EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
EMA/CHMP/327604/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xalkori

International non-proprietary name: crizotinib

Procedure No. EMEA/H/C/002489/II/0039

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALK	Anaplastic lymphoma kinase
ATP	Adenosine triphosphate
BID	Twice daily
BOR	Best overall response
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
DCR	Disease control rate
DR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EML4	Echinoderm microtubule-associated protein-like 4
EU	European Union
EUROS1	European Study of ROS1 Patients
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
HGFR	Hepatocyte growth factor receptor
HR	Hazard ratio
ICH	International Conference on Harmonisation
IRR	Independent radiology review
K-M	Kaplan-Meier
LDT	Laboratory developed test
MedDRA	Medical Dictionary for Regulatory Activities
MET	c-Met receptor tyrosine kinase (hepatocyte growth factor receptor)
MGH	Massachusetts General Hospital
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose

NCI	National Cancer Institute
NGS	Next-generation sequencing
NPM	Nucleophosmin
NR	Not reached
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PD	Pharmacodynamics
PK	Pharmacokinetic
PR	Partial response
PT	Preferred Term
RE	Response-evaluable (population)
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
RON	Recepteur d'Origine Nantais
ROS1	c-ros oncogene 1
RP2D	Recommended Phase 2 dose
RTK	Receptor tyrosine kinase
RT-PCR	Reverse transcription polymerase chain reaction
SA	Safety analysis (population)
SAE	Serious Adverse Event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Stable disease
SOC	System Organ Class
Std Dev	Standard deviation
TTP	Time to progression
TTR	Time to tumour response
US	United States
v	Version

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Limited submitted to the European Medicines Agency on 2 February 2016 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC) based on the results of Study A8081001 (a multinational, multicenter, open-label, single-arm study of the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of crizotinib in patients with advanced cancer). Consequential changes are proposed to SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 and the Package Leaflet is proposed to be updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Annex II. The application included an updated RMP version 7.0.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 22 October 2015. The advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pierre Demolis Co-Rapporteur: Daniela Melchiorri

Timetable	Dates
Start of procedure	27 February 2016
CHMP Rapporteur Assessment Report	22 April 2016
CHMP Co-Rapporteur Assessment Report	22 April 2016
PRAC Rapporteur Assessment Report	25 April 2016
PRAC members comments	2 May 2016
Updated PRAC Rapporteur Assessment Report	3 May 2016
PRAC Outcome	13 May 2016
CHMP members comments	18 May 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 May 2016
Request for Supplementary Information	26 May 2016
Submission of responses	20 June 2016
CHMP Rapporteurs Joint response Assessment Report	5 July 2016
PRAC Rapporteur response Assessment Report	27 June 2016
PRAC members comments	N/A
Updated PRAC Rapporteur response Assessment Report	N/A
PRAC outcome	7 July 2016
CHMP members comments	11 July 2016
Updated CHMP Rapporteurs Joint response Assessment Report	N/A
Opinion	21 July 2016

2. Scientific discussion

2.1. Introduction

About the disease

Lung cancer is the leading cause of cancer-related mortality worldwide. In 2012, the annual incidence of lung cancer worldwide was 23.1 per 100,000 persons, and the incidence was higher in men (34.2 per 100,000) than women (13.6 per 100,000) according to estimates from the World Health Organization and International Agency for Research on Cancer (IARC) GLOBOCAN project. In Europe, lung cancer had an incidence of 46.6 per 100,000 men and 15.1 per 100,000 women (Ferlay et al, 2013). In the US, the

incidence of lung or bronchial cancer was 76.4 per 100,000 men and 52.7 per 100,000 women (Howlander et al, 2012). Most lung cancers (85%) are NSCLC (Tyczynski et al, 2003) that present as inoperable locally advanced (Stage IIIB) or metastatic (Stage IV) disease with no curative treatment available. United States (US) Surveillance, Epidemiology, and End Results (SEER) data indicated that the 5-year survival rate between 2002 and 2008 among all patients with NSCLC was 17.5% (Howlander et al, 2012). However, 5-year survival rates have been shown to be 5% and <1% for Stage IIIB and Stage IV NSLCL, respectively (Reck, 2012).

Until recently, platinum-based chemotherapy has been standard first-line treatment and docetaxel, pemetrexed, and erlotinib were the approved agents after at least 1 prior chemotherapy regimen for patients with advanced NSCLC of any histological subtype. These standard therapies have modest impact on efficacy outcomes in unselected NSCLC with objective response rates (ORRs) of 9 to 35%, median progression-free survival (PFS) of approximately 3 to 6 months across first- and second-line treatment, and median overall survival (OS) of 8 to 12 months in the front line setting (Sandler *et al*, 2006; Scagliotti *et al*, 2008; Schiller et al, 2002; Herbst *et al*, 2004; Herbst *et al*, 2005; Kelly *et al*, 2001).

An emerging paradigm in oncology suggests that robust clinical efficacy can be obtained with well-tolerated inhibitors directed toward oncogenic tyrosine kinases that are genetically altered through activating mutations, gene translocations, or gene amplification.

As the molecular basis of NSCLC became better understood, agents that target specific molecular signalling pathways have become the standard of care particularly in subsets of patients whose tumours contain dominant genetic driver alterations. Similar to the paradigm established for the treatment of epidermal growth factor receptor (EGFR)-mutated NSCLC with erlotinib, gefitinib and afatinib (Lynch et al, 2004; Pao et al, 2004; Wu et al, 2014), and ALK-positive advanced NSCLC (hereafter referred to as ALK-positive NSCLC) with crizotinib and ceritinib (Shaw et al, 2013; Solomon et al, 2014; Shaw, Kim, Mehra et al, 2014), NSCLC defined by ROS1-positive advanced NSCLC (hereafter referred to as ROS1-positive NSCLC) represents an additional subgroup of lung cancer patients who might benefit from specific targeted therapy.

ROS1 oncogene encodes an orphan receptor tyrosine kinase (RTK) related to ALK, leukocyte RTK, and members of the insulin receptor family (Acquaviva *et al,* 2009).

ROS1-positive NSCLC occurs in approximately 1-2% of patients with NSCLC (Gainor and Shaw, 2013; Bergethon *et al*, 2012). Similar to patients with ALK-positive NSCLC, patients with ROS1-positive NSCLC tend to be younger and never smokers with a histologic diagnosis of adenocarcinoma compared to other unselected patients with lung cancer (Gainor and Shaw, 2013; Bergethon *et al*, 2012). ALK and ROS1 gene rearrangements rarely occur in the same tumour, with each defining a unique molecular subgroup of NSCLC (Gainor and Shaw, 2013).

Information regarding the natural history of ROS1-positive NSCLC is currently limited, but several retrospective analyses describing the natural history of ROS1-positive NSCLC have been published (Bergethon et al, 2012; Yoshida et al, 2013; Cai *et al*, 2013; Chen *et al*, 2014; Lee *et al*, 2013; Fu et *al*, 2015; Scheffler *et al*, 2015).

Cumulatively, these findings suggest that ROS1 positivity is unlikely to be a favourable prognostic factor in NSCLC, similar to what has previously been shown in ALK-positive NSCLC (Shaw et al, 2009; Shaw et al, 2011).

ROS1 Diagnostic Testing

Several different testing platforms (i.e., methodologies) are able to directly identify gene rearrangements, including fluorescence in situ hybridization (FISH), reverse transcription polymerase chain reaction (RT-PCR) techniques, and next-generation sequencing (NGS).

Approaches to diagnostic testing in NSCLC continue to evolve given advances in technology. NGS technology in particular enables multiplexed testing of multiple target gene analytes in a single test rather than by sequential testing, providing critical efficiencies in both time to test result and in the use of limiting tissue. The continuing identification of additional, typically uncommon, molecularly-defined subpopulations of patients that may benefit from targeted therapies (ie, patients with genetic alterations in genes encoding ROS1, BRAF, c-Met, and others) highlights the importance of multiplexed approaches to diagnostic testing in NSCLC.

About the product

Xalkori (crizotinib) is a selective small-molecule inhibitor of the ALK receptor tyrosine kinase (RTK) and its oncogenic variants (i.e., ALK fusion events and selected ALK mutations). Crizotinib is also an inhibitor of the hepatocyte growth factor receptor (HGFR, c-Met), c-ros oncogene 1 (ROS1), and Recepteur d'Origine Nantais (RON) RTKs. Xalkori received a conditional approval in the EU on 23 October 2012, for the treatment of adults with previously treated ALK-positive advanced NSCLC. The indication was later extended to first line treatment of ALK-positive advanced NSCLC on 23 November 2015.

The aim of this type II variation is to extend Xalkori indication to treatment of adults with ROS1-positive advanced NSCLC. This application is mainly supported by data for patients with ROS1 positive NSCLC from Study A8081001 (pivotal study) and a review of relevant publications on the efficacy and safety of crizotinib in patients with ROS1 positive NSCLC (supportive information). Study A8081001 (a multinational, multicenter, open-label, single-arm study of the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of crizotinib in patients with advanced cancer), included a dose-escalation phase, and an expansion phase during which several cohorts of patients received the recommended Phase 2 dose (RP2D). The RP2D cohorts included patients with ALK-positive NSCLC and other advanced cancers, including tumours harbouring a ROS1 gene rearrangement as per Amendment 12 of the protocol.

2.2. Non-clinical aspects

2.2.1. Introduction

Crizotinib demonstrated in vitro inhibition of tyrosine kinase in biochemical enzymatic assays and in cell-based assays against echinoderm microtubule-associated protein-like 4 (EML4)-ALK, nucleophosmin (NPM)-ALK, c-Met/HGFR and RON enzyme in several human cell lines. Crizotinib major metabolites were also tested and crizotinib lactam metabolites showed relevant inhibitory activity in the nanomolar range, thus close to crizotinib potency. When tested to its selectivity for different kinases, crizotinib was relatively specific to c-Met/HGFR and ALK fusion proteins.

Crizotinib inhibited cell proliferation, migration, invasion and motility in tumour or endothelial cells expressing EML4-ALK, NPM-ALK or c-Met/HGFR. These data suggest that crizotinib has an effect on both tumour cell growth and survival, and on angiogenesis.

In vivo, Crizotinib demonstrated a dose-dependent cytoreductive antitumour activity in several tumour models expressing EML4-ALK, NPM-ALK or c-Met/HGFR. PK/PD modelling indicated that the extent and duration of the inhibition of target kinase phosphorylation is directly related to the level of anti-tumour efficacy. Near complete inhibition of ALK or c-Met/HGFR activity for the duration of treatment is necessary to get the maximal anti-tumour efficacy (tumour regression). There is a correlation between inhibition of ALK or c-Met/HGFR phosphorylation and modulation of key signalling pathways involved in cancer cell survival, growth, proliferation and apoptosis. Crizotinib also exhibited an antiangiogenic effect when administered for a long time. This effect was not seen in every tumour type.

2.2.2. Pharmacology

The strategy for the characterization of crizotinib for its inhibitory activity against ROS and ROS-dependent functions included the evaluation of: 1) potency for inhibition of tyrosine kinase activity and phosphorylation of ROS and its oncogenic fusion variants in both biochemical enzyme assays and cellular pharmacodynamic assays; 2) the effects on ROS fusion-dependent signal transduction and cellular functions that are altered during cancer progression such as cell proliferation and viability in HCC78 human NSCLC cells harbouring SLC34A2-ROS fusions; and 3) ROS target inhibition and antitumor efficacy in a panel of NIH3T3 tumour models engineered to express human oncogenic ROS fusion variants in vivo, and 4) pharmacokinetic/pharmacodynamic (PK/PD) relationships for inhibition of tumour growth and induction of tumour regression.

Primary pharmacodynamic studies

In vitro studies

Pharmacodynamic Assays Evaluating Inhibition of ROS by Crizotinib in Biochemical and Cellular Assays In Vitro

The capacity of crizotinib to inhibit the enzymatic activity of ROS and ROS fusion proteins was evaluated in vitro in biochemical and cell-based assays (Study Report 144804).

Crizotinib inhibited the phosphorylation of a synthetic substrate using a recombinant ROS catalytic domain in the presence of ATP. In cellular systems, crizotinib inhibited ROS autophosphorylation, evaluated by ELISA on cell lysates, in two cell lines bearing constitutively active ROS fusion kinases. In HCC78, a NSCLC expressing the SLC34A2-ROS fusion produced by a chromosomal translocations, crizotinib inhibited ROS autophosphorylation with an IC50 of 47 nM. Similarly IC50 was 60 nM in U138MG, a human glioblastoma cell line expressing the Fig-ROS fusion protein. The capacity to inhibit also different fusion variants was confirmed using transduced 3T3 mouse fibroblast cell line; the IC50 observed in these cell systems were in the same order of magnitude observed when endogenous mutant kinases were inhibited in human cell lines (see table below).

Table 1. Summary of Crizotinib In Vitro Pharmacodynamic Inhibition of ROS and Selected Fusion Variants

Assay	Crizotinib Concentration	
	nM	ng/mL
Biochemical Activity In Vitro		
ROS enzyme (mean Ki, nM)	0.48	0.22
Cellular Pharmacodynamic Activity In Vitro		
SLC34A2-ROS phosphorylation in HCC78 human lung adenocarcinoma cells (mean IC_{50})	47	21
Fig-ROS phosphorylation in U138MG human glioblastoma cells (mean IC_{50})	60	27
CD74-ROS phosphorylation in NIH-3T3-CD74-ROS cells (mean IC_{50})	11	5
Fig-ROS(s) phosphorylation in NIH-3T3-Fig-ROS(s) cells (mean IC_{50})	74	33
Fig-ROS(L) phosphorylation in NIH-3T3- Fig-ROS(L) cells (mean IC_{50})	35	16
SLC34A2-ROS(L) phosphorylation in NIH-3T3-SLC34A2-ROS(L) cells (mean IC_{50})	104	47
SLC34A2-ROS(s) phosphorylation in NIH-3T3-SLC34A2-ROS(s) cells (mean IC_{50})	42	19
Cellular Activity in Functional Assays In Vitro		
Proliferation of SLC34A2-ROS positive HCC78 lung adenocarcinoma cells (mean EC_{50})	46	21
Proliferation of BaF3 cells transformed by CD74-ROS (mean EC_{50})	5.8	2.6
Antitumor Efficacy In Vivo		
Tumor growth inhibition in the NIH-3T3-CD74-ROS(s) tumor model–unbound plasma C_{stasis}	99	45
Tumor growth inhibition in the NIH-3T3-SLC34A2-ROS(L) tumor model–unbound plasma C_{stasis}	84	38

All values included in PF-02341066_17May12_144804.

In vitro functional assays characterizing inhibition of ROS-dependent cellular phenotypes and signal transduction in vitro

In HCC78 cells, in addition to kinase inhibition, crizotinib inhibited cell proliferation (EC_{50} 46 nM) and increase the cleavage of caspase 3 suggesting that the drug also induces apoptosis. In this cell system, crizotinib reduced, in concentration-dependent manner, the phosphorylation of other proteins downstream in ROS intracellular pathway such as SHP2, ERK1/2, AKT and STAT3 evaluated by immune-blotting. Inhibition of cell proliferation was observed also in BaF3 cells, a pro-B mouse cell line dependant on IL-3, made IL-3 independent by transduction with CD74-ROS (EC_{50} 5.8 nM).

