Study
(Safety Analysis Set, Eye Level)

	Adjudicated SVL		
Parameter, n (%)	**Affected eye (N=4)**	**Unaffected eye (N=2)**	**Unspecified eye (N=4)**
Iritis			
Yes	0	0	0
No	3 (75.0)	1 (50.0)	0
Unknown	1 (25.0)	1 (50.0)	4 (100.0)
Uveitis			
Yes	0	0	0
No	3 (75.0)	1 (50.0)	0
Unknown	1 (25.0)	1 (50.0)	4 (100.0)
History of at least one of the above ocular diseases			
Yes	3 (75.0)	1 (50.0)	0
No	1 (25.0)	1 (50.0)	0
Unknown	0	0	4 (100.0)

Note: If the affected eye is unspecified, both eyes are presented as unspecified eyes. For events where both eyes are affected, the ocular history of both eyes are counted as affected eyes. The history of at least one of the above ocular diseases is counted as 'Unknown' if at least one ocular disease is reported as 'unknown' and no ocular disease is reported as 'Yes'. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected or unspecified eyes, as appropriate.
N, n = Number of affected, unaffected or unspecified eyes, as appropriate. SVL = Severe visual loss.

Table 6
Ocular History Prior to the Occurrence of the Potential Sight Threatening Event (PSTE) among Adjudicated PSTE Patients in the Study (Safety Analysis Set, Eye Level)

	Adjudicated PSTE		
Parameter, n (%)	**Affected eye (N=7)**	**Unaffected eye (N=1)**	**Unspecified eye (N=20)**
Macular Degeneration			
Yes	0	0	0
No	1 (14.3)	1 (100.0)	0
Unknown	6 (85.7)	0	20 (100.0)
Glaucoma			
Yes	0	0	0
No	1 (14.3)	1 (100.0)	0
Unknown	6 (85.7)	0	20 (100.0)
Diabetic Retinopathy			
Yes	0	0	0
No	1 (14.3)	1 (100.0)	0
Unknown	6 (85.7)	0	20 (100.0)
Cataracts			
Yes	0	0	0
No	1 (14.3)	1 (100.0)	0
Unknown	6 (85.7)	0	20 (100.0)

Note: If the affected eye is unspecified, both eyes are presented as unspecified eyes. For events where both eyes are affected, the ocular history of both eyes are counted as affected eyes. The history of at least one of the above ocular diseases is counted as 'Unknown' if at least one ocular disease is reported as 'unknown' and no ocular disease is reported as 'Yes'. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected or unspecified eyes, as appropriate.
N, n = Number of affected, unaffected or unspecified eyes, as appropriate. PSTE = Potential sight threatening event.

Table 6
Ocular History Prior to the Occurrence of the Potential Sight Threatening Event (PSTE) among Adjudicated PSTE Patients in the Study (Safety Analysis Set, Eye Level)

	Adjudicated PSTE		
Parameter, n (%)	Affected eye (N=7)	Unaffected eye (N=1)	Unspecified eye (N=20)
Trauma to the eyes			
Yes	0	0	0
No	1 (14.3)	1 (100.0)	0
Unknown	6 (85.7)	0	20 (100.0)
Optic atrophy			
Yes	0	0	0
No	1 (14.3)	1 (100.0)	0
Unknown	6 (85.7)	0	20 (100.0)
Optic nerve edema			
Yes	0	0	0
No	1 (14.3)	1 (100.0)	0
Unknown	6 (85.7)	0	20 (100.0)
Retinal hemorrhages			
Yes	0	0	0
No	1 (14.3)	1 (100.0)	0
Unknown	6 (85.7)	0	20 (100.0)

Note: If the affected eye is unspecified, both eyes are presented as unspecified eyes. For events where both eyes are affected, the ocular history of both eyes are counted as affected eyes. The history of at least one of the above ocular diseases is counted as 'Unknown' if at least one ocular disease is reported as 'unknown' and no ocular disease is reported as 'Yes'. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected or unspecified eyes, as appropriate.
N, n = Number of affected, unaffected or unspecified eyes, as appropriate. PSTE = Potential sight threatening event.

Table 6
Ocular History Prior to the Occurrence of the Potential Sight Threatening Event (PSTE) among Adjudicated PSTE Patients in the Study (Safety Analysis Set, Eye Level)

	Adjudicated PSTE		
Parameter, n (%)	**Affected eye (N=7)**	**Unaffected eye (N=1)**	**Unspecified eye (N=20)**
Vitreous hemorrhage			
Yes	0	0	0
No	1 (14.3)	1 (100.0)	0
Unknown	6 (85.7)	0	20 (100.0)
Macular edema			
Yes	0	0	0
No	1 (14.3)	1 (100.0)	0
Unknown	6 (85.7)	0	20 (100.0)
Retinal holes			
Yes	0	0	0
No	1 (14.3)	1 (100.0)	0
Unknown	6 (85.7)	0	20 (100.0)
Retinal detachment			
Yes	0	0	0
No	1 (14.3)	1 (100.0)	0
Unknown	6 (85.7)	0	20 (100.0)

Note: If the affected eye is unspecified, both eyes are presented as unspecified eyes. For events where both eyes are affected, the ocular history of both eyes are counted as affected eyes. The history of at least one of the above ocular diseases is counted as 'Unknown' if at least one ocular disease is reported as 'unknown' and no ocular disease is reported as 'Yes'. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected or unspecified eyes, as appropriate.
N, n = Number of affected, unaffected or unspecified eyes, as appropriate. PSTE = Potential sight threatening event.

Table 6
Ocular History Prior to the Occurrence of the Potential Sight Threatening Event (PSTE) among Adjudicated PSTE Patients in the Study (Safety Analysis Set, Eye Level)

	Adjudicated PSTE		
Parameter, n (%)	**Affected eye (N=7)**	**Unaffected eye (N=1)**	**Unspecified eye (N=20)**
Iritis			
Yes	0	0	0
No	1 (14.3)	1 (100.0)	0
Unknown	6 (85.7)	0	20 (100.0)
Uveitis			
Yes	0	0	0
No	1 (14.3)	1 (100.0)	0
Unknown	6 (85.7)	0	20 (100.0)
History of at least one of the above ocular diseases			
Yes	0	0	0
No	1 (14.3)	1 (100.0)	0
Unknown	6 (85.7)	0	20 (100.0)

Note: If the affected eye is unspecified, both eyes are presented as unspecified eyes. For events where both eyes are affected, the ocular history of both eyes are counted as affected eyes. The history of at least one of the above ocular diseases is counted as 'Unknown' if at least one ocular disease is reported as 'unknown' and no ocular disease is reported as 'Yes'. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected or unspecified eyes, as appropriate.
N, n = Number of affected, unaffected or unspecified eyes, as appropriate. PSTE = Potential sight threatening event.

Table 7
Exposure to Medications with Potential Ocular Toxicity Prior to the Occurrence of Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study (Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL cases		
Medication, n (%)	PSTE (N=14)	SVL (N=5)	Total (N=19)
Vigabatrin			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Trametinib			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Hydroxychloroquine			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Amiodarone			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)

Note: Percentages are based on the number of reported PSTE or SVL events. Events where both eyes are affected in the reports are counted as one event. The safety analysis set includes adjudicated PSTE or SVL cases only.
N, n = Number of PSTE or SVL events. PSTE = Potential sight threatening event; SVL = Severe visual loss.
[a] The result is counted as 'Unknown' if at least one of the medications is reported as 'Unknown' and no medication is reported as 'Yes'.

Table 7
Exposure to Medications with Potential Ocular Toxicity Prior to the Occurrence of Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study (Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL cases		
Medication, n (%)	**PSTE (N=14)**	**SVL (N=5)**	**Total (N=19)**
Topiramate			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Ethambutol			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Tamsulosin			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Other			
Yes	1 (7.1)	0	1 (5.3)
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	12 (85.7)	2 (40.0)	14 (73.7)

Note: Percentages are based on the number of reported PSTE or SVL events. Events where both eyes are affected in the reports are counted as one event. The safety analysis set includes adjudicated PSTE or SVL cases only.
N, n = Number of PSTE or SVL events. PSTE = Potential sight threatening event; SVL = Severe visual loss.
[a] The result is counted as 'Unknown' if at least one of the medications is reported as 'Unknown' and no medication is reported as 'Yes'.

Table 7
Exposure to Medications with Potential Ocular Toxicity Prior to the Occurrence of Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study (Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL cases		
Medication, n (%)	**PSTE (N=14)**	**SVL (N=5)**	**Total (N=19)**
Exposed to at least one of the above potential ocular toxicity medications[a]			
Yes	1 (7.1)	0	1 (5.3)
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	12 (85.7)	2 (40.0)	14 (73.7)

Note: Percentages are based on the number of reported PSTE or SVL events. Events where both eyes are affected in the reports are counted as one event. The safety analysis set includes adjudicated PSTE or SVL cases only.
N, n = Number of PSTE or SVL events. PSTE = Potential sight threatening event; SVL = Severe visual loss.
[a] The result is counted as 'Unknown' if at least one of the medications is reported as 'Unknown' and no medication is reported as 'Yes'.

Table 8
Medical History of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL cases		
Condition, n (%)	**PSTE (N=14)**	**SVL (N=5)**	**Total (N=19)**
Diabetes			
Yes	1 (7.1)	2 (40.0)	3 (15.8)
No	0	2 (40.0)	2 (10.5)
Unknown	13 (92.9)	1 (20.0)	14 (73.7)
Hypertension			
Yes	3 (21.4)	1 (20.0)	4 (21.1)
No	0	2 (40.0)	2 (10.5)
Unknown	11 (78.6)	2 (40.0)	13 (68.4)
Hyperlipidemia			
Yes	0	1 (20.0)	1 (5.3)
No	1 (7.1)	2 (40.0)	3 (15.8)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Vascular Disease			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
TIA/Stroke			
Yes	1 (7.1)	0	1 (5.3)
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	12 (85.7)	2 (40.0)	14 (73.7)

Note: Percentages are based on the number of reported PSTE or SVL events. Events where both eyes are affected in the reports are counted as one event. The safety analysis set includes adjudicated PSTE or SVL cases only.

N, n = Number of PSTE or SVL events. PSTE = Potential sight threatening event; SVL = Severe visual loss.

Table 8
Medical History of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL cases		
Condition, n (%)	**PSTE (N=14)**	**SVL (N=5)**	**Total (N=19)**
Thrombophilia			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Hyperviscosity syndromes			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Multiple Sclerosis			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Autoimmune Disease(s)			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)

Note: Percentages are based on the number of reported PSTE or SVL events. Events where both eyes are affected in the reports are counted as one event. The safety analysis set includes adjudicated PSTE or SVL cases only.
N, n = Number of PSTE or SVL events. PSTE = Potential sight threatening event; SVL = Severe visual loss.

Table 9
Presence of Brain Metastases and Treatment for Brain Metastases prior to the Occurrences of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

Parameter	Total Adjudicated PSTE or SVL		
	PSTE	SVL	Total
Presence of brain metastases[a], n(%)	**(N=14)**	**(N=5)**	**(N=19)**
Yes	2 (14.3)	3 (60.0)	5 (26.3)
No	1 (7.1)	1 (20.0)	2 (10.5)
Unknown	11 (78.6)	1 (20.0)	12 (63.2)
Involvement of optic nerve or visual pathway or occipital lobe[b], n(%)	**(N=2)**	**(N=3)**	**(N=5)**
Yes	0	1 (33.3)	1 (20.0)
No	0	1 (33.3)	1 (20.0)
Unknown	2 (100.0)	1 (33.3)	3 (60.0)

Note: N, n = Number of PSTE or SVL events or in a subset of PSTE or SVL events, SD = standard deviation, min = minimum, max = maximum, PSTE = Potential sight threatening event, SVL = severe visual loss, - = data not available. The safety analysis set includes adjudicated PSTE or SVL cases only.

[a]Percentages are calculated based on the number of PSTE or SVL events.

[b]Only for events in patients with present brain metastases at the time of the occurrence of the PSTE or SVL. Percentages are calculated based on the number of PSTE or SVL events in patients with present brain metastases at the time of the occurrence of the PSTE or SVL. For events where both eyes in a patient are affected from the specific PSTE or SVL, the onset of the PSTE or SVL is defined as the first onset date of the affected eyes. Events were both eyes are affected are counted as single event.

[c]Only for patients who had brain surgery prior to the onset of the PSTE or SVL.

[d]Only for patients who had brain radiation prior to the onset of the PSTE or SVL.

Table 9
Presence of Brain Metastases and Treatment for Brain Metastases prior to the Occurrences of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

Parameter	Total Adjudicated PSTE or SVL		
	PSTE	SVL	Total
Time from first diagnosis of brain metastases until onset of PSTE or SVL (months)[b]	**(N=2)**	**(N=3)**	**(N=5)**
n	0	1	1
Mean	-	3.49	3.49
SD	-	-	-
Median	-.-	3.49	3.49
Min, Max	-, -	3.5, 3.5	3.5, 3.5
Unknown	2 (100.0)	2 (66.7)	4 (80.0)
Stereotactic surgery or other surgery for brain metastases[b], n(%)	**(N=2)**	**(N=3)**	**(N=5)**
Yes	0	0	0
No	0	2 (66.7)	2 (40.0)
Unknown	2 (100.0)	1 (33.3)	3 (60.0)

Note: N, n = Number of PSTE or SVL events or in a subset of PSTE or SVL events, SD = standard deviation, min = minimum, max = maximum, PSTE = Potential sight threatening event, SVL = severe visual loss, - = data not available. The safety analysis set includes adjudicated PSTE or SVL cases only.

[a]Percentages are calculated based on the number of PSTE or SVL events.

[b]Only for events in patients with present brain metastases at the time of the occurrence of the PSTE or SVL. Percentages are calculated based on the number of PSTE or SVL events in patients with present brain metastases at the time of the occurrence of the PSTE or SVL. For events where both eyes in a patient are affected from the specific PSTE or SVL, the onset of the PSTE or SVL is defined as the first onset date of the affected eyes. Events were both eyes are affected are counted as single event.

[c]Only for patients who had brain surgery prior to the onset of the PSTE or SVL.

[d]Only for patients who had brain radiation prior to the onset of the PSTE or SVL.

Table 9
Presence of Brain Metastases and Treatment for Brain Metastases prior to the Occurrences of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

Parameter	Total Adjudicated PSTE or SVL		
	PSTE	SVL	Total
Time from last brain surgery until onset of PSTE or SVL (months)[b,c]	**(N=0)**	**(N=0)**	**(N=0)**
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -
Radiotherapy for brain metastases[b], n(%)	**(N=2)**	**(N=3)**	**(N=5)**
Yes	1 (50.0)	1 (33.3)	2 (40.0)
No	0	1 (33.3)	1 (20.0)
Unknown	1 (50.0)	1 (33.3)	2 (40.0)

Note: N, n = Number of PSTE or SVL events or in a subset of PSTE or SVL events, SD = standard deviation, min = minimum, max = maximum, PSTE = Potential sight threatening event, SVL = severe visual loss, - = data not available. The safety analysis set includes adjudicated PSTE or SVL cases only.

[a]Percentages are calculated based on the number of PSTE or SVL events.

[b]Only for events in patients with present brain metastases at the time of the occurrence of the PSTE or SVL. Percentages are calculated based on the number of PSTE or SVL events in patients with present brain metastases at the time of the occurrence of the PSTE or SVL. For events where both eyes in a patient are affected from the specific PSTE or SVL, the onset of the PSTE or SVL is defined as the first onset date of the affected eyes. Events were both eyes are affected are counted as single event.

[c]Only for patients who had brain surgery prior to the onset of the PSTE or SVL.

[d]Only for patients who had brain radiation prior to the onset of the PSTE or SVL.

Table 9
Presence of Brain Metastases and Treatment for Brain Metastases prior to the Occurrences of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

Parameter	Total Adjudicated PSTE or SVL		
	PSTE	SVL	Total
Total dose of radiation for brain metastases (gray units)[d]	**(N=1)**	**(N=1)**	**(N=2)**
n	0	1	1
Mean	-	233.00	233.00
SD	-	-	-
Median	-.-	233.00	233.00
Min, Max	-, -	233.0, 233.0	233.0, 233.0
Unknown	1 (100.0)	0	1 (50.0)

Note: N, n = Number of PSTE or SVL events or in a subset of PSTE or SVL events, SD = standard deviation, min = minimum, max = maximum, PSTE = Potential sight threatening event, SVL = severe visual loss, - = data not available. The safety analysis set includes adjudicated PSTE or SVL cases only.

[a]Percentages are calculated based on the number of PSTE or SVL events.

[b]Only for events in patients with present brain metastases at the time of the occurrence of the PSTE or SVL. Percentages are calculated based on the number of PSTE or SVL events in patients with present brain metastases at the time of the occurrence of the PSTE or SVL. For events where both eyes in a patient are affected from the specific PSTE or SVL, the onset of the PSTE or SVL is defined as the first onset date of the affected eyes. Events were both eyes are affected are counted as single event.

[c]Only for patients who had brain surgery prior to the onset of the PSTE or SVL.

[d]Only for patients who had brain radiation prior to the onset of the PSTE or SVL.

Table 9
Presence of Brain Metastases and Treatment for Brain Metastases prior to the Occurrences of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

Parameter	Total Adjudicated PSTE or SVL		
	PSTE	SVL	Total
Time from last brain radiation until onset of PSTE or SVL (months)[d]	**(N=1)**	**(N=1)**	**(N=2)**
n	0	1	1
Mean	-	6.45	6.45
SD	-	-	-
Median	-.-	6.45	6.45
Min, Max	-, -	6.4, 6.4	6.4, 6.4
Unknown	1 (100.0)	0	1 (50.0)

Note: N, n = Number of PSTE or SVL events or in a subset of PSTE or SVL events, SD = standard deviation, min = minimum, max = maximum, PSTE = Potential sight threatening event, SVL = severe visual loss, - = data not available. The safety analysis set includes adjudicated PSTE or SVL cases only.

[a]Percentages are calculated based on the number of PSTE or SVL events.

[b]Only for events in patients with present brain metastases at the time of the occurrence of the PSTE or SVL. Percentages are calculated based on the number of PSTE or SVL events in patients with present brain metastases at the time of the occurrence of the PSTE or SVL. For events where both eyes in a patient are affected from the specific PSTE or SVL, the onset of the PSTE or SVL is defined as the first onset date of the affected eyes. Events were both eyes are affected are counted as single event.

[c]Only for patients who had brain surgery prior to the onset of the PSTE or SVL.

[d]Only for patients who had brain radiation prior to the onset of the PSTE or SVL.