In vivo studies

Pharmacodynamic inhibition of ROS and antitumor efficacy of crizotinib in vivo

In vivo evaluation was performed using 3T3 mouse fibroblast engineered to express oncogenic human ROS fusion proteins (described in the table above) since the human cell lines HCC78 and U138MG, used for *in vitro* experiments, do not induce tumours in nude mice. After injection in immunodeficient mice all these genetically modified cells produced subcutaneous tumours with a rapid growth pattern whereas the cells transduced with the empty retroviral vector did not. Crizotinib administered by oral route at 75 mg/kg twice a day for 11 to 17 days caused the regression of established tumours in all the cell models evaluated (see figure below).

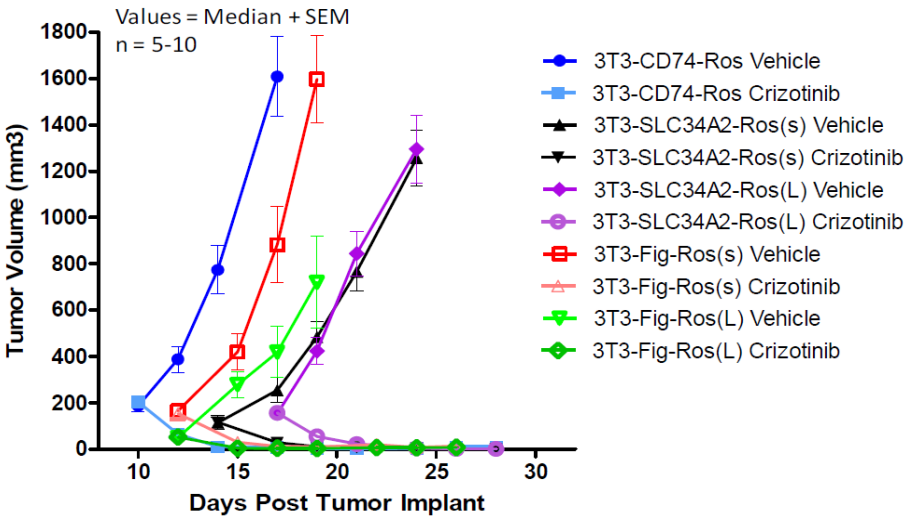


Figure 1: Cytoreductive Effect of Crizotinib in the Engineered NIH-3T3-ROS Xenograft Tumour Models in Athymic Mice

PK/PD Relationship of Tumour Growth Inhibition to Plasma Levels of Crizotinib in the 3T3-CD74-ROS and 3T3-SLC34A2-ROS Xenograft Models

A PK/PD study was performed using different doses of crizotinib in immunodeficient mice bearing tumours induced by 3T3-SLC34A2-ROS(L) or 3T3-CD74-ROS (s); treatment was administered twice daily for 10 or 11 days with daily doses from 20 to 160 mg/kg. In both models crizotinib induced a dose dependent inhibition of tumour growth and ROS phosphorylation without affecting mouse body weight. Doses of 80 to 160 mg/kg/day were associated with almost complete tumour regression. PK analysis estimated a free plasma concentration of 99 nM and 84 nM to induce a total growth inhibition in tumour bearing the CD74-ROS(s) and SCL34A2-ROS(L), respectively.

2.2.3. Pharmacokinetics

No new data related to pharmacokinetics is included in the present submission.

2.2.4. Ecotoxicity / environmental risk assessment

The MAH provided a revised Environmental Risk Assessment (ERA) for the present crizotinib extension of indication in the treatment of patients with ROS1-positive advanced non-small cell lung cancer (NSCLC), in addition to the currently approved indications.

Table 2: Summary of main ERA study results for Xalkori indicated in ALK and ROS1 positive NSCLC patients

Substance (INN/Invented Name):crizotinib					
CAS-number (if available): 877399-52-5					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	**OECD107, OPPTS 830.7550**	log P_{ow} : 0.169, 1.83, 3.89 at pH 4, 7, 9 respectively			Potential PBT: No
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}				B/not B
	BCF				B/not B
Persistence	DT50	OECD 307: DT50soil1-4, 12°C= 209d – 401d OECD 308: No decreasing concentration until day 103 in sediment, reliable DT50sediment calculation not possible			vP
Toxicity	NOEC or CMR				T/not T
PBT-statement :	Crizotinib is very persistent into the environment.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, Fpen refined by prevalence published data	0.029	ug/L			> 0.01 threshold Y
Other concerns (e.g. chemical class)					**N**
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 14,125			List all values
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT50, water =0.95-1.2 d DT50, sediment =37.6 - no reliable calculation possible for the 2nd system DT50, whole system =37.1-109 days % shifting to sediment =44.72			vP, because no decreasing values in sediment in one system
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	0.0093 (growth rate)	mg/L	Pseudokirchneriella subcapitata
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.130	mg/L	Daphnia magna
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	0.070	mg/L	Pimephales promelas
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50	>1000	mg/L	
Phase IIb Studies					
Bioaccumulation Lepomis macrochirus	OECD 305	BCF	10	L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	134.7 (geo mean, 20°C) 0.1-1.3%	days	$DT50_{Loamy\ sand}$: 144 d (20°C) $DT50_{Sandy\ loam}$: 188d (20°C) $DT50_{Clay\ loam}$: 98d (20°C) $DT50_{Sandy\ clay\ loam}$: 124d (20°C) vP in all soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	0.8-5.6%	mg/kg	Day 14

Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	10	mg/kg	Day 21 Allium cepa Lolium perenne Brassica rapa Cucumis sativa Lactuca sativa Lycopersicon esculentum
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	10	mg/kg	Eisenia fetida
Collembola, Reproduction Test	ISO 11267	NOEC	1000	mg/kg	Folsomia candida
Sediment dwelling organism	OECD 218	NOEC	108	mg/kg	Chiromomus riparius

2.2.5. Discussion on non-clinical aspects

Crizotinib demonstrated marked antitumour activity in mouse xenograft studies, where tumours were generated using a panel of NIH-3T3 cell lines engineered to express key ROS1 fusions identified in human tumours. The antitumour efficacy of crizotinib was dose-dependent and demonstrated a correlation with inhibition of ROS1 phosphorylation in vivo.

New data on secondary pharmacodynamic, safety pharmacology and pharmacodynamic drug interaction are not needed for this type of application.

In line with the CHMP guidance EMEA/CHMP/ SWP/4447/00 “Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use”, an updated ERA to cover the ROS1 positive NSCLC patients extension of indication was provided.

The refined Fpen value (0.012%) was calculated on GLOCAN prevalence data (340/100,000) of lung cancer in EU-28 that appears conservative in respect the value calculated by NORDCAN database for Nordic EU Countries, in which the overall prevalence of lung cancer is 74/100.000.

The study on transformation in water/sediment systems (OECD 308) and the study on transformation in soil (OECD 307) show that the active substance crizotinib is very persistent considering e.g. the DT50 values of 401 and 307 d at 12°C in soils (188 and 144 d at 20°C) and the non-decreasing values in sediment.

2.2.6. Conclusion on the non-clinical aspects

The potential role of crizotinib in the treatment of NSCLC with hyperactivated ROS has been adequately demonstrated by the biochemical evidence of enzymatic inhibition of ROS and ROS variants and by in vitro and in vivo inhibition of tumour or transformed cells expressing constitutively active forms of the kinase. Relevant information has been included in section 5.1 of the SmPC.

The nonclinical pharmacology data package for crizotinib supports its intended use for the treatment of patients with ALK-positive or ROS1-positive advanced NSCLC.

This extension of the indication does not lead to a significant increase in environmental exposure further to the use of crizotinib.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community

were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Protocol No. (Country) *Status*	Study Design and Objective	Treatment Groups	No. of Patients	Demographics No. of Patients	Median Duration of Treatment in months (95% CI)	Study Report Location
Safety and Efficacy Study of Crizotinib						
A8081001 – Patients with ROS1-positive advanced NSCLC (Australia, South Korea, United States) *Ongoing*	Phase 1, open-label, multicenter study evaluating dose escalation, safety, PK, pharmacodynamics, and antitumor activity of crizotinib administered as a single oral agent to patients with advanced malignancies (excluding leukemia).	Crizotinib (Route: Oral; Dose Regimen: 250 mg BID in 28-day cycles [21-day cycles for 3 patients in the ALK-marker negative cohort #2])	Planned: 30[a] Treated: 53[b]	Sex: M/F: 23/30 Mean/Median Age (min/max): 54/55 (25/81) years Race: W/B/A/O: 30/2/21/0	K-M estimate: 23.2 months (95% CI: 15.0, NR)	Module 5.3.5.2 A8081001 Study 1001 ROS1 CSR

Abbreviations: A=Asian; ALK=anaplastic lymphoma kinase; B=Black; BID=twice daily; CI=Confidence Interval; CSR=clinical study report; F=female; K-M=Kaplan-Meier; M=male; max=maximum; min=minimum; No.=number; NR=not reached; NSCLC=non-small cell lung cancer; O=other; PK = pharmacokinetics; W = White.

a. 30 patients were planned to be enrolled into the ROS1-positive advanced NSCLC cohort. The sample size was increased per Amendment 20 of the Protocol.

b. Includes 50 patients in the ROS1-positive advanced NSCLC cohort and 3 patients, who were determined to have ROS1-positive retrospectively, after enrollment, in the ALK-marker negative cohort #2.

2.3.2. Pharmacokinetics

Study A8081001 (hereafter referred to as Study 1001) is an ongoing study evaluating the safety, PK, antitumor activity, and PD of crizotinib administered as an oral single agent to patients with advanced cancer (excluding leukemias). Study 1001 included a dose escalation component followed by an expansion phase in which the RP2D established in the initial phase was to be evaluated in molecularly defined cohorts of patients, including patients with ALK-positive advanced NSCLC (ALK-positive NSCLC), patients with ROS1-positive advanced NSCLC (ROS1-positive NSCLC), and patients with ALK negative NSCLC. Crizotinib was to be administered orally at the standard dose of 250 mg BID in continuous 28-day cycles (or 21-day cycles for the 3 patients in the ALK-negative NSCLC cohort).

Methods

Pre-dose sparse PK samples were collected in 53 patients with ROS1-positive NSCLC in Study 1001. This cohort consisted of 50 patients in the ROS1-positive NSCLC cohort and an additional 3 patients from the ALK-negative NSCLC cohort (referred to as the ALK-marker negative Cohort No. 2 in the protocol), who were determined retrospectively to have ROS1-positive NSCLC after enrollment. Of these 53 patients, 46 had at least 1 predose plasma concentration (C_{trough}) of crizotinib and were included in the PKP_C_{trough} population.

The C_{trough} was the pre-dose plasma concentration collected between 1.2 hours and 0 hours before the morning dose on the PK collection day (or 10.8 hours to 13.2 hours after the evening dose on the prior day in the case of a missing morning dose on the PK collection day). Steady-state trough plasma concentrations ($C_{trough,ss}$) were obtained using the arithmetic mean of all evaluable C_{trough} on or after Cycle1 Day15 for each patient in the PKP_$C_{trough,ss}$ population.

Crizotinib was determined using a validated high-performance liquid chromatography-tandem mass spectrometry method.

ROSI FISH Assay

ROS1, encoded by the ROS1 gene on chromosome 6q22, is a receptor tyrosine kinase that belongs to a family of insulin receptors. Recently, ROS1 fusions have been described in 1.7% of non-small cell lung cancer (NSCLC) cases.

A validation report of a Massachusetts General Hospital (MGH) laboratory developed test (LDT) utilizing fluorescence in situ hybridization (FISH) probes targeted against the ROS1 gene was submitted. The probes are being validated to detect the ROS1 gene in interphase cells of formalin-fixed paraffin-embedded (FFPE) tissue samples.

Utilizing a FISH-based detection platform enables comprehensive assessment of ROS1 gene rearrangements in NSCLC FFPE tissue sections with a high degree of sensitivity and specificity.

The specific performance characteristics of the MGH ROS1 FISH assay were determined by studies using FFPE tissue specimens collected from NSCLC patients.

Determinations of correct probe chromosome band location, probe sensitivity, probe specificity, assay accuracy, assay reproducibility and normal range were described and evaluated in the specific validation assay. The validation report showed good performance of the method when considers the above mentioned parameters.

Results

Ctrough values are shown in the following table.

Table 3: Pre-Dose Concentrations (C_{trough}) of Crizotinib in ROS1-Positive NSCLC Patients (PKP_C_{trough} Population)

	ROS1-Positive NSCLC Cohort					
	Day 15 (Cycle 1 Day 15)	Day 29 (Cycle 2 Day 1)	Day 43 (Cycle 2 Day 15)	Day 57 (Cycle 3 Day 1)	Day 85 (Cycle 4 Day 1)	Day 113 (Cycle 5 Day 1)
N	22	29	22	25	23	22
C_{trough}, ng/mL[a]	334.4 (55)	318.0 (52)	317.4 (54)	380.9 (45)	255.1 (52)	329.9 (51)
	ALK-Negative NSCLC Cohort					
	Day 22 (Cycle 2 Day 1)		Day 43 (Cycle 3 Day 1)		Day 85 (Cycle 5 Day 1)	
N	1		3		2	
C_{trough}, ng/mL[a]	326.0 (NC)		168.9 (99)		5.28, 253[b]	

Source: Study 1001 ROS1 CSR, Section 14.4, Table 14.4.3.1.1a.ros.
The ROS1-positive NSCLC and ALK-negative NSCLC cohorts are presented separately, as their C_{trough} samples were collected on different visits.
Cycle length was 4 weeks (28 days) in the ROS1-positive NSCLC cohort and 3 weeks (21 days) in the ALK-negative NSCLC cohort.
NC when number of observations above the lower limit of quantification was >0 and <3.
Summary statistics were calculated by setting concentration values below the lower limit of quantitation to zero.
Abbreviations: ALK=anaplastic lymphoma kinase; C_{trough}=trough concentration; %CV=percentage coefficient of variation; N=number of non-missing concentration measurements collected between -1.2 hours to 0 hours of the morning dose on PK collection day, or if morning dose was not administered on the PK collection day, between 10.8 hours to 13.2 hours of the evening dose on the prior day; NC=not calculated; NSCLC=non-small cell lung cancer; PK=pharmacokinetic(s); PKP_C_{trough}=PK predose concentration evaluable population.
a. Mean (%CV).
b. Individual values presented, because N=2.

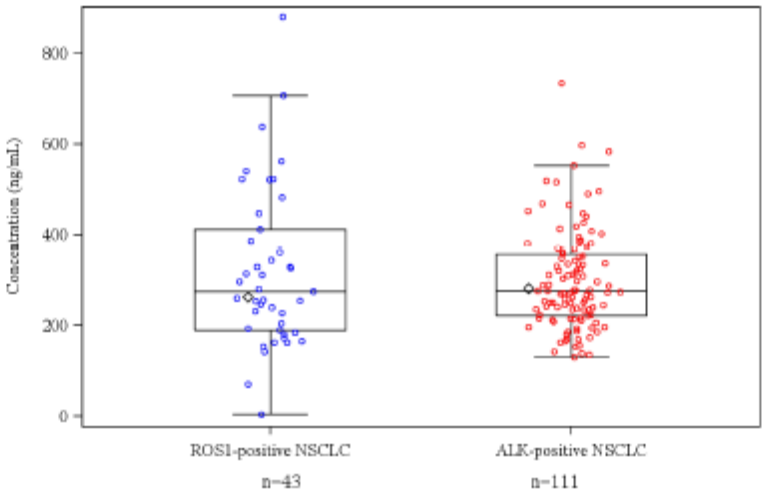
These data show that steady-state was reached by Day 15, which is consistent with the t1/2 of the drug (42 h). Asian patients generally had higher Ctrough,ss values than non-Asian patients (see table below), which is consistent with previous findings (please also refer to Xalkori EPAR).

Table 4: Mean steady-state predose concentrations (Ctrough,ss) of crizotinib in Asian patients, non-asian patients, and overall (PKP_Ctrough,ss population)

	ROS1-Positive NSCLC, 250 mg BID		
	Asian (N=19)	Non-Asian (N=24)	Total (N=43)
$C_{trough,ss}$ (ng/mL)			
Geometric Mean (%CV)	380.3 (46)	195.9 (43)	262.6 (55)
Median (Range)	362.0 (142-880)	239.1 (4.77-448)	275.0 (4.77-880)

Source: Study 1001 ROS1 CSR, Section 14.4, Tables 14.4.3.1.4a.ros and 14.4.3.1.4c.ros.
Abbreviations: BID=twice daily; $C_{trough,ss}$=steady-state trough concentration; %CV=percentage coefficient of variation; N=number of observations for crizotinib; NSCLC=non-small cell lung cancer; PK=pharmacokinetic(s); PKP_$C_{trough,ss}$=PK steady-state predose concentration evaluable population.

The distribution of Ctrough,ss values among crizotinib-treated patients with ROS1-positive NSCLC was similar to that observed for crizotinib-treated patients with ALK-positive NSCLC enrolled in a separate cohort of Study 1001.



Box plot provides median and 25%/75% quartiles, with whiskers for the lowest and highest values within 1.5 times interquartile range. Diamonds represent geometric means, and circles represent individual values.
Source: Appendix 1, Figure 14.4.3.2.2.ros
Abbreviations: ALK=anaplastic lymphoma kinase; NSCLC=non-small cell lung cancer.

Figure 2: Box and Whisker Plot for Comparison of the Steady-State Trough Concentrations (Ctrough,ss) of Crizotinib in Patients with ROS1-Positive NSCLC (Left) Versus Patients with ALK-Positive NSCLC (Right) in Study 1001

2.3.3. Discussion on clinical pharmacology

The MAH investigated the exposure to crizotinib in ROS1-positive NSCLC after repeated administration of the standard 250 mg BID dose. Taking into account that no significant difference in the PK can be expected between ROS1-positive and ALK-positive NSCLC patients, comparison of Ctrough values was adequate in order to confirm a similar exposure in the two patient subsets.

Comparative data show that crizotinib exposures were comparable in patients with either ROS1-positive or ALK-positive NSCLC, as expected.

2.3.4. Conclusions on clinical pharmacology

The current data show that exposure is similar in both ROS1-positive and ALK-positive NSCLC patients. No changes to the pharmacokinetic characteristics described in the SmPC are recommended.

2.4. Clinical efficacy

The clinical efficacy data is based on results from the ROS1-positive NSCLC cohort of the study A8081001, whose data in ALK-positive NSCLC were pivotal for the initial approval in previously treated patients.

Overall, efficacy data have been provided for 53 patients, including 50 patients who were in the ROS1-positive NSCLC cohort and 3 additional patients initially included in the ALK-negative NSCLC cohort and, after enrolment, retrospectively determined to have ROS1-positive NSCLC.

To provide the context for the obtained efficacy results, supportive information on the natural history of ROS1-positive NSCLC, results from recently published retrospective/prospective analyses in ROS1-positive NSCLC patients treated with crizotinib, and data on response to previous systemic standard treatments observed in patients with ROS1-positive NSCLC, have been also submitted.

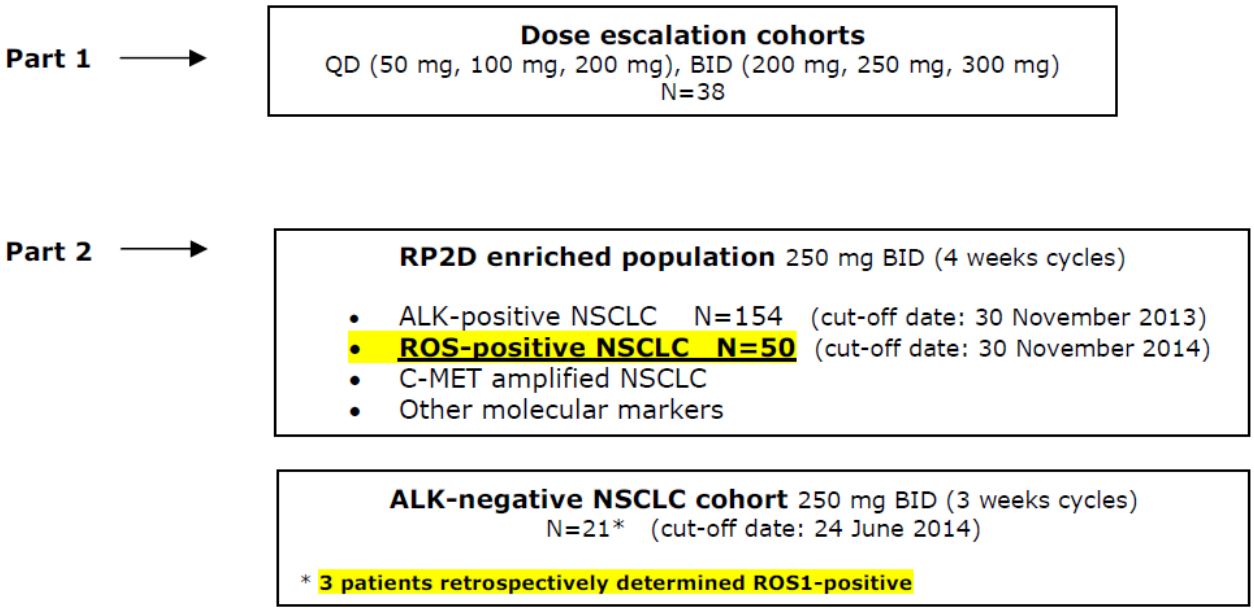
2.4.1. Dose response study(ies)

The recommended starting dose for treatment of patients with ALK-positive advanced NSCLC is 250 mg orally BID continuously. This dosing regimen was determined from the dose-escalation phase of Study 1001 and was confirmed in the dose-expansion phase of Study 1001, where both the maximum tolerated dose (MTD) and RP2D were determined to be 250 mg BID. Patients with a variety of advanced cancers, including ROS1-positive NSCLC, were included in the dose expansion phase of Study 1001 and received the crizotinib RP2D of 250 mg BID (see initial marketing authorization EPAR).

2.4.2. Main study

Study A8081001: Phase 1 safety, pharmacokinetic and pharmacodynamic study of PF-02341066, a C-Met/HGFR selective tyrosine kinase inhibitor, administered orally to patients with advanced cancer.

This is an open-label, multicenter, Phase 1 study originally designed to include an initial dose-escalation phase, followed by an expansion phase in which the recommended Phase 2 dose (RP2D) established in the initial phase would be evaluated in molecularly defined cohorts of patients. Through a protocol amendment, an expansion RP2D cohort of ROS1-positive NSCLC patients was included (see below in the Section “Conduct of the study”).



Methods

Study participants

Female or male, 18 years of age or older, signed informed consent.

Key Inclusion Criteria:

- Histologically confirmed NSCLC positive for chromosomal translocations at *ROS* gene including but not limited to CD74-ROS and SLC34A2-ROS fusion events.
- At least 1 measurable tumour lesion according to the RECIST version 1.0.
- Able to receive at least 2 cycles of treatment (investigator's opinion)
- ECOG 0 or 1 (ECOG 2 possible if agreed by investigator and sponsor)
- Resolution of all acute toxic effects of prior therapy or surgical procedures to Grade ≤1 (except alopecia).
- Adequate organ (bone marrow, hepatic and renal) function (defined as: AST and ALT ≤2.5 x ULN), or AST and ALT ≤5 x ULN if liver function abnormalities were due to underlying malignancy, Total serum bilirubin ≤1.5 x ULN, except for patients with documented Gilbert's syndrome); ANC ≥1500/µL, Platelets ≥100,000/µL, Hemoglobin ≥9.0 g/dL; Serum creatinine ≤2.0 x ULN).

Key exclusion criteria:

- Major surgery, radiation therapy, or systemic anticancer therapy within 2 weeks of starting study treatment.
- Brain metastases, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease unless appropriately treated and neurologically stable for at least 2 weeks.
- Any of the following within the 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, cerebrovascular accident including transient ischemic attack, or pulmonary embolus. However, upon agreement between the investigator and sponsor, the 6 month post-event-free period for a patient with a pulmonary embolus can be waived if due to advanced cancer. Appropriate treatment with anticoagulants is

permitted.

- Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, or QTc interval >470 msec (atrial fibrillation was restricted to uncontrolled atrial fibrillation after IRB/EC approval of Protocol Amendment 13).
- uncontrolled hypertension (>150/100 mm Hg despite optimal medical therapy), known HIV infection (prior to IRB/EC approval of Protocol Amendment 16), patients with known interstitial fibrosis or interstitial lung disease.
- Use within 7 days of known strong CYP3A4 inhibitors, including but not limited to atazanavir, clarithromycin, ketoconazole, itraconazole, telithromycin, troleandomycin, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and voriconazole.
- Use within 12 days of known strong CYP3A4 inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort.
- Concurrent use of CYP3A4 substrates with narrow therapeutic indices, including but not limited to dihydroergotamine, ergotamine, pimozide, astemizole, cisapride, and terfenadine.

The ROS1 rearrangement testing was performed by Massachusetts General Hospital (MGH) or by a local laboratory using a FISH assay or reverse transcriptase polymerase chain reaction (RT-PCR). For the MGH laboratory-developed test, on enumeration of 50 nuclei, a tissue sample was classified as negative if <15% of nuclei (7 nuclei or fewer) were positive for gene rearrangement and classified as positive if >15% (8 nuclei or more) were positive. If more than 50 nuclei were enumerated, a sample was classified as positive if ≥15% of nuclei were positive. For the 3 patients enrolled in the ALK-negative NSCLC cohort, the ROS1 rearrangement testing by FISH was performed retrospectively by MGH.

Treatments

Crizotinib was administered at the standard dose of 250 mg BID in continuous 28-day cycles (or 21-day cycles for the 3 ROS1-positive patients enrolled in the ALK-negative NSCLC cohort).

Treatment was continued until the occurrence of RECIST-defined disease progression or clinical deterioration, unacceptable toxicity effects, withdrawal from the study or death.

Objectives

The objectives of the overall study applicable to patients with ROS1-positive NSCLC were to determine the antitumor activity, and the PK and safety profile of crizotinib.

Outcomes / endpoints

Efficacy endpoints to evaluate the antitumor activity of crizotinib in patients with ROS1-positive NSCLC were Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DR), Time to Response (TTR), Progression Free Survival (PFS), Time to progression (TTP), Overall Survival (OS) and probability of survival at 6 and 12 months. The definition of each endpoint is reported in the Table on Summary of Efficacy for trial A8081001.

All efficacy analyses dependent on disease assessments (ORR, DCR, DR, TTR, PFS and TTP) were based on the derived investigator assessment of tumour data.

Best overall response (BOR) was derived per RECIST version 1.0 (ROS1-positive NSCLC cohort) or version 1.1 (the 3 patients in the ALK-negative NSCLC cohort who were retrospectively determined to be ROS1-positive). This derived tumour assessment was based on the target lesion measurements, non-target

lesion assessments, and new lesion records provided by the investigator, independent of the overall response category provided by the investigator.

In addition, an independent radiology review (IRR), consisting of sequential locked reads by two radiologists blinded to outside radiology reports and investigator assessments, was performed by an independent third-party core imaging laboratory. Adjudication of the best response was to be performed and in case of discrepancies in this variable between the two radiologists, a third radiologist had to determine the interpretation (Reader 1, Reader 2, or a third interpretation) to be used in the analyses.

Tumour assessments were to be performed by the investigators every second cycle (every 8 weeks in the ROS1-positive NSCLC cohort and every 6 weeks in the ALK-negative NSCLC cohort) until RECIST-defined disease progression. Only areas of known disease were to be assessed unless other sites of disease were suspected. Once a patient had completed 15 cycles, tumour assessments could have been performed every 4 cycles (every 16 weeks in the ROS1-positive NSCLC cohort and every 12 weeks in the ALK-negative NSCLC cohort). Following Protocol Amendment 20 (see below the Section *Conduct of the study*) and once a patient had completed 24 cycles (35 cycles in the ALK negative NSCLC cohort), tumour imaging could have been performed every 24 weeks (every sixth cycle in the ROS1-positive NSCLC cohort and every eighth cycle in the ALK-negative NSCLC cohort). All tumour responses were to be confirmed at least 4 weeks after the initial response.

Follow-up survival data were to be collected at least every 3 months after discontinuing crizotinib for a minimum of 1 year after the final dose.

Sample size

To evaluate the crizotinib anti-tumour activity in ROS1-positive NSCLC patients, a sample size including approximately 30 patients (of whom 27 evaluable) was originally planned. An ORR of 10% was considered to be uninteresting for further study for this cohort with 30% considered interesting for further exploration. With 27 evaluable patients, there is at least 85% power to test the null hypothesis that the ORR is less than or equal to 0.10 vs. the alternative hypothesis that it is greater than 0.10 assuming an alternative target rate of 0.30 with a one-sided alpha=0.05 using a single stage design. The null hypothesis was to be rejected in case of greater than or equal to 6 objective responses observed among the initially 27 evaluable patients. The sample size was subsequently increased to a total of 50 patients in order to provide a more robust estimation of efficacy in this patient population (Protocol Amendment #20).

Randomisation

Not applicable as this is a single arm study

Blinding (masking)

Not applicable

Statistical methods

Analyses of ORR, DR, TTR and DCR were to be performed in the Response Evaluable (RE) population. The Safety Analysis Population (SA) population was to be used for the analyses of PFS and OS. There was no planned formal statistical hypothesis testing.

The point estimates of the rates of binary endpoints (i.e, ORR and DCR) were to be provided along with the corresponding exact 2-sided 95% confidence intervals using the exact method based on the F-distribution.

For continuous endpoints, such as DR and TTR, descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values, were provided. The number and percentage of patients in each category (defined by time interval) were presented for categorical variables.

Time-to-event endpoints, including DR, PFS, TTP and OS, were to be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times (and other quartiles) and 2-sided 95% confidence intervals for each quartile were to be provided.

No formal interim analysis was planned. The final analysis was to be performed after the last patient last visit. However, earlier data analyses may be performed for publication and regulatory reporting purposes.

For the purposes of efficacy analyses, three groups were to be used, as appropriate: 1) ROS1-positive NSCLC, including all patients in the ROS1-positive NSCLC cohort (50 patients) plus the 3 ROS1-positive patients in the ALK-negative NSCLC cohort; 2) ROS1-positive NSCLC Cohort, including the 50 patients who were enrolled into this group; 3) ROS1-positive NSCLC Cohort (First 27 evaluable patients), includes the first 27 evaluable patients enrolled into the ROS1-positive NSCLC Cohort for the planned test of the hypothesis specified in the main SAP.