Table 10
Intracranial Pressure Prior to the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
Parameter	**PSTE**	**SVL**	**Total**
Elevated intracranial pressure, n (%)[a]	**(N=14)**	**(N=5)**	**(N=19)**
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Cause of elevated intracranial pressure known, n (%)[b]	**(N=0)**	**(N=0)**	**(N=0)**
Yes	0	0	0
No	0	0	0
Unknown	0	0	0

Note: PSTE or SVL events where both eyes are affected are counted as one event. The safety analysis set includes adjudicated PSTE or SVL cases only.
N, n = Number of PSTE or SVL events or in a subset of PSTE or SVL events, SD = standard deviation, min = minumum, max = maximum, PSTE = potential sight threatening event, SVL = severe visual loss, - = data not available.
[a]Percentages are based on the number of reported PSTE or SVL events.
[b]Only for PSTE or SVL events in patients with elevated intracranial pressure. Percentages are based on the number of events in patients with elevated intracranial pressure at the time of onset of the PSTE or SVL.
[c]Time from last available intracranial pressure prior to the onset of the PSTE or SVL to the onset of the PSTE or SVL is calculated as onset date of the PSTE or SVL event - date of measurement + 1 day . For events where both eyes in a patient are affected from the specific PSTE or SVL, the onset of the PSTE or SVL is defined as the first onset date of the affected eyes.

Table 10
Intracranial Pressure Prior to the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

Parameter	Total Adjudicated PSTE or SVL		
	PSTE	SVL	Total
Last available intracranial pressure prior to the onset of the PSTE or SVL (mmHg)[b]	**(N=0)**	**(N=0)**	**(N=0)**
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -
Time from last available intracranial pressure prior to the onset of the PSTE or SVL to the onset of the PSTE or SVL (days)[b,c]	**(N=0)**	**(N=0)**	**(N=0)**
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -

Note: PSTE or SVL events where both eyes are affected are counted as one event. The safety analysis set includes adjudicated PSTE or SVL cases only. N, n = Number of PSTE or SVL events or in a subset of PSTE or SVL events, SD = standard deviation, min = minumum, max = maximum, PSTE = potential sight threatening event, SVL = severe visual loss, - = data not available.
[a]Percentages are based on the number of reported PSTE or SVL events.
[b]Only for PSTE or SVL events in patients with elevated intracranial pressure. Percentages are based on the number of events in patients with elevated intracranial pressure at the time of onset of the PSTE or SVL.
[c]Time from last available intracranial pressure prior to the onset of the PSTE or SVL to the onset of the PSTE or SVL is calculated as onset date of the PSTE or SVL event - date of measurement + 1 day . For events where both eyes in a patient are affected from the specific PSTE or SVL, the onset of the PSTE or SVL is defined as the first onset date of the affected eyes.

Table 11
Relevant Examinations within One Year Prior to the Occurrence of Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

Parameter	Total Adjudicated PSTE or SVL		
	PSTE	SVL	Total
At least one Carotid Doppler performed, n (%)	**(N=14)**	**(N=5)**	**(N=19)**
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Significant stenosis >70%, n (%)[a,b]	**(N=0)**	**(N=0)**	**(N=0)**
Yes	0	0	0
No	0	0	0
Unknown	0	0	0
Abnormalities, n (%)[a,b]	**(N=0)**	**(N=0)**	**(N=0)**
Yes	0	0	0
No	0	0	0
Unknown	0	0	0

Note: PSTE or SVL events in patients who had assessments only after the onset date of the PSTE or SVL are counted as not having had an assessment one year prior to the onset of the PSTE or SVL. PSTE or SVL events where both eyes are affected are counted only once. Clinical significance is evaluated by the Investigator who reported the PSTE or SVL event to Pfizer Safety. The safety analysis set includes adjudicated PSTE or SVL cases only.

N, n = Number of PSTE or SVL events or in a subset of PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum, PSTE = Potential sight threatening event, SVL = Severe visual loss, - = data not available. Examinations with unknown assessment dates or unknown onset date of the PSTE or SVL were counted as 'Unknown'.

[a] Last available examinations prior to the PSTE or SVL are used.

[b] Percentages are calculated based on the number of PSTE or SVL events in patients who had at least one examination within 1 year prior to the onset of the PSTE or SVL.

Table 11
Relevant Examinations within One Year Prior to the Occurrence of Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

Parameter	Total Adjudicated PSTE or SVL		
	PSTE	SVL	Total
Erythrocyte sedimentation rate measured at least once, n (%)	**(N=14)**	**(N=5)**	**(N=19)**
Yes	0	0	0
No	1 (7.1)	2 (40.0)	3 (15.8)
Unknown	13 (92.9)	3 (60.0)	16 (84.2)
Erythrocyte sedimentation rate (mm/hr)[a]	**(N=0)**	**(N=0)**	**(N=0)**
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-	-	-
Min, Max	-, -	-, -	-, -

Note: PSTE or SVL events in patients who had assessments only after the onset date of the PSTE or SVL are counted as not having had an assessment one year prior to the onset of the PSTE or SVL. PSTE or SVL events where both eyes are affected are counted only once. Clinical significance is evaluated by the Investigator who reported the PSTE or SVL event to Pfizer Safety. The safety analysis set includes adjudicated PSTE or SVL cases only.

N, n = Number of PSTE or SVL events or in a subset of PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum, PSTE = Potential sight threatening event, SVL = Severe visual loss, - = data not available. Examinations with unknown assessment dates or unknown onset date of the PSTE or SVL were counted as 'Unknown'.

[a] Last available examinations prior to the PSTE or SVL are used.

[b] Percentages are calculated based on the number of PSTE or SVL events in patients who had at least one examination within 1 year prior to the onset of the PSTE or SVL.

Table 11
Relevant Examinations within One Year Prior to the Occurrence of Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

Parameter	Total Adjudicated PSTE or SVL		
	PSTE	SVL	Total
Erythrocyte sedimentation rate clinically significant, n (%)[a,b]	**(N=0)**	**(N=0)**	**(N=0)**
Yes	0	0	0
No	0	0	0
Unknown	0	0	0
C-reactive protein measured at least once, n (%)	**(N=14)**	**(N=5)**	**(N=19)**
Yes	1 (7.1)	1 (20.0)	2 (10.5)
No	1 (7.1)	1 (20.0)	2 (10.5)
Unknown	12 (85.7)	3 (60.0)	15 (78.9)

Note: PSTE or SVL events in patients who had assessments only after the onset date of the PSTE or SVL are counted as not having had an assessment one year prior to the onset of the PSTE or SVL. PSTE or SVL events where both eyes are affected are counted only once. Clinical significance is evaluated by the Investigator who reported the PSTE or SVL event to Pfizer Safety. The safety analysis set includes adjudicated PSTE or SVL cases only.

N, n = Number of PSTE or SVL events or in a subset of PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum, PSTE = Potential sight threatening event, SVL = Severe visual loss, - = data not available. Examinations with unknown assessment dates or unknown onset date of the PSTE or SVL were counted as 'Unknown'.

[a] Last available examinations prior to the PSTE or SVL are used.

[b] Percentages are calculated based on the number of PSTE or SVL events in patients who had at least one examination within 1 year prior to the onset of the PSTE or SVL.

Table 11
Relevant Examinations within One Year Prior to the Occurrence of Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

Parameter	Total Adjudicated PSTE or SVL		
	PSTE	SVL	Total
C-reactive protein (mg/dl)[a]	**(N=1)**	**(N=1)**	**(N=2)**
n	1	1	2
Mean	1.64	0.89	1.26
SD	-	-	0.530
Median	1.64	0.89	1.26
Min, Max	1.6, 1.6	0.9, 0.9	0.9, 1.6
C-reactive protein clinically significant, n (%)[a,b]	**(N=1)**	**(N=1)**	**(N=2)**
Yes	0	0	0
No	0	1 (100.0)	1 (50.0)
Unknown	1 (100.0)	0	1 (50.0)

Note: PSTE or SVL events in patients who had assessments only after the onset date of the PSTE or SVL are counted as not having had an assessment one year prior to the onset of the PSTE or SVL. PSTE or SVL events where both eyes are affected are counted only once. Clinical significance is evaluated by the Investigator who reported the PSTE or SVL event to Pfizer Safety. The safety analysis set includes adjudicated PSTE or SVL cases only.

N, n = Number of PSTE or SVL events or in a subset of PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum, PSTE = Potential sight threatening event, SVL = Severe visual loss, - = data not available. Examinations with unknown assessment dates or unknown onset date of the PSTE or SVL were counted as 'Unknown'.

[a] Last available examinations prior to the PSTE or SVL are used.

[b] Percentages are calculated based on the number of PSTE or SVL events in patients who had at least one examination within 1 year prior to the onset of the PSTE or SVL.

Table 12
Carotid Doppler, C-reactive Protein, and Erythrocyte Sedimentation Rate within One Year Subsequent to the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study (Safety Analysis Set, Event Level)

Parameter	Total Adjudicated PSTE or SVL		
	PSTE	SVL	Total
At least one Carotid Doppler performed, n (%)	**(N=14)**	**(N=5)**	**(N=19)**
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Significant stenosis >70%, n (%)[a,b]	**(N=0)**	**(N=0)**	**(N=0)**
Yes	0	0	0
No	0	0	0
Unknown	0	0	0
Abnormalities, n (%)[a,b]	**(N=0)**	**(N=0)**	**(N=0)**
Yes	0	0	0
No	0	0	0
Unknown	0	0	0

Note: PSTE or SVL events in patients who had assessments only after the onset date of the PSTE or SVL are counted as not having had an assessment one year prior to the onset of the PSTE or SVL. PSTE or SVL events where both eyes are affected are counted only once. Clinical significance is evaluated by the Investigator who reported the PSTE or SVL event to Pfizer Safety. The safety analysis set includes adjudicated PSTE or SVL cases only.

N, n = Number of PSTE or SVL events or in a subset of PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum, PSTE = Potential sight threatening event, SVL = Severe visual loss, - = data not available. Examinations with unknown assessment dates or unknown onset date of the PSTE or SVL were counted as 'Unknown'.

[a] First available examinations subsequent to the PSTE or SVL are used.

[b] Percentages are calculated based on the number of PSTE or SVL events in patients who had an examination within 1 year subsequent to the onset of of the PSTE or SVL.