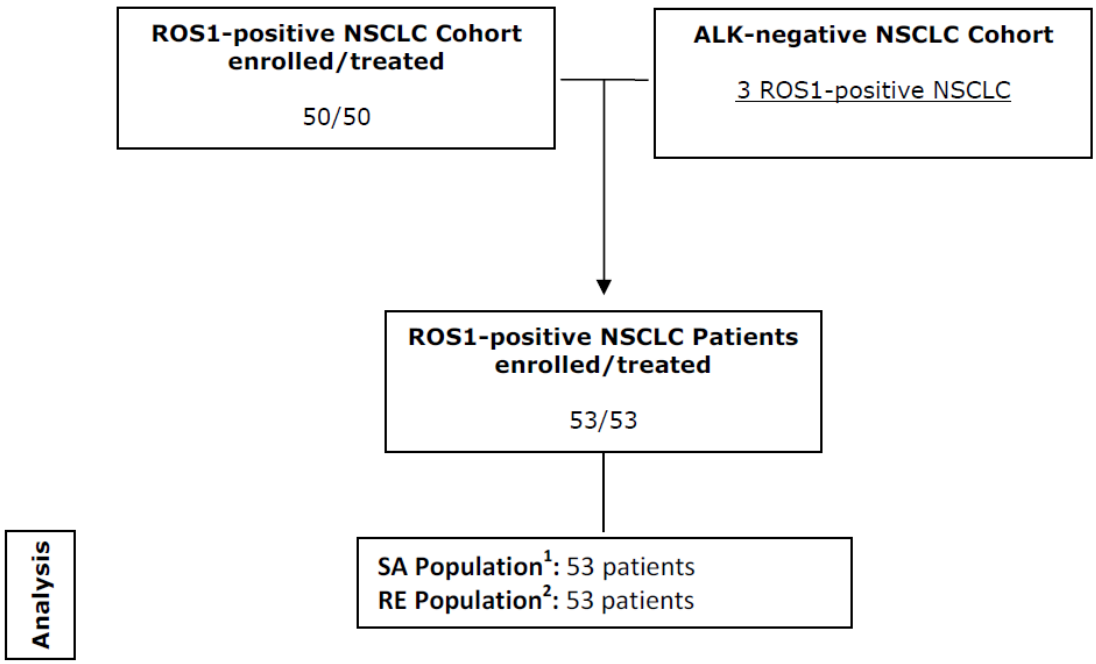
For analyses using group #1, tumour assessments are based on RECIST 1.0 except for the 3 patients from ALK-Negative Cohort for whom RECIST 1.1 is used.

The best overall response and objective response rate were summarized for each of the 3 above groups.

Analysis of DCR at weeks 8 and 16, DR, TTR, PFS, PFS at week 6, TTP, OS and OS at 6 and 12 months were to be summarized separately for ROS1-positive NSCLC patients (group #1 above) and the ROS1-positive NSCLC Cohort (group #2 above).

Results

Participant flow



[1] All enrolled patients who received at least 1 dose of crizotinib.
[2] All patients in the SA population who had an adequate baseline disease assessment. In addition, for this and any interim reporting of the data, patients also needed to meet 1 of the following 2 criteria: (1) had at least one post-baseline disease assessment at least 6 weeks from first dose of crizotinib or (2) withdrew from the study or experienced progressive disease/death at any time on study.

Table 5: Patients disposition at End of Treatment ROS1-positive NSCLC population Safety Analysis Population

	ROS1-positive NSCLC, 250 mg BID N=53 n (%)
Ongoing in the study at data cutoff	25 (47.2)
Discontinued	28 (52.8)
Reason for discontinuation	
Adverse event	1 (1.9)
Lost to follow-up	1 (1.9)
Progressive disease	13 (24.5)
Patient died	2 (3.8)
Patient no longer willing to participate in the study	5 (9.4)
Other[a]	6 (11.3)

Source: Section 14.1, Table 14.1.1.3.1.ros.
Abbreviations: BID=twice daily; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer.
a Other is 3 patients with clinical progression and 3 patients who switched to a commercial supply of crizotinib.

Recruitment

Fifty-three ROS1-positive NSCLC patients were enrolled from 15 October 2010 to 9 September 2013 at 8 centers in 3 countries (Australia and South Korea, 1 center each; US, 6 centers).

Conduct of the study

The original study protocol (dated 05 December 2005) was amended 20 times. The ROS1-positive NSCLC cohort and ALK-negative NSCLC cohort were introduced by Amendment #12 (dated 09 November 2009) and Amendment # 17 (dated 27 September 2011), respectively. A summary of the reasons for each Protocol Amendment after introduction of the ROS1-positive and ALK-negative NSCLC cohorts is provided in the following Table:

Table 6: Summary of Changes Relevant to Patients with ROS1-Positive NSCLC in Protocol Amendments 13 to 20

Document	Version Date	Summary of Changes
Amendment 13	28 April 2010	Atrial fibrillation criteria were modified to only exclude uncontrolled atrial fibrillation, Coumadin dosing restriction was removed, PK sampling time points for ALK-negative and Asian patients were modified.
Amendment 14	1 June 2010	The survival monitoring period was modified, the food restriction criteria for prior to Cycle 2 Day 1 was removed, and evaluation of active metabolites in addition to the parent was added.
Amendment 15	5 August 2010	Safety monitoring for potential AEs of pneumonitis was added, exclusion criteria were updated to exclude patients with interstitial fibrosis or interstitial lung disease, and treatment guidelines of selected crizotinib-related AEs was added.
Amendment 16	08 August 2011	Added monitoring guidance for patients developing renal cysts and guidelines to manage potential cases of drug-induced liver injury. Increased the number of patients enrolling in the dose escalation cohort and enriched population cohort. Removed the Day -7 dosing requirement for all patients except those enrolled in the dose escalation cohort. Modified the minimal acceptable platelet count eligibility criterion only for patients enrolled into the enriched population cohort. Clarified the dose reduction levels for patients enrolling into the enriched population cohort. Updated and clarified the dose modification guidelines. Allowed solution dosing as an alternative to tablet dosing. Clarified ophthalmologic examination guidelines. Updated adverse event guidelines to be consistent with Sponsor standards.
Amendment 17	27 September 2011	Added a second cohort of ALK-marker negative NSCLC. Added more detailed ophthalmologic testing for NSCLC patients.
Amendment 18	24 February 2012	Included rationale for the number of ROS1-positive (positive for chromosomal translocations in the ROS gene) NSCLC patients to be enrolled. Updated concomitant medications for consistency across all crizotinib studies. Clarified required imaging frequency should renal cysts be diagnosed. Updated AE guidelines to be consistent with Sponsor standards.
Amendment 19	27 April 2012	Administrative changes made: outdated information "italicized". Text previously italicized, was bolded and text previously bolded was underlined. Clarified cohort requirements by adding Appendices for ROS1-positive NSCLC and ALK-negative NSCLC cohorts. Cross-referenced sections of main protocol to appendices, as applicable. Clarified that patients with Gilbert's syndrome are permitted to enter the study with Sponsor approval. Patients eligible to enter the study if they experienced any of the following within 6 months prior to starting study drug: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, cerebrovascular accident including transient ischemic attack or pulmonary embolus.
Amendment 20	30 June 2014	Administrative changes made: outdated information "italicized". For ALK-negative NSCLC Cohort #2, requirement for no c-Met or ROS testing to occur prior to enrollment was removed. A Note to File was issued 19 June 2012. Yearly ophthalmologic testing (±2 weeks) added for NSCLC patients who have the expanded ophthalmologic testing. Clarified that intraocular pressure testing should be done twice for each eye and if test results deviate by more than 2 mmHg of each other a third reading must be obtained. Updated the protocol language of several exclusion criteria to ensure consistency with the current version of the Investigator's Brochure and Sponsor standards. In addition, the exclusion criteria for QTc was modified to allow patients with a QTc >470 msec but <490 msec in the presence of a right bundle branch block or with an implanted cardiac pacemaker to enroll

		into the study upon agreement between the Investigator and Sponsor. For sites using the Western Institutional Review Board, patients who lack capacity to consent for themselves will be excluded from this study. Clarified that if tumor imaging was done within 6 weeks of last dose of crizotinib, it will not be required to be repeated at the End of Treatment visit. Added requirement for collection and shipment of tumor scans to an independent radiology laboratory for central review for the ROS1-positive NSCLC cohort. Increased sample size for ROS1-positive NSCLC cohort from 30 to 50 patients and provided the rationale for change. Note to File was issued 12 November 2012. Increased the overall sample size to approximately 550 patients based on additional patient enrollment into the ROS1-positive NSCLC cohort, the Enriched Other cohort and the rifampin and itraconazole drug-drug interaction sub-studies. Protocol template language updated to be consistent with Sponsor standards. Corrected typographical errors.

Source: Protocol and Protocol Amendments (Appendix 16.1.1).
Abbreviations: AE=adverse event; ALK=anaplastic lymphoma kinase; NSCLC=non-small cell lung cancer; PK=pharmacokinetic(s); QTc=corrected QT interval.

Baseline data

Baseline demographic and disease characteristics are shown in the following Tables:

Table 7: Demographic and Other Baseline Characteristics (ROS1-Positive NSCLC) - Safety Analysis Population

	ROS1-positive NSCLC, 250 mg BID (N=53)
Sex, n (%)	
Male	23 (43.4)
Female	30 (56.6)
Age (years)	
n	53
Mean (SD)	54.1 (13.44)
Median	55.0
Range	25-81
Age Category (years), n (%)	
<65	38 (71.7)
≥65	15 (28.3)
Race, n (%)	
White	30 (56.6)
Black	2 (3.8)
Asian	21 (39.6)
Racial designation for Asian	
Korean	13 (24.5)
Chinese	4 (7.5)
Other	4 (7.5)
Weight (kg)	
n	53
Mean (SD)	71.9 (15.97)
Median	70.0
Range	48.0-106.3
Smoking Classification, n (%)	
Never smoked	40 (75.5)
Ex-smoker	13 (24.5)
ECOG Performance Status, n (%)[a]	
0	23 (43.4)
1	29 (54.7)
2	1 (1.9)

Source: Section 14.1, Tables 14.1.2.1.1.1.ros, 14.1.2.1.2.1.ros, and 14.1.2.4.1.ros.
Weight is based on the information collected at screening from the Demographics CRF page.
Abbreviations: BID=twice daily; CRF=case report form; ECOG=Eastern Cooperative Oncology Group; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer; SD=standard deviation.
a Baseline is the Cycle 1 Day 1 value, unless missing, then Baseline is the Screening value.

Table 8: Prior Treatments for Primary Diagnosis (ROS1-Positive NSCLC) - Safety Analysis Population

	ROS1-positive NSCLC, 250 mg BID N=53 n (%)
Prior surgeries	
Yes	53 (100)
Prior radiation therapies	
No	34 (64.2)
Yes	19 (35.8)
Prior systemic advanced/metastatic therapies	
No	7 (13.2)
Yes	46 (86.8)
Number of regimens	
1	20 (37.7)
2	13 (24.5)
3	3 (5.7)
4	2 (3.8)
5	5 (9.4)
6	3 (5.7)

Source: Section 14.4, Table 14.4.2.2.1.ros.
Patients could have reported more than 1 type of prior treatment.
Abbreviations: BID=twice daily; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer.

Table 9: Best Overall Response to Prior Lines of Metastatic Treatments for the Primary Diagnosis (ROS1-Positive NSCLC) - Safety Analysis Population

	ROS1-positive NSCLC, 250 mg BID (N=53) n (%)
Patients with any line of metastatic treatments	46
Patients with first-line metastatic therapy	46 (100)
BOR to first-line metastatic therapy	
Complete response	0
Partial response	10 (21.7)
Stable disease	17 (37.0)
Progressive disease	13 (28.3)
Unknown	6 (13.0)
Patients with first-line metastatic therapy with pemetrexed	17
BOR to first-line metastatic therapy with pemetrexed	
Complete response	0
Partial response	5 (29.4)
Stable disease	6 (35.3)
Progressive disease	5 (29.4)
Unknown	1 (5.9)
Patients with second-line metastatic therapy	24
BOR to second-line metastatic therapy	
Complete response	0
Partial response	4 (16.7)
Stable disease	12 (50.0)
Progressive disease	4 (16.7)
Unknown	4 (16.7)
Patients with second-line metastatic therapy with pemetrexed	13
BOR to second-line metastatic therapy with pemetrexed	
Complete response	0
Partial response	4 (30.8)
Stable disease	4 (30.8)
Progressive disease	2 (15.4)
Unknown	3 (23.1)
Patients with third-line or greater metastatic therapy	12
BOR to third-line or greater metastatic therapy	
Complete response	0
Partial response	0
Stable disease	8 (66.7)
Progressive disease	2 (16.7)
Unknown	2 (16.7)
Patients with last line of metastatic therapy	46
BOR to last line of metastatic therapy before crizotinib	
Complete response	0
Partial response	10 (21.7)
Stable disease	16 (34.8)
Progressive disease	10 (21.7)
Unknown	10 (21.7)
Patients with any line of metastatic therapy with pemetrexed	38
BOR to any line of metastatic therapy with pemetrexed	
Complete response	0
Partial response	9 (23.7)
Stable disease	16 (42.1)
Progressive disease	8 (21.1)
Unknown	5 (13.2)

Source: Section 14.4, Tables 14.4.2.2.2.ros and 14.4.2.2.2.1.ros.
Abbreviations: BID=twice daily; BOR=best overall response; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer.

Most patients (96.2%) had a histological classification of Adenocarcinoma at diagnosis, with the remaining having Squamous cell carcinoma (1 patient) and other (1 patient).

All 53 patients had advanced NSCLC (either Stage III or IV) at baseline, with a median time since diagnosis of 1.16 (0.0 to 11.2) years. All patients presented with measurable disease and adequate baseline assessments.

For ROS1-positive NSCLC patients in Study 1001 (N=53), the median duration of treatment was 101 weeks.

Diagnostic Marker Test Results

Due to additional follow up information related to 2 patients that were identified as ROS1-positive via a MGH research ROS1 FISH assay rather than the clinically-validated MGH laboratory-developed test, a second snapshot of Marker test data was taken on 30 April 2015:

Table 10: Diagnostic ROS1 Marker Testing and Test Characteristics by Type of Local Test (ROS1-Positive NSCLC) - Safety Analysis Population

	ROS1-positive NSCLC, 250 mg BID (N=53) n (%)
Number (%) of patients tested	53 (100.0)
MGH	26 (49.1)
FISH	26 (49.1)
Non-MGH	27 (50.9)
FISH	25 (47.2)
PCR	2 (3.8)

Source: Section 14.2, Tables 14.2.8.1.ros and 14.2.8.2.ros.
Abbreviations: BID=twice daily; FISH=fluorescence in situ hybridization; MGH=Massachusetts General Hospital; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer; PCR=polymerase chain reaction.

Available tissue samples (n=37 from 36 patients) were retrospectively tested for ALK gene rearrangement. One patient with a ROS1 rearrangement identified by FISH testing at MGH, an atypical hybridization pattern was noted (isolated 5′ green signal), and next-generation sequencing subsequently revealed normal, non-rearranged ROS1. In a second patient the tumour was positive for both ROS1 and ALK rearrangement based on FISH, but next-generation sequencing revealed only an EML4-ALK fusion and no ROS1 rearrangement. None of the other available tumour tissue samples (n=36 from 35 patients) tested for ALK were positive.

Two patients, both previously treated with systemic therapy before crizotinib, were not ROS1 positive based on next-generation sequencing.

Among 16 ROS1-positive tumours tested for c-Met amplification by FISH or other testing methodologies, only 1 was determined to be positive based on a c-Met receptor tyrosine kinase (MET)/centromere 7 (CEP7) ratio of 1.8, meeting the criteria for the Low Level c-Met Gene Amplified category (MET/CEP7 ratio ≥1.8 to ≤2.2) established for enrolment into the c-Met amplified cohort of Study 1001. In this patient, the percentage of ROS1-positive cells was 60%.

A summary of descriptive statistics for percentage of ROS1-positive cells is presented below:

Table 11: Descriptive Statistics for percentage of cells that are ROS1-Positive by FISH Testing (ROS1-Positive NSCLC) - Safety Analysis Population

	ROS1-positive NSCLC, 250 mg BID (N=53)		
	MGH	Non-MGH	Total
Number of patients with evaluation by FISH, n (%)	26 (49.1)	25 (47.2)[a]	51 (96.2)[a]
Percentage of ROS1-positive cells by FISH			
n (%)	25 (96.2)[c]	17 (68.0)[c]	42 (82.4)[c]
Mean (SD)	59.4 (21.76)	55.3 (26.38)	57.7 (23.51)
Median	64.0	54.0	59.0
Range	22.0-96.0	16.0-92.0	16.0-96.0

Source: Section 14.2, Tables 14.2.8.2.ros and 14.2.8.3.ros.
Abbreviations: BID=twice daily; FISH=fluorescence in situ hybridization; MGH=Massachusetts General Hospital; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer; RT-PCR=reverse transcriptase polymerase chain reaction; SD=standard deviation.
a Two patients (Patients 10061435 and 10021144) are excluded from this table because ROS1-positivity was determined by RT-PCR testing which does not provide data for percentage of ROS1-positive cells (Appendix 16.2, Table 16.2.4.6.ros).
b Percentage based on number of patients with evaluation by FISH.
c Data on the percentage of ROS1-positive cells is not available for 1 patient assessed by MGH (Patient 10014009) and 8 patients assessed by non-MGH laboratories (Patients 10021143, 10021145, 10051018, 10061057, 10061183, 10061432, 10081016, and 10051019) (Appendix 16.2, Table 16.2.4.6.ros).

Numbers analysed

The analysis populations defined for the efficacy evaluations of patients with ROS1-positive NSCLC in Study 1001 were:

Safety Analysis (SA) Population (53 patients): all enrolled patients who received at least 1 dose of crizotinib. This was the primary population for patient characteristics, and analyses of PFS, TTP, OS and safety.

Response-Evaluable (RE) Population (53 patients): all patients in the SA population who had an adequate baseline disease assessment. In addition, for this and any interim reporting of the data, patients also needed to meet 1 of the following 2 criteria: (1) had at least one post-baseline disease assessment at least 6 weeks from first dose of crizotinib or (2) withdrew from the study or experienced progressive disease/death at any time on study. This was the primary population for analyses of ORR, DR, time to tumour response (TTR), and disease control rate (DCR).

Outcomes and estimation

Objective Response Rate (ORR)

- Based on Derived-Tumour Assessment in the 53 patients with ROS1-positive NSCLC:

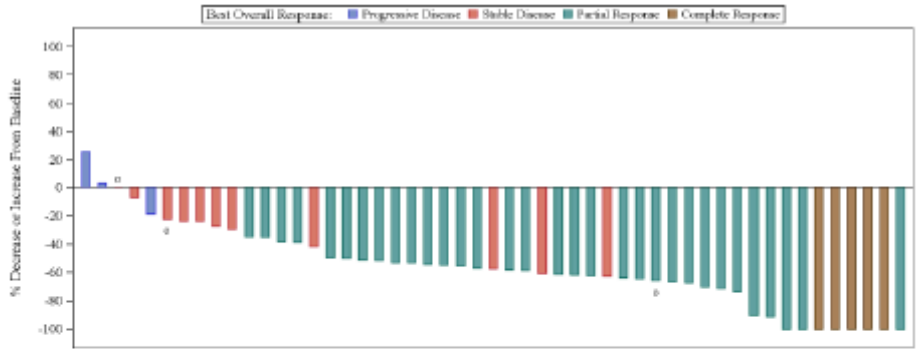
Table 12: Best Overall Response (ROS1-Positive NSCLC patients) - Response-Evaluable Population

Efficacy Parameter	Crizotinib (N=53)
Best Response, n (%)	
Complete response	5 (9.4)
Partial response[a]	32 (60.4)
Stable disease[b]	11 (20.8)
Objective progression[c]	3 (5.7)
Early death	1 (1.9)
Indeterminate	1 (1.9)
ORR (CR + PR), n (%) [95% CI][d]	37 (69.8) [55.7, 81.7]
DCR (CR+PR+SD) at Week 8, n (%) [95% CI][d]	46 (86.8) [74.7, 94.5]
DCR (CR+PR+SD) at Week 16, n (%) [95% CI][d]	42 (79.2) [65.9, 89.2]

Source: Study 1001 ROS1 CSR Tables 14, 14.2.1.1.ros and 14.2.2.ros.
Best overall response is based on the derived tumor assessment.
Response-Evaluable population is defined as all patients in the Safety Analysis population who have an adequate baseline disease assessment and who meet 1 of the 2 following criteria: (1) had at least 1 postbaseline assessment at least 6 weeks from the first dose, (2) withdrew from the trial or experienced progression/death at any time on study.
Early death is death within 42 days (6 weeks) from first dose.
Tumor assessments were based on RECIST version 1.0 except for 3 patients from the ALK-negative NSCLC cohort for whom RECIST version 1.1 was used.
Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; CR=complete response; CSR=clinical study report; DCR=disease control rate; FISH=fluorescence in situ hybridization; n/N=number of patients; NSCLC=non-small cell lung cancer; ORR=objective response rate; PR=partial response; SD=stable disease.

a. Of the patients with partial response, Patient 10024057 from the ALK-negative cohort was retrospectively determined to be ROS1-positive. Patient 10061381, who was ROS1-positive by FISH and was subsequently found to be positive for an ALK rearrangement and ROS1-negative by next-generation sequencing, had a best overall response of partial response (Study 1001 ROS1 CSR Section 11.2.3 and Table 16.2.6.4.ros)
b. Of the patients with stable disease, Patient 10014009 and Patient 10024056 from the ALK-negative cohort were retrospectively determined to be ROS1-positive (Study 1001 ROS1 CSR Table 16.2.6.4.ros)
c. Of the patients with objective progression, Patient 10021130, identified as ROS1-positive, had an atypical hybridization pattern and was subsequently found to be ROS1-negative by next-generation sequencing. (Study 1001 ROS1 CSR Section 11.2.3 and Table 16.2.6.4.ros)
d. Using exact method based on F-distribution

In order to characterize the tumour shrinkage activity of crizotinib, a waterfall plot of best percentage change in target lesions from baseline is reported:



Source: Section 14.2, Figure 14.2.1.2.ros.
N*=51 is based on the Response-Evaluable population, excluding patients with early death or indeterminate response.
The 3 patients included from the ALK-negative NSCLC cohort based on ROS1-positive status in retrospective review are marked with 'o'; derived tumor assessment for these patients uses RECIST version 1.1 criteria.
For patients enrolled into the ROS1-positive NSCLC cohort, derived tumor assessment is based on RECIST version 1.0 criteria.
Abbreviations: ALK=anaplastic lymphoma kinase; NSCLC=non-small cell lung cancer; RECIST=Response Evaluation Criteria in Solid Tumors.

Figure 3: Waterfall Plot of Best Percentage (%) Change from Baseline in Target Lesions by Patient Based on Derived Tumour Assessment - (ROS1-Positive NSCLC) - Response-Evaluable Population (N*=51)

- Based on Independent Radiology Review (IRR) in the 50 patients treated in the ROS1-positive NSCLC cohort:

Table 13: Best Overall Response based on IRR (ROS1-Positive NSCLC Cohort) - IRR Response-Evaluable Population

	ROS1-Positive, NSCLC, 250 MG BID (N=50) n (%)
Complete Response	1 (2.0)
Partial Response	32 (64.0)
Stable Disease	12 (24.0)
Objective progression	4 (8.0)
Early death	1 (2.0)
Indeterminate	0
Objective Response Rate (CR+PR)	33 (66.0)
95% Exact CI [1]	[51.2, 78.8]

The corresponding derived tumour assessed ORR for the 50 patients in the ROS1-positive NSCLC cohort was 72.0% (95% CI: 57.5, 83.8). The total event agreement rate between the derived tumour assessment and IRR assessment was 82.0%, with agreement on response and non-response for 30 and 11 patients, respectively.

The Best Overall Response by type of assessment (derived tumour assessment vs IRR assessment) is summarized below:

Table 14: Best Overall Response by Type of Assessment in ROS1-Positive NSCLC Cohort (IRR RE or RE Populations)

Derived Tumor Assessment	IRR Assessment						
	CR	PR	SD	Objective Progression	Early Death	Indeterminate	Total
CR	1	3	1	0	0	0	5
PR	0	26	5	0	0	0	31
SD	0	2	6	1	0	0	9
Objective progression	0	1	0	2	0	0	3
Early Death	0	0	0	0	1	0	1
Indeterminate	0	0	0	1	0	0	1
Total	1	32	12	4	1	0	50

Source: Table 14.2.3.2.ros.

Abbreviations: CR=Complete response; IRR=Independent radiology review; NSCLC=Non-small cell lung cancer; PR=Partial response; RE=Response-evaluable; SD=Stable disease.

- Based on the first 27 evaluable patients in the ROS1-positive NSCLC cohort:

Table 15: Best Overall Response (First 27 evaluable ROS1-Positive NSCLC patients) - Response-Evaluable Population

	ROS1-Positive, NSCLC, 250 MG BID (N=27) n (%)
Complete response	2 (7.4)
Partial response	16 (59.3)
Stable disease	6 (22.2)
Objective progression	2 (7.4)
Early death	1 (3.7)
Indeterminate	0
Objective Response Rate (CR+PR)	18 (66.7)
95% Exact CI [1]	[46.0, 83.5]
SD Duration (months) [2]	
0 - <3 months	1 (16.7)
3 - <6 months	2 (33.3)
6 - <9 months	0
9 - <12 months	0
>= 12 months	3 (50.0)

[1] Using exact method based on F-distribution.
[2] % is based on the number of SD patients.
Best Overall Response is based on the Derived Investigator Tumor Assessment.
Early Death is death within 42 days (6 weeks) from first dose.
The Response-Evaluable population is defined as all patients in the Safety Analysis set who have an adequate baseline disease assessment, in addition patients also need to meet 1 of the following 2 criteria:
a) Had at least one post-baseline disease assessment at least 6 weeks from the first dose.
b) Withdrew from the trial or experienced progression/death at any time on study.
Tumor Assessments are based on RECIST 1.0 .
Abbreviations: BID = Twice a day; CI = Confidence Interval; NSCLC = Non-small cell lung cancer;RECIST = Response Evaluation Criteria in Solid Tumors; CR = complete response; PR = partial response; SD = stable disease.
PFIZER CONFIDENTIAL Source Data: Table 16.2.6.4.ros Date of Reporting Dataset Creation: 10MAY2015 Date of Table Generation: 12MAY2015(03:47)

Disease control rate

Table 16: Disease Control Rate at Week 8 and Week 16 (ROS1-Positive NSCLC) - Response-Evaluable Population

	ROS1-positive NSCLC, 250 mg BID (N=53)
Disease control rate at Week 8, n (%)	46 (86.8)
95% exact CI[a]	74.7, 94.5
Disease control rate at Week 16, n (%)	42 (79.2)
95% exact CI[a]	65.9, 89.2

Source: Section 14.2, Table 14.2.2.ros.
Tumor assessment was based on the derived tumor assessment.
Abbreviations: BID=twice daily; CI=confidence interval; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer.
a Using exact method based on F-distribution.

Duration of Response

Table 17: Duration of Response (ROS1-Positive NSCLC Patients) - Response-Evaluable Population (Objective Responders Only)

	ROS1-positive NSCLC, 250 mg BID (N=37)
Patients with confirmed objective response (CR or PR), n (%)	37 (100)
Objective response (CR or PR) status, n (%)*:	
With subsequent progression or death	15 (40.5)
Without subsequent progression or death	22 (59.5)
Kaplan-Meier estimates of duration of response (months)	
25% quartile (95% CI)[b]	13.6 (10.2, 17.6)
50% quartile (95% CI)[b]	NR (15.2, NR)
75% quartile (95% CI)[b]	NR
Duration of response (months)[c]	
n	15
Mean (SD)	11.4 (5.1)
Median	13.0
Range	2.8-18.1

Source: Section 14.2, Table 14.2.4.1.ros.
Duration of response (in months) is the number of days from date of first documented CR or PR to the date of first documented objective progression or death due to any cause divided by 30.44.
Abbreviations: BID=twice daily; CI=confidence interval; CR=complete response; n=number of patients with data; N=total number of patients in population; NR=not reached; NSCLC=non-small cell lung cancer; PR=partial response; SD=standard deviation.
a % is based on the number of patients with confirmed objective response (CR or PR).
b Based on the Brookmeyer and Crowley Method.
c Descriptive statistics are presented for patients with an event of either progressive disease or death.

Time to Tumour Response

Table 18: Time to First Response (ROS1-Positive NSCLC) - Response-Evaluable Population (Objective Responders Only)

	ROS1-positive NSCLC, 250 mg BID (N=37)
Time to response (weeks)[a]	
n	37
Mean (SD)	11.5 (6.5)
Median	7.9
Range	4.3-32.0
Time to response category (weeks), n (%)[a]	
0 - <8	19 (51.4)
8 - <16	10 (27.0)
16 - <24	6 (16.2)
≥24	2 (5.4)

Source: Section 14.2, Table 14.2.4.2.ros.
Time to response in weeks was calculated as the (date of first documented objective tumor response [CR or PR] that was subsequently confirmed - date of first dose +1)/7.
Abbreviations: BID=twice daily; CR=complete response; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer; PR=partial response; SD=standard deviation.
a Percentage (%) is based on the number of patients with confirmed objective response (CR or PR).

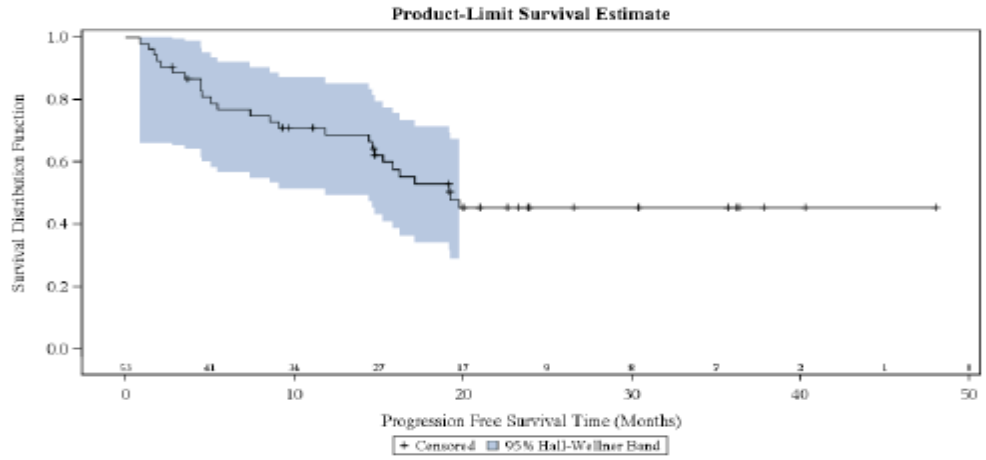
Progression Free Survival

At the time of the data cutoff, 39.6% of patients were still in follow-up for PFS.