Table 12
Carotid Doppler, C-reactive Protein, and Erythrocyte Sedimentation Rate within One Year Subsequent to the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study (Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
Parameter	**PSTE**	**SVL**	**Total**
Erythrocyte sedimentation rate measured at least once, n (%)	**(N=14)**	**(N=5)**	**(N=19)**
Yes	0	0	0
No	1 (7.1)	2 (40.0)	3 (15.8)
Unknown	13 (92.9)	3 (60.0)	16 (84.2)
Erythrocyte sedimentation rate (mm/hr)[a]	**(N=0)**	**(N=0)**	**(N=0)**
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-	-	-
Min, Max	-, -	-, -	-, -

Note: PSTE or SVL events in patients who had assessments only after the onset date of the PSTE or SVL are counted as not having had an assessment one year prior to the onset of the PSTE or SVL. PSTE or SVL events where both eyes are affected are counted only once. Clinical significance is evaluated by the Investigator who reported the PSTE or SVL event to Pfizer Safety. The safety analysis set includes adjudicated PSTE or SVL cases only.

N, n = Number of PSTE or SVL events or in a subset of PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum, PSTE = Potential sight threatening event, SVL = Severe visual loss, - = data not available. Examinations with unknown assessment dates or unknown onset date of the PSTE or SVL were counted as 'Unknown'.

[a] First available examinations subsequent to the PSTE or SVL are used.

[b] Percentages are calculated based on the number of PSTE or SVL events in patients who had an examination within 1 year subsequent to the onset of of the PSTE or SVL.

Table 12
Carotid Doppler, C-reactive Protein, and Erythrocyte Sedimentation Rate within One Year Subsequent to the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study (Safety Analysis Set, Event Level)

Parameter	Total Adjudicated PSTE or SVL		
	PSTE	SVL	Total
Erythrocyte sedimentation rate clinically significant, n (%)[a,b]	**(N=0)**	**(N=0)**	**(N=0)**
Yes	0	0	0
No	0	0	0
Unknown	0	0	0
C-reactive protein measured at least once, n (%)	**(N=14)**	**(N=5)**	**(N=19)**
Yes	1 (7.1)	1 (20.0)	2 (10.5)
No	1 (7.1)	1 (20.0)	2 (10.5)
Unknown	12 (85.7)	3 (60.0)	15 (78.9)

Note: PSTE or SVL events in patients who had assessments only after the onset date of the PSTE or SVL are counted as not having had an assessment one year prior to the onset of the PSTE or SVL. PSTE or SVL events where both eyes are affected are counted only once. Clinical significance is evaluated by the Investigator who reported the PSTE or SVL event to Pfizer Safety. The safety analysis set includes adjudicated PSTE or SVL cases only.

N, n = Number of PSTE or SVL events or in a subset of PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum, PSTE = Potential sight threatening event, SVL = Severe visual loss, - = data not available. Examinations with unknown assessment dates or unknown onset date of the PSTE or SVL were counted as 'Unknown'.

[a] First available examinations subsequent to the PSTE or SVL are used.

[b] Percentages are calculated based on the number of PSTE or SVL events in patients who had an examination within 1 year subsequent to the onset of of the PSTE or SVL.

Table 12
Carotid Doppler, C-reactive Protein, and Erythrocyte Sedimentation Rate within One Year Subsequent to the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study (Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
Parameter	**PSTE**	**SVL**	**Total**
C-reactive protein (mg/dl)[a]	**(N=1)**	**(N=1)**	**(N=2)**
n	1	1	2
Mean	4.18	0.17	2.18
SD	-	-	2.837
Median	4.18	0.17	2.18
Min, Max	4.2, 4.2	0.2, 0.2	0.2, 4.2
C-reactive protein clinically significant, n (%)[a,b]	**(N=1)**	**(N=1)**	**(N=2)**
Yes	0	0	0
No	0	1 (100.0)	1 (50.0)
Unknown	1 (100.0)	0	1 (50.0)

Note: PSTE or SVL events in patients who had assessments only after the onset date of the PSTE or SVL are counted as not having had an assessment one year prior to the onset of the PSTE or SVL. PSTE or SVL events where both eyes are affected are counted only once. Clinical significance is evaluated by the Investigator who reported the PSTE or SVL event to Pfizer Safety. The safety analysis set includes adjudicated PSTE or SVL cases only.

N, n = Number of PSTE or SVL events or in a subset of PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum, PSTE = Potential sight threatening event, SVL = Severe visual loss, - = data not available. Examinations with unknown assessment dates or unknown onset date of the PSTE or SVL were counted as 'Unknown'.

[a] First available examinations subsequent to the PSTE or SVL are used.

[b] Percentages are calculated based on the number of PSTE or SVL events in patients who had an examination within 1 year subsequent to the onset of of the PSTE or SVL.

Table 13
Exposure to Crizotinib Prior to the Onset of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
Parameter	**PSTE (N=14)**	**SVL (N=5)**	**Total (N=19)**
Time from first exposure to crizotinib until onset of the PSTE or SVL (days)			
n	9	4	13
Mean	241.3	86.8	193.8
SD	391.89	51.99	329.51
Median	8.0	77.0	41.0
Min, Max	1, 1068	41, 152	1, 1068

Note: Time from first exposure until onset of PSTE or SVL is calculated as date of onset of PSTE or SVL - date of first exposure to crizotinib + 1 day. The number of cumulative days being treated with crizotinib is defined as the sum of days the patient who experienced the PSTE or SVL has been treated with any dose of crizotinib between the treatment start date with crizotinib and the onset date of the PSTE or SVL event. The total cumulative dose prior to the onset of the PSTE or SVL is calculated as the cumulative dose a patient with the PSTE or SVL was exposed to from the date of the first exposure to crizotinib until (and including) the date of the onset of the PSTE or SVL. The total daily dose immediately prior to the onset of the PSTE or SVL is defined as the total daily dose the patient who experienced a PSTE or SVL was taking the day before the onset of the PSTE or SVL. The average daily dose is defined as the cumulative dose of crizotinib prior to the onset of the PSTE or SVL divided by the cumulative number of days treated with crizotinib. PSTE or SVL events where both eyes are affected are counted only once. The safety analysis set includes adjudicated PSTE or SVL cases only.
N = Number of PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum. PSTE = Potential sight threatening event; SVL = Severe visual loss.

Table 13
Exposure to Crizotinib Prior to the Onset of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

Parameter	Total Adjudicated PSTE or SVL		
	PSTE (N=14)	SVL (N=5)	Total (N=19)
Number of cumulative days being treated with crizotinib prior to the onset of the PSTE or SVL (days)			
n	7	4	11
Mean	155.6	86.5	130.5
SD	271.57	52.23	215.14
Median	4.0	76.5	41.0
Min, Max	1, 671	41, 152	1, 671

Note: Time from first exposure until onset of PSTE or SVL is calculated as date of onset of PSTE or SVL - date of first exposure to crizotinib + 1 day. The number of cumulative days being treated with crizotinib is defined as the sum of days the patient who experienced the PSTE or SVL has been treated with any dose of crizotinib between the treatment start date with crizotinib and the onset date of the PSTE or SVL event. The total cumulative dose prior to the onset of the PSTE or SVL is calculated as the cumulative dose a patient with the PSTE or SVL was exposed to from the date of the first exposure to crizotinib until (and including) the date of the onset of the PSTE or SVL. The total daily dose immediately prior to the onset of the PSTE or SVL is defined as the total daily dose the patient who experienced a PSTE or SVL was taking the day before the onset of the PSTE or SVL. The average daily dose is defined as the cumulative dose of crizotinib prior to the onset of the PSTE or SVL divided by the cumulative number of days treated with crizotinib. PSTE or SVL events where both eyes are affected are counted only once. The safety analysis set includes adjudicated PSTE or SVL cases only.
N = Number of PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum. PSTE = Potential sight threatening event; SVL = Severe visual loss.

Table 13
Exposure to Crizotinib Prior to the Onset of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
Parameter	**PSTE (N=14)**	**SVL (N=5)**	**Total (N=19)**
Total cumulative dose of crizotinib prior to onset of the PSTE or SVL (mg)			
n	7	4	11
Mean	70942.9	36687.5	58486.4
SD	129756.45	26314.90	102997.45
Median	2000.0	25125.0	20500.0
Min, Max	250, 335500	20500, 76000	250, 335500

Note: Time from first exposure until onset of PSTE or SVL is calculated as date of onset of PSTE or SVL - date of first exposure to crizotinib + 1 day. The number of cumulative days being treated with crizotinib is defined as the sum of days the patient who experienced the PSTE or SVL has been treated with any dose of crizotinib between the treatment start date with crizotinib and the onset date of the PSTE or SVL event. The total cumulative dose prior to the onset of the PSTE or SVL is calculated as the cumulative dose a patient with the PSTE or SVL was exposed to from the date of the first exposure to crizotinib until (and including) the date of the onset of the PSTE or SVL. The total daily dose immediately prior to the onset of the PSTE or SVL is defined as the total daily dose the patient who experienced a PSTE or SVL was taking the day before the onset of the PSTE or SVL. The average daily dose is defined as the cumulative dose of crizotinib prior to the onset of the PSTE or SVL divided by the cumulative number of days treated with crizotinib. PSTE or SVL events where both eyes are affected are counted only once. The safety analysis set includes adjudicated PSTE or SVL cases only.
N = Number of PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum. PSTE = Potential sight threatening event; SVL = Severe visual loss.

Table 13
Exposure to Crizotinib Prior to the Onset of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
Parameter	**PSTE (N=14)**	**SVL (N=5)**	**Total (N=19)**
Total daily dose of crizotinib immediately prior to onset of the PSTE or SVL (mg)			
n	7	4	11
Mean	392.9	437.5	409.1
SD	133.63	125.00	126.13
Median	500.0	500.0	500.0
Min, Max	250, 500	250, 500	250, 500

Note: Time from first exposure until onset of PSTE or SVL is calculated as date of onset of PSTE or SVL - date of first exposure to crizotinib + 1 day. The number of cumulative days being treated with crizotinib is defined as the sum of days the patient who experienced the PSTE or SVL has been treated with any dose of crizotinib between the treatment start date with crizotinib and the onset date of the PSTE or SVL event. The total cumulative dose prior to the onset of the PSTE or SVL is calculated as the cumulative dose a patient with the PSTE or SVL was exposed to from the date of the first exposure to crizotinib until (and including) the date of the onset of the PSTE or SVL. The total daily dose immediately prior to the onset of the PSTE or SVL is defined as the total daily dose the patient who experienced a PSTE or SVL was taking the day before the onset of the PSTE or SVL. The average daily dose is defined as the cumulative dose of crizotinib prior to the onset of the PSTE or SVL divided by the cumulative number of days treated with crizotinib. PSTE or SVL events where both eyes are affected are counted only once. The safety analysis set includes adjudicated PSTE or SVL cases only.
N = Number of PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum. PSTE = Potential sight threatening event; SVL = Severe visual loss.

Table 13
Exposure to Crizotinib Prior to the Onset of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
Parameter	**PSTE (N=14)**	**SVL (N=5)**	**Total (N=19)**
Average daily dose of crizotinib prior to onset of the PSTE or SVL (mg)			
n	7	4	11
Mean	411.8	437.5	421.2
SD	118.55	125.00	115.27
Median	500.0	500.0	500.0
Min, Max	250, 500	250, 500	250, 500

Note: Time from first exposure until onset of PSTE or SVL is calculated as date of onset of PSTE or SVL - date of first exposure to crizotinib + 1 day. The number of cumulative days being treated with crizotinib is defined as the sum of days the patient who experienced the PSTE or SVL has been treated with any dose of crizotinib between the treatment start date with crizotinib and the onset date of the PSTE or SVL event. The total cumulative dose prior to the onset of the PSTE or SVL is calculated as the cumulative dose a patient with the PSTE or SVL was exposed to from the date of the first exposure to crizotinib until (and including) the date of the onset of the PSTE or SVL. The total daily dose immediately prior to the onset of the PSTE or SVL is defined as the total daily dose the patient who experienced a PSTE or SVL was taking the day before the onset of the PSTE or SVL. The average daily dose is defined as the cumulative dose of crizotinib prior to the onset of the PSTE or SVL divided by the cumulative number of days treated with crizotinib. PSTE or SVL events where both eyes are affected are counted only once. The safety analysis set includes adjudicated PSTE or SVL cases only.
N = Number of PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum. PSTE = Potential sight threatening event; SVL = Severe visual loss.

Table 14
Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) by Preferred Term and by PSTE or SVL Characteristics and Associated Symptoms of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL			
Preferred Term	**Unilateral (N=3) n (%)**	**Bilateral (N=4) n (%)**	**Unspecified (N=12) n (%)**	**Total (N=19) n (%)**
Blindness cortical	0	1 (100.0)	0	1 (5.3)
Blindness unilateral	1 (100.0)	0	0	1 (5.3)
Candida infection	0	0	1 (100.0)	1 (5.3)
Cerebral infarction	0	1 (100.0)	0	1 (5.3)
Flashing lights	0	0	1 (100.0)	1 (5.3)
Headache	1 (100.0)	0	0	1 (5.3)
Nausea	0	0	1 (100.0)	1 (5.3)
Neuritis optic	0	0	1 (100.0)	1 (5.3)
Optic atrophy	0	0	1 (100.0)	1 (5.3)
Optic neuropathy	0	0	1 (100.0)	1 (5.3)
Papilledema	0	0	1 (100.0)	1 (5.3)
Retinopathy	0	1 (100.0)	0	1 (5.3)
Amaurosis	0	2 (100.0)	0	2 (10.5)
Uveitis	0	0	2 (100.0)	2 (10.5)
Blindness	0	0	3 (100.0)	3 (15.8)
Retinal detachment	2 (66.7)	0	1 (33.3)	3 (15.8)

Note: Percentages for the total column are based on the total number of PSTE or SVLs. A single PSTE or SVL can consist of more than one preferred term (e.g. if a diagnosis and several different symptoms are specified). Therefore, the percentages of the total column may sum to more than 100%. All other percentages are based on the number of the reported PSTE or SVLs containing the appropriate preferred term. PSTE or SVLs are coded based on MedDRA Version 23.0. The safety analysis set includes adjudicated PSTE or SVL cases only.
N, n = Number of PSTE or SVL events, PSTE = Potential sight threatening event; SVL = Severe visual loss.

Table 14
Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) by Preferred Term and by PSTE or SVL Characteristics and Associated Symptoms of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL			
Preferred Term	Unilateral (N=3) n (%)	Bilateral (N=4) n (%)	Unspecified (N=12) n (%)	Total (N=19) n (%)
Vision blurred	0	0	1 (100.0)	1 (5.3)
Visual disturbance NOS	0	0	1 (100.0)	1 (5.3)
Visual disturbances	0	0	1 (100.0)	1 (5.3)
Visual field defect	0	0	1 (100.0)	1 (5.3)
Visual field tests abnormal	0	0	1 (100.0)	1 (5.3)
Visual impairment	0	0	1 (100.0)	1 (5.3)

Note: Percentages for the total column are based on the total number of PSTE or SVLs. A single PSTE or SVL can consist of more than one preferred term (e.g. if a diagnosis and several different symptoms are specified). Therefore, the percentages of the total column may sum to more than 100%. All other percentages are based on the number of the reported PSTE or SVLs containing the appropriate preferred term. PSTE or SVLs are coded based on MedDRA Version 23.0. The safety analysis set includes adjudicated PSTE or SVL cases only.
N, n = Number of PSTE or SVL events, PSTE = Potential sight threatening event; SVL = Severe visual loss.

Table 15
Severe Visual Loss (SVL) by Preferred Term and by SVL Characteristics and Associated Symptoms of All Adjudicated SVL Patients in the Study
(Safety Analysis Set, Event Level)

	Adjudicated SVL			
Preferred Term	Unilateral (N=2) n (%)	Bilateral (N=1) n (%)	Unspecified (N=2) n (%)	Total (N=5) n (%)
Blindness	0	0	1 (100.0)	1 (20.0)
Blindness cortical	0	1 (100.0)	0	1 (20.0)
Blindness unilateral	1 (100.0)	0	0	1 (20.0)
Cerebral infarction	0	1 (100.0)	0	1 (20.0)
Headache	1 (100.0)	0	0	1 (20.0)
Optic atrophy	0	0	1 (100.0)	1 (20.0)
Retinal detachment	1 (100.0)	0	0	1 (20.0)

Note: Percentages for the total column are based on the total number of SVLs. A single SVL can consist of more than one preferred term (e.g. if a diagnosis and several different symptoms are specified). Therefore, the percentages of the total column may sum to more than 100%. All other percentages are based on the number of the reported SVLs containing the appropriate preferred term. SVLs are coded based on MedDRA Version 23.0. The safety analysis set includes adjudicated PSTE or SVL cases only.

N, n = Number of SVL events, SVL = Severe visual loss.

Table 16
Potential Sight Threatening Event (PSTE) by Preferred Term and by PSTE Characteristics and Associated Symptoms of All Adjudicated PSTE Patients in the Study
(Safety Analysis Set, Event Level)

	Adjudicated PSTE			
Preferred Term	Unilateral (N=1) n (%)	Bilateral (N=3) n (%)	Unspecified (N=10) n (%)	Total (N=14) n (%)
Candida infection	0	0	1 (100.0)	1 (7.1)
Flashing lights	0	0	1 (100.0)	1 (7.1)
Nausea	0	0	1 (100.0)	1 (7.1)
Neuritis optic	0	0	1 (100.0)	1 (7.1)
Optic neuropathy	0	0	1 (100.0)	1 (7.1)
Papilledema	0	0	1 (100.0)	1 (7.1)
Retinopathy	0	1 (100.0)	0	1 (7.1)
Vision blurred	0	0	1 (100.0)	1 (7.1)
Visual disturbance NOS	0	0	1 (100.0)	1 (7.1)
Visual disturbances	0	0	1 (100.0)	1 (7.1)
Visual field defect	0	0	1 (100.0)	1 (7.1)
Visual field tests abnormal	0	0	1 (100.0)	1 (7.1)
Amaurosis	0	2 (100.0)	0	2 (14.3)
Blindness	0	0	2 (100.0)	2 (14.3)
Retinal detachment	1 (50.0)	0	1 (50.0)	2 (14.3)
Uveitis	0	0	2 (100.0)	2 (14.3)

Note: Percentages for the total column are based on the total number of PSTEs. A single PSTE can consist of more than one preferred term (e.g. if a diagnosis and several different symptoms are specified). Therefore, the percentages of the total column may sum to more than 100%. All other percentages are based on the number of the reported PSTEs containing the appropriate preferred term. PSTEs are coded based on MedDRA Version 23.0. The safety analysis set includes adjudicated PSTE or SVL cases only.

N, n = Number of PSTE events, PSTE = Potential sight threatening event.

Table 16
Potential Sight Threatening Event (PSTE) by Preferred Term and by PSTE Characteristics and Associated Symptoms of All Adjudicated PSTE Patients in the Study
(Safety Analysis Set, Event Level)

	Adjudicated PSTE			
Preferred Term	Unilateral (N=1) n (%)	Bilateral (N=3) n (%)	Unspecified (N=10) n (%)	Total (N=14) n (%)
Visual impairment	0	0	1 (100.0)	1 (7.1)

Note: Percentages for the total column are based on the total number of PSTEs. A single PSTE can consist of more than one preferred term (e.g. if a diagnosis and several different symptoms are specified). Therefore, the percentages of the total column may sum to more than 100%. All other percentages are based on the number of the reported PSTEs containing the appropriate preferred term. PSTEs are coded based on MedDRA Version 23.0. The safety analysis set includes adjudicated PSTE or SVL cases only.
N, n = Number of PSTE events, PSTE = Potential sight threatening event.