Table 19: Progression Free Survival (ROS1-Positive NSCLC Patients) - Safety Analysis Population

	ROS1-positive NSCLC, 250 mg BID (N=53)
Patients with event, n (%)	26 (49.1)
Type of event	
Objective progression	23 (43.4)
Death without objective progression	3 (5.7)
Patients censored, n (%)	27 (50.9)
Reason for censorship	
No adequate baseline assessments	0
Given new anti-cancer treatment prior to tumor progression	2 (3.8)
Withdrew consent for follow-up	2 (3.8)
Lost to follow-up	1 (1.9)
Off treatment prior to progression	1 (1.9)
In follow-up for progression	21 (39.6)
Probability of being event free at Month 6[a] (95% CI[b])	76.9 (62.8, 86.1)
Kaplan-Meier estimates of time to event (months)	
25% quartile (95% CI)[c]	7.4 (4.4, 15.2)
50% quartile (95% CI)[c]	19.3 (14.8, NR)
75% quartile (95% CI)[c]	NR

Source: Section 14.2, Table 14.2.5.1.ros.
Abbreviations: BID=twice daily; CI=confidence interval; n=number of patients with data; N=total number of patients in population; NR=not reached; NSCLC=non-small cell lung cancer.
a Estimated from the Kaplan-Meier curve.
b Calculated using the normal approximation to the log-transformed cumulative hazard function.
c Based on the Brookmeyer and Crowley Method.
Tumor assessment was based on the derived tumor assessment.



Source: Section 14.2, Figure 14.2.2.1.ros.
Note: tumor assessment is based on the derived tumor assessment using RECIST version 1.0 criteria and (for the 3 patients included from the ALK-negative NSCLC cohort only) RECIST version 1.1 criteria.
Numbers above the x-axis are numbers of patients at risk.
Abbreviations: ALK=anaplastic lymphoma kinase; NSCLC=non-small cell lung cancer; RECIST=Response Evaluation Criteria in Solid Tumors.

Figure 4: Kaplan-Meier Plot of Progression-Free Survival (ROS1-Positive NSCLC Patients) - Safety Analysis Population

Table 20: Progression Free Survival by the Number of Prior Advanced / Metastatic Therapies (ROS1-Positive NSCLC Patients) - Safety Analysis Population

	ROS1-Positive, NSCLC, 250 MG BID (N=53)	
	Untreated	**Pretreated ≥1 line**
Number (%) of Subjects	7 (13.2)	46 (86.8)
Number with event	3 (42.9)	23 (50.0)
• Objective progression	2 (28.6)	21 (45.7)
• Death without objective Progression	1 (14.3)	2 (4.3)
Number censored	4 (57.1)	23 (50.0)
• New anti-cancer treatment prior to PD	0	2 (4.3)
• Withdrew consent for follow-up	1 (14.3)	1 (2.2)
• Lost to follow-up	0	1 (2.2)
• Off treatment prior to progression	0	1 (2.2)
• In follow-up for progression	3 (42.9)	18 (39.1)

Time To Tumour Progression

A median TTP of 19.8 months (95% CI: 15.2, NR) was reported. Of the 53 ROS1-positive NSCLC patients, 43.4% had objective progression and the remaining (56.6%) were censored, including 39.6% who were still in follow-up for progression.

The median TTP for the last regimen of prior treatment before crizotinib is shown below:

Table 21: Time to Progressive Disease of the Last Line of Prior Treatment Before Crizotinib (ROS1-Positive NSCLC Patients) - Safety Analysis Population

	ROS1-Positive, NSCLC, 250 MG BID (N=53)
Number of Subjects with Prior Metastatic Treatment	45
Number (%) with event	27 (60.0)
Number (%) censored	18 (40.0)
Probability of being event free at Month 6 [1] (95% CI [2])	59.0[41.0, 73.1]
Kaplan-Meier estimates of Time to Event (Month)	
Quartiles (95% CI) [3]	
25%	2.8[1.8, 6.7]
50%	8.1[5.6, 11.0]
75%	15.3[10.9, 34.0]

Results of a within-patient TTP analysis, in which TTP on crizotinib was compared with TTP on last prior therapy: the median TTP with crizotinib vs last prior therapy was 19.8 vs 8.1 months (HR 0.588; 95% CI: 0.308, 1.125; p-value=0.1089).

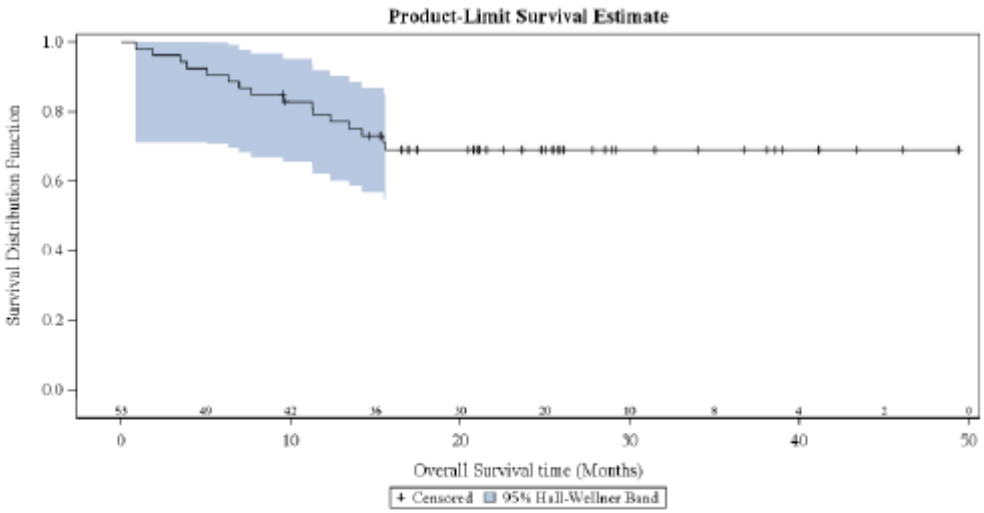
Overall Survival

At the time of the data cutoff, the median duration of OS follow-up (reverse Kaplan-Meier method) was 25.4 months (95% CI: 22.5, 28.5).

Table 22: Overall Survival (ROS1-Positive NSCLC) - Safety Analysis Population

	ROS1-positive NSCLC, 250 mg BID (N=53)
Number of deaths, n (%)	16 (30.2)
Number censored, n (%)	37 (69.8)
Patient remains in follow-up	33 (62.3)
Patient no longer willing to participate	1 (1.9)
Lost to follow-up	1 (1.9)
Completed required 1-year follow-up	2 (3.8)
Survival probability at Month 6[a] (95% CI[b])	90.6 (78.8, 96.0)
Survival probability at Month 12[a] (95% CI[b])	79.0 (65.3, 87.8)
Kaplan-Meier estimates of time to event (month)	
25% quartile (95% CI)[c]	14.2 (9.6, NR)
50% quartile (95% CI)[c]	NR
75% quartile (95% CI)[c]	NR

Source: Section 14.2, Table 14.2.6.1.ros.
Patients in the follow-up included patients who were still on-treatment.
In the follow-up as of the cutoff date.
Abbreviations: BID=twice daily; CI=confidence interval; n=number of patients with data; N=total number of patients in population; NR=not reached; NSCLC=non-small cell lung cancer.
a Estimated from the Kaplan-Meier curve
b Calculated using the normal approximation to the log-transformed cumulative hazard function.
c Based on the Brookmeyer and Crowley Method.



Source: Section 14.2, Figure 14.2.3.1.ros.
Numbers above the x-axis are numbers of patients at risk.
Abbreviations: NSCLC=non-small cell lung cancer.

Figure 5: Kaplan-Meier Plot of Overall Survival (ROS1-Positive NSCLC Patients) - Safety Analysis Population

Table 23: Overall Survival by the Number of Prior Advanced / Metastatic Therapies (ROS1-Positive NSCLC Patients) - Safety Analysis Population

	ROS1-Positive, NSCLC, 250 MG BID (N=53)	
	Untreated	**Pretreated ≥1 line**
Number (%) of Subjects	7 (13.2)	46 (86.8)
Number of Deaths	2 (28.6)	14 (30.4)
Number censored	5 (71.4)	32 (69.6)
• Subject remain in follow up	4 (57.1)	29 (63.0)
• Subject no longer willing to participate	1 (14.3)	0
• Lost to follow-up	0	1 (2.2)
• Completed required 1 year follow up	0	2 (4.3)

Ancillary analyses

Subgroup analyses were performed to examine the influence of various baseline characteristics on BOR:

Table 24: Objective Response Rate by Baseline Characteristics (ROS1-Positive NSCLC Patients) Response-Evaluable Population

	ROS1-positive NSCLC, 250 mg BID (N=53)	
	n/N*	ORR % (95% exact CI)[a]
Number of prior advanced/metastatic therapies		
0	6/7	85.7 (42.1, 99.6)
≥1	31/46	67.4 (52.0, 80.5)
ECOG PS at baseline		
0	18/23	78.3 (56.3, 92.5)
1	19/29	65.5 (45.7, 82.1)
2	0/1	0 (0.0, 97.5)
Age group		
<65 years	27/38	71.1 (54.1, 84.6)
≥65 years	10/15	66.7 (38.4, 88.2)
Gender		
Male	17/23	73.9 (51.6, 89.8)
Female	20/30	66.7 (47.2, 82.7)
Race group		
Asian	15/21	71.4 (47.8, 88.7)
Non-Asian	22/32	68.8 (50.0, 83.9)

Source: Section 14.2, Tables 14.2.1.2.ros, 14.2.1.3.ros, 14.2.1.4.ros, 14.2.1.5.ros, and 14.2.1.6.ros.
Best overall response is based on the investigator tumor assessment.
Abbreviations: BID=twice daily; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; n=number of patients with data; N=total number of patients in population; N*=number of patients in subgroup; NSCLC=non-small cell lung cancer; ORR=objective response rate; PS=performance status.
a Using exact method based on F-distribution.

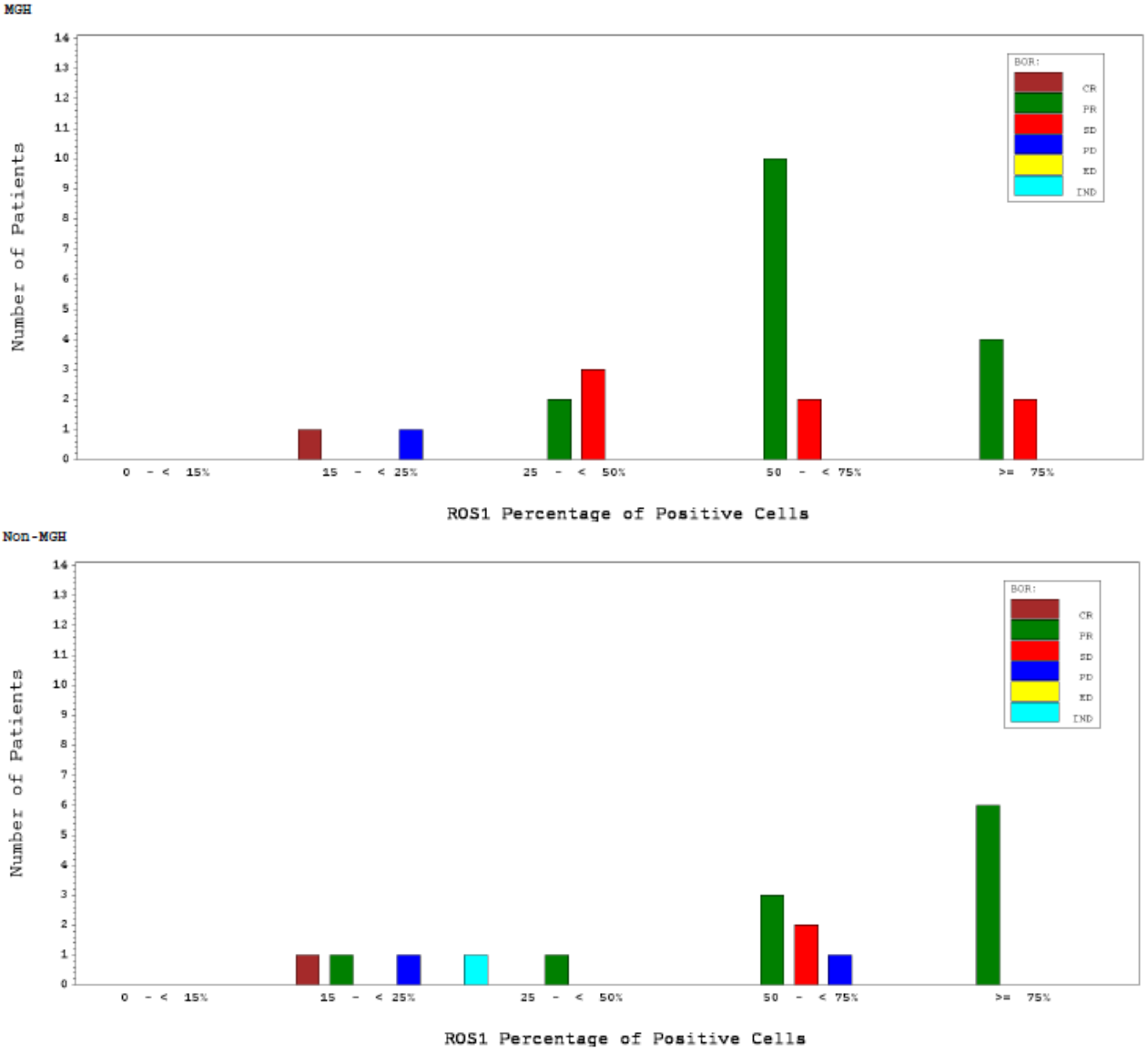
Of the 42 patients with available data, the mean percentage of ROS1-positive cells was 19.0% for the 2 patients with a CR and 64.1% for the 27 patients with a PR. The mean percentages of ROS1-positive cells for patients with stable disease/no response and objective progression were 59.8% and 34.0%, respectively. Of note, the results based on ROS1 rearrangement testing performed by MGH were consistent with the overall results.