Table 17
Ophthalmologic Examinations Before the Start of Crizotinib Treatment, Before the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Vision Loss (SVL) and After the Start of Crizotinib Treatment, and Subsequent to the Occurrence of the PSTE or SVL of All Adjudicated PSTE or SVL Patients in the Study (Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
	PSTE (N=14)	SVL (N=5)	Total (N=19)
Number of ophthalmologic examinations within 1 year prior to the start of crizotinib treatment, n (%)			
0	0	2 (40.0)	2 (10.5)
1	1 (7.1)	1 (20.0)	2 (10.5)
2	0	0	0
3	0	0	0
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Any examination within 1 year prior to the start of treatment with crizotinib, n (%)			
Yes	1 (7.1)	1 (20.0)	2 (10.5)
No	0	2 (40.0)	2 (10.5)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)

Note: The safety analysis includes adjudicated PSTE or SVL cases only.

N, n = Number of PSTE or SVL events or subset of PSTE or SVL events, SD = standard deviation, min = minimum, max = maximum, PSTE = potential sight threatening event, SVL = severe visual loss, - = data not available.

[a]Only PSTE or SVL events in patients who had any ophthalmologic examinations within 1 year prior to the start of crizotinib treatment. Percentages are based on the number of events in patients who had any ophthalmologic examinations within 1 year prior to the start of crizotinib treatment.

[b]Only for events in patients who had any ophthalmologic examinations between treatment start with crizotinib and the onset of the PSTE or SVL event. Percentages are based on the number of events in patients who had any ophthalmologic examinations between treatment start with crizotinib and the onset of the PSTE or SVL.

Table 17
Ophthalmologic Examinations Before the Start of Crizotinib Treatment, Before the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Vision Loss (SVL) and After the Start of Crizotinib Treatment, and Subsequent to the Occurrence of the PSTE or SVL of All Adjudicated PSTE or SVL Patients in the Study (Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
	PSTE (N=14)	SVL (N=5)	Total (N=19)
Number of ophthalmologic examinations between the start of crizotinib treatment and onset of PSTE or SVL, n (%)			
0	1 (7.1)	2 (40.0)	3 (15.8)
1	0	1 (20.0)	1 (5.3)
2	0	0	0
3	0	0	0
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Any examination between start of treatment with crizotinib and onset of the PSTE or SVL, n (%)			
Yes	0	1 (20.0)	1 (5.3)
No	1 (7.1)	2 (40.0)	3 (15.8)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)

Note: The safety analysis includes adjudicated PSTE or SVL cases only.

N, n = Number of PSTE or SVL events or subset of PSTE or SVL events, SD = standard deviation, min = minimum, max = maximum, PSTE = potential sight threatening event, SVL = severe visual loss, - = data not available.

[a]Only PSTE or SVL events in patients who had any ophthalmologic examinations within 1 year prior to the start of crizotinib treatment. Percentages are based on the number of events in patients who had any ophthalmologic examinations within 1 year prior to the start of crizotinib treatment.

[b]Only for events in patients who had any ophthalmologic examinations between treatment start with crizotinib and the onset of the PSTE or SVL event. Percentages are based on the number of events in patients who had any ophthalmologic examinations between treatment start with crizotinib and the onset of the PSTE or SVL.

Table 17
Ophthalmologic Examinations Before the Start of Crizotinib Treatment, Before the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Vision Loss (SVL) and After the Start of Crizotinib Treatment, and Subsequent to the Occurrence of the PSTE or SVL of All Adjudicated PSTE or SVL Patients in the Study (Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
	PSTE (N=14)	SVL (N=5)	Total (N=19)
Number of ophthalmologic examinations subsequent to the PSTE or SVL, n (%)			
0	0	0	0
1	2 (14.3)	3 (60.0)	5 (26.3)
2	0	0	0
3	0	0	0
Unknown	12 (85.7)	2 (40.0)	14 (73.7)
Any examination subsequent to the onset of the PSTE or SVL, n (%)			
Yes	2 (14.3)	3 (60.0)	5 (26.3)
No	0	0	0
Unknown	12 (85.7)	2 (40.0)	14 (73.7)

Note: The safety analysis includes adjudicated PSTE or SVL cases only.

N, n = Number of PSTE or SVL events or subset of PSTE or SVL events, SD = standard deviation, min = minimum, max = maximum, PSTE = potential sight threatening event, SVL = severe visual loss, - = data not available.

[a]Only PSTE or SVL events in patients who had any ophthalmologic examinations within 1 year prior to the start of crizotinib treatment. Percentages are based on the number of events in patients who had any ophthalmologic examinations within 1 year prior to the start of crizotinib treatment.

[b]Only for events in patients who had any ophthalmologic examinations between treatment start with crizotinib and the onset of the PSTE or SVL event. Percentages are based on the number of events in patients who had any ophthalmologic examinations between treatment start with crizotinib and the onset of the PSTE or SVL.

Table 17
Ophthalmologic Examinations Before the Start of Crizotinib Treatment, Before the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Vision Loss (SVL) and After the Start of Crizotinib Treatment, and Subsequent to the Occurrence of the PSTE or SVL of All Adjudicated PSTE or SVL Patients in the Study (Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
	PSTE (N=14)	SVL (N=5)	Total (N=19)
Time from last ophthalmologic exam until the onset of the PSTE or SVL (days)			
n	1	1	2
Mean	407.00	8.00	207.50
SD	-	-	282.136
Median	407.00	8.00	207.50
Min, Max	407.0, 407.0	8.0, 8.0	8.0, 407.0
Time from onset of the PSTE or SVL until first ophthalmologic exam (days)			
n	2	3	5
Mean	45.50	31.67	37.20
SD	62.933	47.120	46.451
Median	45.50	7.00	7.00
Min, Max	1.0, 90.0	2.0, 86.0	1.0, 90.0

Note: The safety analysis includes adjudicated PSTE or SVL cases only.

N, n = Number of PSTE or SVL events or subset of PSTE or SVL events, SD = standard deviation, min = minimum, max = maximum, PSTE = potential sight threatening event, SVL = severe visual loss, - = data not available.

[a]Only PSTE or SVL events in patients who had any ophthalmologic examinations within 1 year prior to the start of crizotinib treatment. Percentages are based on the number of events in patients who had any ophthalmologic examinations within 1 year prior to the start of crizotinib treatment.

[b]Only for events in patients who had any ophthalmologic examinations between treatment start with crizotinib and the onset of the PSTE or SVL event. Percentages are based on the number of events in patients who had any ophthalmologic examinations between treatment start with crizotinib and the onset of the PSTE or SVL.

Table 17
Ophthalmologic Examinations Before the Start of Crizotinib Treatment, Before the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Vision Loss (SVL) and After the Start of Crizotinib Treatment, and Subsequent to the Occurrence of the PSTE or SVL of All Adjudicated PSTE or SVL Patients in the Study (Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
	PSTE (N=14)	SVL (N=5)	Total (N=19)
Presence of significant findings in the ophthalmologic examination within 1 year prior to the start of crizotinib treatment, n (%)[a]			
Yes	0	1 (100.0)	1 (50.0)
No	1 (100.0)	0	1 (50.0)
Presence of significant findings in the ophthalmologic examination between treatment start with crizotinib and onset of the PSTE or SVL, n (%)[b]			
Yes	0	0	0
No	0	1 (100.0)	1 (100.0)

Note: The safety analysis includes adjudicated PSTE or SVL cases only.

N, n = Number of PSTE or SVL events or subset of PSTE or SVL events, SD = standard deviation, min = minimum, max = maximum, PSTE = potential sight threatening event, SVL = severe visual loss, - = data not available.

[a]Only PSTE or SVL events in patients who had any ophthalmologic examinations within 1 year prior to the start of crizotinib treatment. Percentages are based on the number of events in patients who had any ophthalmologic examinations within 1 year prior to the start of crizotinib treatment.

[b]Only for events in patients who had any ophthalmologic examinations between treatment start with crizotinib and the onset of the PSTE or SVL event. Percentages are based on the number of events in patients who had any ophthalmologic examinations between treatment start with crizotinib and the onset of the PSTE or SVL.

Table 19
Best Corrected Distance Visual Acuity and Change from Before the Start of Crizotinib Treatment, Before the Occurrence of the Severe Visual Loss (SVL) and After the Start of Crizotinib Treatment, and Subsequent to the Occurrence of the SVL by Outcome of the SVL of all Adjudicated Patients in the Study
(Safety analysis set, Eye Level)

	Adjudicated SVL		
	Affected Eye (N=4)	Unaffected Eye (N=2)	Unspecified Eye (N=4)
Within 1 year prior to treatment start with crizotinib (logMAR)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -
Between start of crizotinib treatment and onset of SVL (logMAR)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -

[a]Change from pre-treatment value is calculated as value after onset of the Severe Visual Loss (SVL) - value within 1 year prior to start with crizotinib treatment. If the value prior to treatment start with crizotinib is missing, the value between treatment start with crizotinib and the onset of the Severe Visual Loss (SVL) is used as pre-treatment value.
Note: If the affected eye is not specified, both eyes are summarized as unspecified eyes. The safety analysis set includes adjudicated PSTE/SVL cases only. LogMAR describes visual loss, i.e. higher values are associated with lower visual acuity.
N = Number of affected, unaffected or unspecified eyes, SD=standard deviation, min=minimum, max=maximum, SVL = Severe visual loss, - = data not available.