A summary of the percentage of ROS1-positive cells, as detected by ROS1 FISH analysis, by BOR is reported below:

Table 25: Percentage of ROS1 Positive Cells By Best Overall Response (ROS1-Positive NSCLC) - Response-Evaluable Population

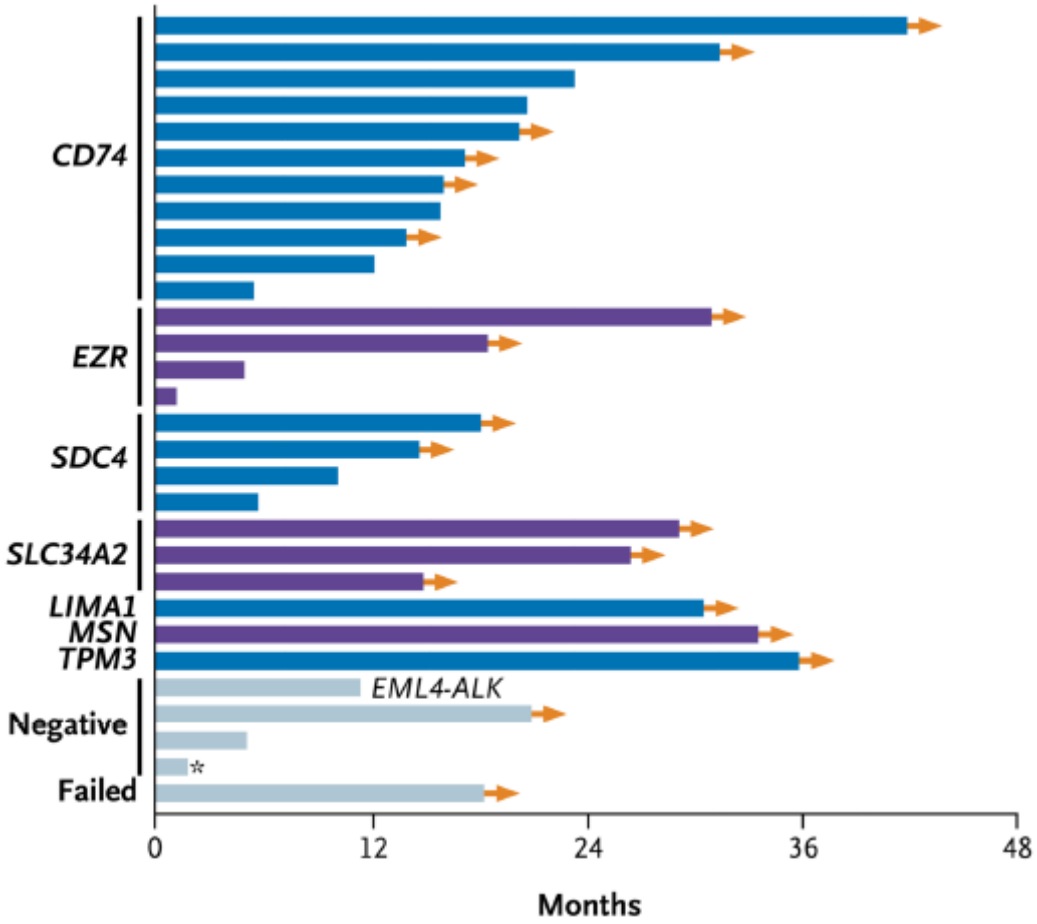
	ROS1-positive NSCLC, 250 mg BID (N=53)	
	MGH	Total
Number of patients with percentage of ROS1-positive cells by FISH	25[a]	42[a]
Complete response		
n	1	2
Mean (SD)	22.0 (NA)	19.0 (4.24)
Median	22.0	19.0
Range	22.0-22.0	16.0-22.0
Partial response		
n	16	27
Mean (SD)	64.0 (18.73)	64.1 (20.39)
Median	66.0	66.0
Range	28.0-96.0	24.0-96.0
Stable disease/no response		
n	7	9
Mean (SD)	59.1 (22.77)	59.8 (20.16)
Median	64.0	64.0
Range	30.0-92.0	30.0-92.0
Objective progression		
n	1	3
Mean (SD)	24.0 (NA)	34.0 (22.72)
Median	24.0	24.0
Range	24.0-24.0	18.0-60.0
Indeterminate		
n	0	1
Mean (SD)		16.0 (NA)
Median		16.0
Range		16.0-16.0

Source: Section 14.2, Tables 14.2.8.3.ros and 14.2.8.5.ros.
Abbreviations: BID=twice daily; n=number of patients with data; FISH=fluorescence in situ hybridization; MGH=Massachusetts General Hospital; N=total number of patients in population; NA=not applicable; NSCLC=non-small cell lung cancer; RT-PCR=reverse transcriptase polymerase chain reaction; SD=standard deviation.
a Data on the percentage of ROS1-positive cells is not available for 1 patient assessed by MGH (Patient 10014009) and 8 patients assessed by non-MGH laboratories (Patients 10021143, 10021145, 10051018, 10061057, 10061183, 10061432, 10081016, and 10051019) (Appendix 16.2, Table 16.2.4.6.ros). For 2 patients (Patients 10061435 and 10021144), ROS1-positivity was determined by RT-PCR testing which does not provide data for percentage of ROS1-positive cells (Appendix 16.2, Table 16.2.4.6.ros).



Derived Investigator Assessment used RECIST 1.0 criteria and (for the 3 subjects included from the ALK-Negative Cohort #2 only) RECIST 1.1 criteria.
Abbreviations: NSCLC = Non-small cell lung cancer; BOR = Best Overall Response; CR = complete response; PR = partial response; SD = stable disease; ED = Early death; IND = Indeterminate.
PFIZER CONFIDENTIAL Source Data: Table 16.2.4.6.ros,16.2.6.6.ros Date of Reporting Dataset Creation: 10MAY2015 Date of Table Generation: 10JUN2015(01:47)

Figure 6: Bar Graph by Level of ROS1 Percentage of Positive Cells Category by BOR Based on the Derived Investigator Assessment (ROS1-Positive NSCLC) - Response-Evaluable Population



Shaw et al, N Engl J Med 2014. The duration of crizotinib treatment is shown for the 25 patients in whom the ROS1 fusion partner was identified with the use of either a next-generation sequencing assay or a reverse-transcriptase-polymerase-chain reaction assay. Patients are grouped according to the ROS1 fusion partner, as indicated on the left. The four patients with negative results on next-generation sequencing and the one patient in whom the next-generation sequencing failed are indicated by gray bars. One of the four patients with negative results was positive for EML4-ALK rearrangement, as indicated. One patient had negative results on next-generation sequencing and had an atypical FISH pattern (as indicated by an asterisk). The arrows indicate patients who were continuing to receive crizotinib at the time of data cutoff (16 May 2014).

Figure 7: Duration of crizotinib treatment in patients grouped per ROS1 fusion partner

Summary of main study

The following tables summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 26: Summary of Efficacy for trial A8081001

Title: Phase 1 safety, pharmacokinetic and pharmacodynamic study of PF-02341066, a C-Met/HGFR selective tyrosine kinase inhibitor, administered orally to patients with advanced cancer	
Study identifier	A8081001, NCT00585195
Design	Open-label, multicenter, multinational, dose escalation, safety, PD, PK, and antitumor activity study of crizotinib administered as a single oral agent to patients with advanced malignancies.

	Duration of main phase:		Study treatment was to be continued until the occurrence of disease progression or clinical deterioration, unacceptable toxicity, patient's withdrawal of consent, or protocol noncompliance. Treatment could be continued after disease progression if the patient was considered to be deriving clinical benefit as judged by the investigator.
Hypothesis	Exploratory		
Treatments groups	ROS1-positive NSCLC cohort		crizotinib 250 mg BID administered orally continuously (28-day cycles)
	ALK-negative NSCLC cohort (3 ROS1-positive patients)		crizotinib 250 mg BID administered orally continuously (21-day cycles)
Endpoints and definitions	Objective Response Rate	ORR	percentage of patients with confirmed CR or confirmed PR according to RECIST v. 1.0 (ROS1-positive NSCLC cohort) or RECIST v. 1.1 (ALK-negative NSCLC cohort), relative to the RE population.
	Disease Control Rate at Weeks 8 and 16	DCR	percentage of patients with a confirmed CR, PR or SD according to RECIST v. 1.0 (ROS1-positive NSCLC cohort) or RECIST v.1.1 (ALK-negative NSCLC cohort) based on the response at Weeks 8 and 16, relative to the RE population.
	Duration of Response	DR	time from the first documentation of CR or PR that was subsequently confirmed, to the first documentation of objective tumour progression or death on-study due to any cause, whichever occurred first.
	Time to Response	TTR	time from the date of first dose to first documentation of CR or PR that was subsequently confirmed.
	Progression Free Survival	PFS	time from the date of first dose to the date of the first documentation of objective tumour progression or death on-study due to any cause, whichever occurred first.
	Time To Progression	TTP	time from the date of first dose to the date of the first documentation of objective tumour progression.
	Overall Survival	OS	time from the date of the first dose to the date of death due to any cause.
Data cut-off date Database snapshot	30 November 2014 03 April 2015		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Response-Evaluable (RE) Population	
Descriptive statistics and estimate variability	Treatment group	crizotinib ROS1-positive NSCLC patients
	Number of subject	**53**
	Objective Response Rate (ORR)	
	n(%)	37 (**69.8**) *including 5 CR
	95% exact CI	55.7, 81.7
	Disease Control Rate (DCR)	
	at week 8, n(%)	46 (**86.8**)
	95% exact CI	74.7, 94.5
	at week 16, n(%)	42 (**79.2**)
	95% exact CI	65.9, 89.2

	Number of subject	**37**
	Duration of Response (DR)	
	median (months) range	NR (15.2, NR)
	Time to Tumour Response (TTR)	
	median (weeks) range	7.9 (4.3, 32.0)
Analysis population and time point description	Safety Analysis (SA) Population	
Descriptive statistics and estimate variability	Treatment group	crizotinib ROS1-positive NSCLC patients
	Number of subject	**53**
	Progression Free Survival (PFS)	
	N. with events (%)	26 (49.1)
	median (months) 95% CI	**19.3** (14.8, NR)
	Time To Progression (TTP)	
	N. with events (%)	23 (43.4)
	median (months) 95% CI	19.8 (15.2, NR)
	Overall Survival (OS)	
	N. with events (%)	16 (30.2)
	median (months) 95% CI	NR
Analysis description	**Additional analysis: Independent Radiology Review (IRR)**	
	Treatment group	crizotinib ROS1-positive NSCLC cohort patients
	Number of subject	**50**
	Objective Response Rate (ORR)	
	n(%)	33* (**66.0**) *including 1 CR
	95% exact CI	51.2, 78.8

Supportive study(ies)

No additional study was conducted by the MAH with crizotinib in ROS1-positive NSCLC patients.

However, in order to provide context for the efficacy results, the MAH presented data on the natural history of ROS1-positive NSCLC, results from recently published retrospective/prospective analyses of ROS1-positive NSCLC patients who received crizotinib, and data on response to previous systemic standard treatments from patients with ROS1-positive NSCLC.

ROS1-positive NSCLC Natural History

Information is currently limited, but several retrospective analyses describing the natural history of ROS1-positive NSCLC have been published (Bergethon et al, 2012; Yoshida et al, 2013; Cai et al, 2013; Chen et al, 2014; Lee, Seol, Kim et al, 2013; Fu et al, 2015; Scheffler et al, 2015; Jin et al, 2015).

Several limitations, including the small number of patients (4 to 33 patients) and the differences in patients baseline characteristics, ROS1 testing methodology and definition of the ROS1-negative comparison group, need to be taken into account.

Scheffler et al, 2015 reported that OS was significantly better (p-value=0.005) in 14 patients with ROS1-positive NSCLC compared to that of 115 patients with ROS1-negative NSCLC (median OS of 36.7 months and 17.5 months, respectively). It is important to note that 5 out of the 14 patients with ROS1-positive NSCLC in this report received crizotinib which could have confounded the observed result.

In the analysis by Cai et al, 2013 a significantly shorter OS (p-value=0.041) was reported for 8 patients with ROS1-positive NSCLC, none of whom were treated with crizotinib, compared to 384 ROS1-negative NSCLC patients (median OS of 32 months and 54 months, respectively).

Bergethon et al, 2012 reported no significant difference (p-value=0.42) in median OS for 18 patients with ROS1-positive NSCLC (663 days) compared to the median OS for 1055 patients with ROS1-negative NSCLC (607 days). No significant difference in OS for 4 to 33 ROS1-positive NSCLC patients and 144 to 1055 ROS1-negative NSCLC patients was reported by 5 additional studies (Yoshida et al, 2013; Chen et al, 2014; Fu et al, 2015; Lee, Seol, & Kim et al, 2013; Jin et al, 2015).

Supportive data on patients with ROS1-Positive NSCLC who received crizotinib

The high ORR observed in Study 1001 (69.8%, 95% CI: 55.7, 81.7) was independently supported by 3 recent publications.

The European Study of ROS1 Patients (EUROS1) Cohort of a European retrospective study included 31 patients with ROS1-positive NSCLC who received crizotinib therapy through individual off-label use (Mazieres et al, 2015). In this study, all but 1 patient had received at least 1 prior line of standard chemotherapy for advanced NSCLC, and the ORR was 80% (calculated-not reported in publication 95% CI: 61, 92).

In a retrospective analysis, ORR in 5 patients who received crizotinib after 1-8 lines of prior therapies was 100% (calculated- not reported in publication 95% CI: 48,100) (Scheffler et al, 2015).

The results of a prospective investigator-initiated study (secured access [AcSé]) of 24 evaluable patients who received crizotinib after 1-12 lines of treatment showed an ORR of 63% (95% CI: 41, 81) (Moro-Sibilot et al, 2015).

The results from these 3 independent studies help to substantiate ROS1-positive NSCLC as a molecularly selected indication for crizotinib.

In Study 1001 for patients with ROS1-positive NSCLC, the median PFS on crizotinib treatment was 19.3 months (95% CI: 14.8, NR), with 40% of patients remaining in follow-up for progression at the time of the data cutoff. In the EUROS1 retrospective analysis, the median PFS was reported as 9.1 months with 60% of

patients still receiving treatment at the time of analysis (Mazieres et al, 2015). While it is unknown why there is an apparent difference in median PFS value between Study 1001 and EUROS1, this may be due to the length of follow-up, number of lines of prior therapies (approximately twice as many patients in the EUROS1 study received 3 or more lines of therapy prior to receiving crizotinib than in Study 1001), and the smaller sample size of EUROS1 analysis.

2.4.3. Discussion on clinical efficacy

An extension of crizotinib indication for the treatment of patients with ROS1-positive advanced NSCLC is requested by the MAH based on efficacy data from 53 patients treated in Study A8081001 (referred to as study 1001). At the time of the initial MAA, further investigation on the role of the ROS1 status in ALK-negative patients was requested as post-approval recommendation.

ROS1 positivity is expected in around 1%-2% of NSCLC patients. Due to the limited and in some cases conflicting results provided by retrospective analyses, it is not possible to conclude on the prognostic value of ROS1 positivity. Thus the rational and benefit of a therapy selectively addressing ROS1-positive NSCLC patients is at present not fully evaluable.

Design and conduct of clinical studies

Efficacy data have been collected in the expansion phase of the ongoing, open-label, phase I study 1001 in which several cohorts of patients, including ROS1-positive NSCLC, received crizotinib at the 250 mg twice daily dose (500 mg daily), already recommended for ALK-positive advanced NSCLC.

Efficacy data and additional analyses

Several CE-marked test for *in vitro* diagnostic, utilizing platforms such as FISH, RT-PCR and NGS are available for detection of ROS1 positivity in Europe.

Similarly to what was observed for NSCLC ALK-positive patients, ROS-1 positive NSCLC patients are typically young, non-smokers and with adenocarcinoma histology. More than half of the patients enrolled in study 1001 were female. Median age was 55 years; patients had baseline ECOG performance status of 0 or 1 (98%) or 2 (2%) and 75% were never smokers. The disease characteristics were 91% metastatic, 96% adenocarcinoma histology. Overall, 7 out of 53 (13.2%) ROS1-positive NSCLC patients previously untreated with systemic therapy for advanced disease received crizotinib in Study 1001.

The benefit observed in terms of ORR (69.8%, 95%CI: 55.7, 81.7) is outstanding and supported by a meaningful duration of response. Six out the 7 previously untreated patients achieved an objective response. Patients tended to respond early, with a median time to response of 7.9 weeks (i.e. the 1st tumour re-assessment) although some late responses (up to 32 weeks) were also observed.