Table 19
Best Corrected Distance Visual Acuity and Change from Before the Start of Crizotinib Treatment, Before the Occurrence of the Severe Visual Loss (SVL) and After the Start of Crizotinib Treatment, and Subsequent to the Occurrence of the SVL by Outcome of the SVL of all Adjudicated Patients in the Study
(Safety analysis set, Eye Level)

	Adjudicated SVL		
	Affected Eye (N=4)	Unaffected Eye (N=2)	Unspecified Eye (N=4)
After onset of SVL (logMAR)			
n	1	1	0
Mean	0.88	0.18	-
SD	-	-	-
Median	0.88	0.18	-.-
Min, Max	0.9, 0.9	0.2, 0.2	-, -
Change from pre-treatment value (logMAR)			
n[a]	0	0	0
Mean[a]	-	-	-
SD[a]	-	-	-
Median[a]	-.-	-.-	-.-
Min, Max[a]	-, -	-, -	-, -

[a]Change from pre-treatment value is calculated as value after onset of the Severe Visual Loss (SVL) - value within 1 year prior to start with crizotinib treatment. If the value prior to treatment start with crizotinib is missing, the value between treatment start with crizotinib and the onset of the Severe Visual Loss (SVL) is used as pre-treatment value.
Note: If the affected eye is not specified, both eyes are summarized as unspecified eyes. The safety analysis set includes adjudicated PSTE/SVL cases only. LogMAR describes visual loss, i.e. higher values are associated with lower visual acuity.
N = Number of affected, unaffected or unspecified eyes, SD=standard deviation, min=minimum, max=maximum, SVL = Severe visual loss, - = data not available.

Table 22
Best Corrected Distance Visual Acuity and Change from Before the Start of Crizotinib Treatment, Before the Occurrence of the Severe Visual Loss (SVL) and After the Start of Crizotinib Treatment, and Subsequent to the Occurrence of the SVL by Outcome of the SVL of all Adjudicated Patients in the Study
(Safety analysis set, Eye Level)

Outcome: Resolved

	Adjudicated SVL		
	Affected Eye (N=4)	Unaffected Eye (N=2)	Unspecified Eye (N=4)
Within 1 year prior to treatment start with crizotinib (logMAR)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -
Between start of crizotinib treatment and onset of PSTE/SVL (logMAR)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -

[a]**Change from pre-treatment value is calculated as value after onset of the Severe Visual Loss (SVL) - value within 1 year prior to start with crizotinib treatment. If the value prior to treatment start with crizotinib is missing, the value between treatment start with crizotinib and the onset of the Severe Visual Loss (SVL) is used as pre-treatment value.**
Note: If the affected eye is not specified, both eyes are summarized as unspecified eyes. The safety analysis set includes adjudicated PSTE/SVL cases only. LogMAR describes visual loss, i.e. higher values are associated with lower visual acuity.
N = Number of affected, unaffected or unspecified eyes, SD=standard deviation, min=minimum, max=maximum, SVL = Severe visual loss, - = data not available.

Table 22
Best Corrected Distance Visual Acuity and Change from Before the Start of Crizotinib Treatment, Before the Occurrence of the Severe Visual Loss (SVL) and After the Start of Crizotinib Treatment, and Subsequent to the Occurrence of the SVL by Outcome of the SVL of all Adjudicated Patients in the Study
(Safety analysis set, Eye Level)

Outcome: Resolved

	Adjudicated SVL		
	Affected Eye (N=4)	Unaffected Eye (N=2)	Unspecified Eye (N=4)
After onset of PSTE/SVL (logMAR)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -
Change from pre-treatment value (logMAR)			
n[a]	0	0	0
Mean[a]	-	-	-
SD[a]	-	-	-
Median[a]	-.-	-.-	-.-
Min, Max[a]	-, -	-, -	-, -

[a]Change from pre-treatment value is calculated as value after onset of the Severe Visual Loss (SVL) - value within 1 year prior to start with crizotinib treatment. If the value prior to treatment start with crizotinib is missing, the value between treatment start with crizotinib and the onset of the Severe Visual Loss (SVL) is used as pre-treatment value.
Note: If the affected eye is not specified, both eyes are summarized as unspecified eyes. The safety analysis set includes adjudicated PSTE/SVL cases only. LogMAR describes visual loss, i.e. higher values are associated with lower visual acuity.
N = Number of affected, unaffected or unspecified eyes, SD=standard deviation, min=minimum, max=maximum, SVL = Severe visual loss, - = data not available.

Table 22
Best Corrected Distance Visual Acuity and Change from Before the Start of Crizotinib Treatment, Before the Occurrence of the Severe Visual Loss (SVL) and After the Start of Crizotinib Treatment, and Subsequent to the Occurrence of the SVL by Outcome of the SVL of all Adjudicated Patients in the Study
(Safety analysis set, Eye Level)

Outcome: Resolved with sequelae

	Adjudicated SVL		
	Affected Eye (N=4)	Unaffected Eye (N=2)	Unspecified Eye (N=4)
Within 1 year prior to treatment start with crizotinib (logMAR)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -
Between start of crizotinib treatment and onset of PSTE/SVL (logMAR)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -

[a]Change from pre-treatment value is calculated as value after onset of the Severe Visual Loss (SVL) - value within 1 year prior to start with crizotinib treatment. If the value prior to treatment start with crizotinib is missing, the value between treatment start with crizotinib and the onset of the Severe Visual Loss (SVL) is used as pre-treatment value.
Note: If the affected eye is not specified, both eyes are summarized as unspecified eyes. The safety analysis set includes adjudicated PSTE/SVL cases only. LogMAR describes visual loss, i.e. higher values are associated with lower visual acuity.
N = Number of affected, unaffected or unspecified eyes, SD=standard deviation, min=minimum, max=maximum, SVL = Severe visual loss, - = data not available.

Table 22
Best Corrected Distance Visual Acuity and Change from Before the Start of Crizotinib Treatment, Before the Occurrence of the Severe Visual Loss (SVL) and After the Start of Crizotinib Treatment, and Subsequent to the Occurrence of the SVL by Outcome of the SVL of all Adjudicated Patients in the Study
(Safety analysis set, Eye Level)

Outcome: Resolved with sequelae

	Adjudicated SVL		
	Affected Eye (N=4)	Unaffected Eye (N=2)	Unspecified Eye (N=4)
After onset of PSTE/SVL (logMAR)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -
Change from pre-treatment value (logMAR)			
n[a]	0	0	0
Mean[a]	-	-	-
SD[a]	-	-	-
Median[a]	-.-	-.-	-.-
Min, Max[a]	-, -	-, -	-, -

[a]Change from pre-treatment value is calculated as value after onset of the Severe Visual Loss (SVL) - value within 1 year prior to start with crizotinib treatment. If the value prior to treatment start with crizotinib is missing, the value between treatment start with crizotinib and the onset of the Severe Visual Loss (SVL) is used as pre-treatment value.
Note: If the affected eye is not specified, both eyes are summarized as unspecified eyes. The safety analysis set includes adjudicated PSTE/SVL cases only. LogMAR describes visual loss, i.e. higher values are associated with lower visual acuity.
N = Number of affected, unaffected or unspecified eyes, SD=standard deviation, min=minimum, max=maximum, SVL = Severe visual loss, - = data not available.

Table 22
Best Corrected Distance Visual Acuity and Change from Before the Start of Crizotinib Treatment, Before the Occurrence of the Severe Visual Loss (SVL) and After the Start of Crizotinib Treatment, and Subsequent to the Occurrence of the SVL by Outcome of the SVL of all Adjudicated Patients in the Study
(Safety analysis set, Eye Level)

Outcome: Ongoing

	Adjudicated SVL		
	Affected Eye (N=4)	Unaffected Eye (N=2)	Unspecified Eye (N=4)
Within 1 year prior to treatment start with crizotinib (logMAR)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -
Between start of crizotinib treatment and onset of PSTE/SVL (logMAR)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -

[a]Change from pre-treatment value is calculated as value after onset of the Severe Visual Loss (SVL) - value within 1 year prior to start with crizotinib treatment. If the value prior to treatment start with crizotinib is missing, the value between treatment start with crizotinib and the onset of the Severe Visual Loss (SVL) is used as pre-treatment value.
Note: If the affected eye is not specified, both eyes are summarized as unspecified eyes. The safety analysis set includes adjudicated PSTE/SVL cases only. LogMAR describes visual loss, i.e. higher values are associated with lower visual acuity.
N = Number of affected, unaffected or unspecified eyes, SD=standard deviation, min=minimum, max=maximum, SVL = Severe visual loss, - = data not available.

Table 22
Best Corrected Distance Visual Acuity and Change from Before the Start of Crizotinib Treatment, Before the Occurrence of the Severe Visual Loss (SVL) and After the Start of Crizotinib Treatment, and Subsequent to the Occurrence of the SVL by Outcome of the SVL of all Adjudicated Patients in the Study
(Safety analysis set, Eye Level)

Outcome: Ongoing

	Adjudicated SVL		
	Affected Eye (N=4)	**Unaffected Eye (N=2)**	**Unspecified Eye (N=4)**
After onset of PSTE/SVL (logMAR)			
n	1	1	0
Mean	0.88	0.18	-
SD	-	-	-
Median	0.88	0.18	-.-
Min, Max	0.9, 0.9	0.2, 0.2	-, -
Change from pre-treatment value (logMAR)			
n[a]	0	0	0
Mean[a]	-	-	-
SD[a]	-	-	-
Median[a]	-.-	-.-	-.-
Min, Max[a]	-, -	-, -	-, -

[a]Change from pre-treatment value is calculated as value after onset of the Severe Visual Loss (SVL) - value within 1 year prior to start with crizotinib treatment. If the value prior to treatment start with crizotinib is missing, the value between treatment start with crizotinib and the onset of the Severe Visual Loss (SVL) is used as pre-treatment value.
Note: If the affected eye is not specified, both eyes are summarized as unspecified eyes. The safety analysis set includes adjudicated PSTE/SVL cases only. LogMAR describes visual loss, i.e. higher values are associated with lower visual acuity.
N = Number of affected, unaffected or unspecified eyes, SD=standard deviation, min=minimum, max=maximum, SVL = Severe visual loss, - = data not available.

Table 27
Reaction of the Pupils to Light, Pupil Size and Intraocular Pressure Subsequent to the Occurrence of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study (Safety Analysis Set, Eye Level)

	Total Adjudicated PSTE or SVL		
	Affected Eye (N=11)	Unaffected Eye (N=3)	Unspecified Eye (N=24)
Reaction of the pupils to light, n (%)			
Yes	1 (9.1)	1 (33.3)	0
No	2 (18.2)	0	0
Unknown	8 (72.7)	2 (66.7)	24 (100.0)
Pupil size (mm)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -
Intraocular pressure (mmHg)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -

Note: If the affected eye is not specified, both eyes are counted as unspecified eyes. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected, and unspecified eyes, as appropriate.
N, n = Number of affected, unaffected, or unspecified eyes as appropriate. SD=standard deviation, min=minimum, max=maximum, PSTE=Potential sight threatening event, SVL=Severe visual loss , - = data not available.

Table 28
Reaction of the Pupils to Light, Pupil Size and Intraocular Pressure Subsequent to the Occurrence of the Severe Visual Loss (SVL) of All Adjudicated SVL Patients in the Study
(Safety Analysis Set, Eye Level)

	Adjudicated SVL		
	Affected Eye (N=4)	Unaffected Eye (N=2)	Unspecified Eye (N=4)
Reaction of the pupils to light, n (%)			
Yes	1 (25.0)	1 (50.0)	0
No	2 (50.0)	0	0
Unknown	1 (25.0)	1 (50.0)	4 (100.0)
Pupil size (mm)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -
Intraocular pressure (mmHg)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -

Note: If the affected eye is not specified, both eyes are counted as unspecified eyes. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected, and unspecified eyes, as appropriate.
N, n = Number of affected, unaffected, or unspecified eyes as appropriate. SD=standard deviation, min=minimum, max=maximum, SVL=Severe visual loss , - = data not available.

Table 29
Reaction of the Pupils to Light, Pupil Size and Intraocular Pressure Subsequent to the Occurrence of the Potential Sight Threatening Event (PSTE) of All Adjudicated PSTE Patients in the Study
(Safety Analysis Set, Eye Level)

	Adjudicated PSTE		
	Affected Eye (N=7)	Unaffected Eye (N=1)	Unspecified Eye (N=20)
Reaction of the pupils to light, n (%)			
Yes	0	0	0
No	0	0	0
Unknown	7 (100.0)	1 (100.0)	20 (100.0)
Pupil size (mm)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -
Intraocular pressure (mmHg)			
n	0	0	0
Mean	-	-	-
SD	-	-	-
Median	-.-	-.-	-.-
Min, Max	-, -	-, -	-, -

Note: If the affected eye is not specified, both eyes are counted as unspecified eyes. The safety analysis set includes adjudicated PSTE or SVL cases only. Percentages are calculated based on the number of affected, unaffected, and unspecified eyes, as appropriate.
N, n = Number of affected, unaffected, or unspecified eyes as appropriate. SD=standard deviation, min=minimum, max=maximum, PSTE=Potential sight threatening event , - = data not available.

Table 30
Frequency of Slit Lamp Examinations After Onset of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) and Results of the Examination of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
Parameter	**PSTE (N=14)**	**SVL (N=5)**	**Total (N=19)**
Slit lamp examination performed			
Yes	0	2 (40.0)	2 (10.5)
No	0	1 (20.0)	1 (5.3)
Unknown	14 (100.0)	2 (40.0)	16 (84.2)
Presence of any abnormalities in the anterior chamber[a]	**(N=0)**	**(N=2)**	**(N=2)**
Yes	0	0	0
No	0	2 (100.0)	2 (100.0)
Unknown	0	0	0

N, n = Number of PSTE or SVL events or in a subset based of PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum, PSTE=Potential sight threatening event, SVL=Severe visual loss. The safety analysis set includes adjudicated PSTE or SVL cases only.
[a]Presence of any abnormalities in the anterior chamber will only be presented for events in patients who had a slit lamp examination performed. Percentages for the presence of any abnormalities in the anterior chamber are calculated based on the number of events in patients who had a slit lamp examination within 1 year prior to the PSTE or SVL event.

Table 32
Results of Slit Lamp Examinations After Onset of the Severe Vision Loss (SVL) of Adjudicated SVL Patients in the Study
(Safety analysis set, Eye Level)

	Total Adjudicated SVL		
	Affected Eye (N=4)	Unaffected Eye (N=2)	Unspecified Eye (N=4)
Number of eyes with known results of the slit lamp examinations	0	0	4
Abnormalities of the affected eye			
Corneal scars or edema			
Yes	0	0	0
No	0	0	4 (100.0)
Cells or flare in the anterior chamber			
Yes	0	0	0
No	0	0	4 (100.0)
Cataracts			
Yes	0	0	0
No	0	0	4 (100.0)
Iritis			
Yes	0	0	0
No	0	0	4 (100.0)
Other			
Yes	0	0	0
No	0	0	4 (100.0)

Note: If the affected eye is not specified, both eyes are summarized as unspecified eyes. The safety analysis set includes adjudicated PSTE/SVL cases only.
N = Number of affected, unaffected or unspecified eyes, SD=standard deviation, min=minimum, max=maximum, SVL = Severe visual loss.

Table 34
Frequency of Visual Field Tests and Defects in the Visual Field After the Onset of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
Parameter	**PSTE (N=14)**	**SVL (N=5)**	**Total (N=19)**
Visual field test performed			
Yes	1 (7.1)	2 (40.0)	3 (15.8)
No	1 (7.1)	2 (40.0)	3 (15.8)
Unknown	12 (85.7)	1 (20.0)	13 (68.4)
Any defects in the visual field test[a]	**(N=1)**	**(N=2)**	**(N=3)**
Yes	1 (100.0)	1 (50.0)	2 (66.7)
No	0	1 (50.0)	1 (33.3)
Unknown	0	0	0

N, n = Number of PSTE or SVL events or in a subset based on PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum, PSTE=Potential sight threatening event, SVL=Severe visual loss. The safety analysis set includes adjudicated PSTE or SVL cases only.
[a]Defects in the visual field are only presented for events in patients where a visual field test was performed. Percentages are based on the number of PSTE or SVL events whereas the percentages for any defect in the visual field test are based on the number of PSTE or SVL events in patients with visual field tests.

Table 35
Optical Coherence Tomography After the Onset of the Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) of All Adjudicated PSTE or SVL Patients in the Study
(Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
Parameter	**PSTE (N=14)**	**SVL (N=5)**	**Total (N=19)**
Optical coherence tomography performed			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Any abnormalities noted[a]	**(N=0)**	**(N=0)**	**(N=0)**
Yes	0	0	0
No	0	0	0
Unknown	0	0	0

N, n = Number of PSTE or SVL events or in a subset based of PSTE or SVL events, SD=standard deviation, min=minimum, max=maximum, PSTE=Potential sight threatening event, SVL=Severe visual loss, OCT=Optical Coherence Tomography. The safety analysis set includes adjudicated PSTE or SVL cases only.
[a]Any abnormalities noted are only summarized for events in patients who had an OCT performed. Percentages are calculated based on the number of events in patients who had an OCT performed.

Table 39
Examinations of the Retina and Retinal Photographs of All Adjudicated Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) Patients in the Study
(Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
	PSTE (N=14)	SVL (N=5)	Total (N=19)
Retinal examinations within 1 year prior to start of crizotinib treatment, n (%)			
Yes	0	1 (20.0)	1 (5.3)
No	1 (7.1)	2 (40.0)	3 (15.8)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Retinal examinations between start of crizotinib treatment and onset of the PSTE or SVL, n (%)			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Retinal examinations subsequent to the PSTE or SVL, n (%)			
Yes	0	0	0
No	1 (7.1)	2 (40.0)	3 (15.8)
Unknown	13 (92.9)	3 (60.0)	16 (84.2)

Note: The safety analysis set includes adjudicated PSTE or SVL cases only.
N, n = Number of PSTE/SVL events. PSTE = Potential sight threatening event, SVL = Severe visual loss.

Table 39
Examinations of the Retina and Retinal Photographs of All Adjudicated Potential Sight Threatening Event (PSTE) or Severe Visual Loss (SVL) Patients in the Study
(Safety Analysis Set, Event Level)

	Total Adjudicated PSTE or SVL		
	PSTE (N=14)	SVL (N=5)	Total (N=19)
Retinal photographs taken within 1 year prior to start of crizotinib treatment, n (%)			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)
Retinal photographs taken between start of crizotinib treatment and onset of the PSTE or SVL, n(%)			
Yes	0	0	0
No	1 (7.1)	2 (40.0)	3 (15.8)
Unknown	13 (92.9)	3 (60.0)	16 (84.2)
Retinal photographs taken subsequent to the PSTE or SVL, n (%)			
Yes	0	0	0
No	1 (7.1)	3 (60.0)	4 (21.1)
Unknown	13 (92.9)	2 (40.0)	15 (78.9)

Note: The safety analysis set includes adjudicated PSTE or SVL cases only.
N, n = Number of PSTE/SVL events. PSTE = Potential sight threatening event, SVL = Severe visual loss.

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