These data favourably compare with response to prior therapy for the 46 patients with ROS1-positive NSCLC who received prior treatment for their advanced disease in study 1001. The ORR was 21.7% for prior first-line chemotherapy (29.4% with pemetrexed), 16.7% for prior second-line chemotherapy (30.8% with pemetrexed), and 23.7% for any line therapy with pemetrexed. Responses to prior treatment in patients with ROS1-positive NSCLC in Study 1001 were comparable to those reported for unselected NSCLC patients treated with standard therapy (9-35% across first-line and second-line treatments (Scagliotti et al, 2002; Schiller et al, 2002; Hanna et al, 2004; Herbst et al, 2004; Herbst et al, 2005; Sandler et al, 2006; Scagliotti et al, 2009).

At the time of the data cutoff, the median PFS was 19.3 months (95% CI: 14.8, NR) and although the median OS had not yet been reached, the probability of survival at 12 months was 79.0% (95% CI: 65.3, 87.8).

A statistical analysis was also provided in which TTP on crizotinib was compared with TTP on last prior therapy: the median TTP with crizotinib vs last prior therapy was 19.8 vs 8.1 months (HR=0.59, 95% CI: 0.31, 1.13). Although not statistically significant, there was a numerical decrease in the risk of progression with crizotinib compared with last prior therapy.

Subgroup analysis of clinical efficacy based on specific ROS1 rearrangements was not performed in Study 1001 because the FISH assay, used to detect rearrangements involving the ROS1 gene, does not identify specific ROS1 fusion partners. However, tumour responses and the duration of crizotinib treatment in patients with specific ROS1 fusion partners detected using alternative testing methods were evaluated (Shaw et al, N Engl J Med 2014). Targeted NGS or an RT-PCR assay was used to identify ROS1 fusion partners in available tumour samples from 25 of the 50 patients who were in the ROS1-positive NSCLC cohort. Seven different ROS1 fusion partners were identified. Tumour responses (based on the derived tumour assessment) appeared to be independent of the ROS1 fusion partner. There was also no apparent relationship between the duration of treatment and the specific ROS1 rearrangement for the 25 patients in whom ROS1 fusion partners were identified using an NGS or RT-PCR assay. No conclusion can be drawn regarding the relationship between ROS1 fusion partner and crizotinib activity.

To support the clinical efficacy of crizotinib in ROS1-positive NSCLC, published data from Investigator-Initiated Research studies were discussed by the MAH.

However, seemingly conflicting results have been published in terms of objective response to prior therapy for patients with ROS1-positive NSCLC. In the EUROS1 retrospective study (Mazieres et al, 2015), for the 26 patients who received pemetrexed-based chemotherapy, the ORR was 58% (not reported, calculated 95% CI: 37, 77). These results are difficult to interpret because patients received pemetrexed either alone or in combination with platinum agents and either before or after receiving crizotinib. Scheffler et al, 2015 reported that 9 out of 14 (64%) ROS1-positive patients had at least 1 radiological response to chemotherapy, with 4 out of 5 (80%, calculated- not reported in publication 95% CI: 28, 99) patients having radiological response to pemetrexed-containing regimens. These results are also difficult to interpret because the definition of radiological response was not specified in the latter publication, and the sample size is especially limited in this retrospective analysis.

Lower responses in terms of PFS were observed in the largest of these three trials compared to Study 1001.

Information regarding TTP/PFS with standard therapies is available from the literature only for the EUROS1 retrospective analysis in which median PFS with pemetrexed-based chemotherapy was 7.2 months (95% CI: 4.8 to 9.6 months) (Mazieres et al, 2015).

Data from previously untreated patients with ROS1-positive NSCLC in Study 1001 (7 patients) is considered limited. However there are significant parallels between ALK-fusion positive and ROS1-fusion positive NSCLC. ROS1 oncogene encodes an orphan RTK related to ALK, leukocyte RTK, and members of the insulin receptor family (Acquaviva et al, 2009). In both patient segments, genetic translocation events lead to gene fusions that result in deregulated expression of the respective kinase domain, ALK or ROS1, with consequent constitutive activation of the kinase activity (Soda et al, 2007; Rikova et al, 2007; Takeuchi et al, 2012). Collectively, these data indicate that the biology of ALK- and ROS1 fusions in NSCLC is in many ways analogous.

The antitumor activity in first line setting suggested in Study 1001 for ALK-positive NSCLC patients was subsequently corroborated by the results of a randomized Phase 3 study (crizotinib vs chemotherapy in previously untreated [Study 1014] patients with ALK-positive NSCLC) which clearly demonstrated that crizotinib provided statistically significant, robust, and clinically meaningful improvement in PFS and ORR in this patient population.

Thus, based on the pre-clinical and anti-tumour similarities between ALK-positive NSCLC and ROS1-positive NSCLC, there is no concern regarding the efficacy of crizotinib in the first line treatment of patients with ROS1-positive NSCLC.

2.4.4. Conclusions on the clinical efficacy

Available data are considered to sufficiently support the efficacy of crizotinib in ROS-1 NSCLC patients regardless of the line of treatment. Results from the cohort of 53 ROS1- positive NSCLC patients are included in section 5.1 of the SmPC.

2.5. Clinical safety

Introduction

The crizotinib safety profile reported across clinical studies in ALK-positive advanced NSCLC patients is mainly characterized by vision disorder, Gastrointestinal disorders (nausea, diarrhoea, vomiting, constipation), General disorders (oedema and fatigue), elevated transaminases, decreased appetite, dizziness, and neuropathy.

In this application, the safety analysis (SA) population includes 53 ROS1-positive NSCLC patients treated in the Study 1001 whose data were submitted to support the extension of indication in this target population.

A pooled safety analysis in a total of 1722 patients, including 1669 ALK-positive and 53 ROS1-positive advanced NSCLC, was presented to support the proposed changes of the Xalkori SmPC .

Patient exposure

At the time of the data cutoff date (30 November 2014), the median duration of crizotinib treatment was 23.2 months (95% CI: 15.0, NR), with 47.2% of patients still actively receiving crizotinib.

Overall, median relative dose intensity was 99.0% (range: 70.1% to 100.0%). In total, 28 patients had a dose interruption (any missed dose for more than 1 day in a cycle), that was at maximum of less than 1 week for 13 (46.4%) patients. In total, 7 (13.2%) patients had a dose reduction below 500 mg/day lasting more than 1 day.

In general, the baseline demographic characteristics of patients in the SA population of Study 1001 were consistent with those of the 1669 ALK+ positive NSCLC:

Table 27: Demographic and Other Characteristics

	ROS1-positive NSCLC (N=53)	**ALK-positive NSCLC (N=1669)**
Sex, n (%)		
• Male	23 (43.4)	717 (43.0)
• Female	30 (56.6)	952 (57.0)
Age, years		
• Mean (SD)	54.1 (13.44)	51.9 (12.47)
• Median (Range)	55.0 (25-81)	52.0 (19-86)
Age category, n (%)		
• <65 years	38 (71.7)	1404 (84.1)
• ≥65 years	15 (28.3)	265 (15.9)
Race, n (%)		
• White	30 (56.6)	853 (51.1)
• Black	2 (3.8)	28 (1.7)
• Asian	21 (39.6)	753 (45.1)

Smoking classification, n (%) • Never smoked • Ex-smoker	 40 (75.5) 13 (24.5)	

There were no ROS1-positive patients >85 years old in Study 1001.

Adverse events

Registered AEs were coded according to MedDRA version 17.1. A summary of reported AEs is shown in the following Table:

Table 28: Treatment-Emergent AEs (All-Causality and Treatment-Related, ROS1-Positive NSCLC) - Safety Analysis Population

	ROS1-positive NSCLC, 250 mg BID (N=53)	
	All-Causality n (%)	Treatment-Related n (%)
Number of patients:		
With AEs	53 (100)	52 (98.1)
With SAEs[a]	22 (41.5)	2 (3.8)
With Grade 3 or 4 AEs	28 (52.8)	16 (30.2)
With Grade 5 AEs	9 (17.0)	0
With AEs associated with:		
Permanent discontinuation[b]	4 (7.5)	1 (1.9)
Dose reduction	6 (11.3)	6 (11.3)
Temporary discontinuation	24 (45.3)	13 (24.5)

Source: Section 14.3, Tables 14.3.1.2.1.1.ros and 14.3.1.3.1.1.ros.
Patients are counted only once in each row.
Abbreviations: AE=adverse event; BID=twice daily; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer. SAE=serious adverse event.
a According to the investigator's assessment.
b AEs associated with permanent discontinuation are based on the Adverse Event case report form page; the AE may not be the patient's primary reason for discontinuation, as documented on the End of Treatment case report form and summarized in Section 14.1, Table 14.1.1.3.1.ros.

Because some frequency may have been underestimated by reliance on single Preferred Term (PT), certain PTs were analyzed in aggregate using clustered terms (presented in capital letters). Not all MedDRA preferred terms within each clustered term were actually reported in this study.

The most common all-causality and treatment-related AEs are listed in the following Table:

Table 29: Most Common (≥10%) Treatment-Emergent AEs by Decreasing Order of All-Causality Frequency (All-Causality and Treatment-Related, All Cycles, ROS1-Positive NSCLC) - Safety Analysis Population

MedDRA Preferred Term or Clustered Term	ROS1-positive NSCLC, 250 mg BID (N=53)	
	All-Causality n (%)	Treatment-Related n (%)
VISION DISORDER	46 (86.8)	45 (84.9)
Nausea	31 (58.5)	26 (49.1)
EDEMA	29 (54.7)	24 (45.3)
Vomiting	27 (50.9)	20 (37.7)
Diarrhoea	24 (45.3)	22 (41.5)
Constipation	23 (43.4)	18 (34.0)
DIZZINESS	21 (39.6)	10 (18.9)
UPPER RESPIRATORY INFECTION	21 (39.6)	0
ELEVATED TRANSAMINASES	19 (35.8)	16 (30.2)
Fatigue	17 (32.1)	10 (18.9)
NEUROPATHY	16 (30.2)	5 (9.4)
DYSPNOEA	15 (28.3)	1 (1.9)
Rash	14 (26.4)	7 (13.2)
BRADYCARDIA	14 (26.4)	11 (20.8)
Decreased appetite	13 (24.5)	6 (11.3)
Headache	13 (24.5)	0
ABDOMINAL PAIN	12 (22.6)	3 (5.7)
Dysgeusia	12 (22.6)	10 (18.9)
COUGH	11 (20.8)	0
Pyrexia	10 (18.9)	0
Disease progression	9 (17.0)	0
Hypophosphataemia	9 (17.0)	8 (15.1)
NEUTROPENIA	9 (17.0)	7 (13.2)
Arthralgia	8 (15.1)	0
Pneumonia	8 (15.1)	0
Back pain	7 (13.2)	0
PULMONARY EMBOLISM	7 (13.2)	0
Pain in extremity	7 (13.2)	0
Pruritus	7 (13.2)	3 (5.7)
BLOOD CREATININE INCREASED	6 (11.3)	2 (3.8)
CHEST PAIN	6 (11.3)	0
Dyspepsia	6 (11.3)	5 (9.4)
Fall	6 (11.3)	0
STOMATITIS	6 (11.3)	1 (1.9)
Wheezing	6 (11.3)	0

Source: Section 14.3, Tables 14.3.1.2.11.ros and 14.3.1.3.11.ros.
MedDRA version 17.1 coding dictionary applied.
Abbreviations: BID=twice daily; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer.

VISION DISORDER: PTs Chromatopsia; Diplopia; Halo Vision; Photophobia; Photopsia; Vision Blurred; Visual Acuity Reduced; Visual Brightness; Visual Field Defect; Visual Impairment; Vitreous Floaters.
EDEMA: PTs Face Oedema; Generalised Oedema; Local Swelling; Localised Oedema; Oedema; Periorbital Oedema; Oedema Peripheral.
DIZZINESS: PTs Balance disorder; Dizziness; Dizziness exertional; Dizziness postural; Presyncope.
UPPER RESPIRATORY INFECTION: PTs Laryngitis; Nasopharyngitis; Pharyngitis; Rhinitis; Upper respiratory tract infection.
ELEVATED TRANSAMINASES: PTs Alanine aminotransferase; Alanine aminotransferase abnormal; Alanine aminotransferase increased; Aspartate aminotransferase; Aspartate aminotransferase abnormal; Aspartate aminotransferase increased; Gamma-glutamyltransferase abnormal; Gamma-glutamyltransferase increased; Hepatic enzyme abnormal; Hepatic enzyme increased; Hepatic function abnormal; Hypertransaminasaemia; Liver function test abnormal; Transaminases; Transaminases abnormal; Transaminases increased.
NEUROPATHY: PTs Acute polyneuropathy; Amyotrophy; Areflexia; Autoimmune neuropathy; Autonomic failure syndrome; Autonomic neuropathy; Axonal neuropathy; Biopsy peripheral nerve abnormal; Burning feet syndrome; Burning sensation; Decreased vibratory sense; Demyelinating polyneuropathy; Dysaesthesia; Electromyogram abnormal; Formication; Gait disturbance; Genital hypoaesthesia; Guillain-Barre syndrome; Hyperaesthesia; Hypoaesthesia; Hyporeflexia; Hypotonia; Ischaemic neuropathy; Loss of proprioception; Miller Fisher syndrome; Mononeuritis; Mononeuropathy; Mononeuropathy multiplex; Motor dysfunction or Multifocal motor neuropathy; Muscle atrophy; Muscular weakness; Myelopathy; Nerve conduction studies abnormal; Nerve degeneration; Neuralgia; Neuritis; Neuromuscular toxicity; Neuromyopathy; Neuropathy peripheral; Neuropathy vitamin B6 deficiency; Neurotoxicity; Paraesthesia; Peripheral motor

neuropathy; Peripheral nerve lesion; Peripheral nerve palsy; Peripheral nervous system function test abnormal; Peripheral sensorimotor neuropathy; Peripheral sensory neuropathy; Peroneal muscular atrophy; Peroneal nerve palsy; Phrenic nerve paralysis; Polyneuropathy; Polyneuropathy chronic; Polyneuropathy idiopathic progressive; Radiation neuropathy; Sensorimotor disorder; Sensory disturbance; Sensory loss; Skin burning sensation; Temperature perception test decreased; Tinel's sign; Toxic neuropathy; Ulnar neuritis.
DYSPNOEA: PTs Dyspnoea; Dyspnoea at rest; Dyspnoea exertional; Dyspnoea paroxysmal Nocturnal; Nocturnal Dyspnoea; Orthopnoea.
BRADYCARDIA: PTs Bradyarrhythmia; Bradycardia; Heart rate decreased; Sinus arrest; Sinus bradycardia.
ABDOMINAL PAIN: PTs Abdominal Discomfort; Abdominal Pain; Abdominal Pain Upper; Abdominal Pain Lower; Abdominal Tenderness.
COUGH: PTs Cough; Productive cough.
NEUTROPENIA: PTs Febrile neutropenia; Neutropenia; Neutrophil count decreased.
PULMONARY EMBOLISM: PTs Pulmonary artery thrombosis; Pulmonary embolism; Pulmonary thrombosis.
BLOOD CREATININE INCREASED: PTs blood creatinine abnormal; blood creatinine increased; creatinine renal clearance abnormal; creatinine renal clearance decreased; glomerular filtration rate abnormal; glomerular filtration rate decreased.
CHEST PAIN: PTs Chest Pain; Chest Discomfort; Musculoskeletal Chest Pain; Non-Cardiac Chest Pain.
STOMATITIS: PTs Cheilitis; Glossitis; Glossodynia; Mouth Ulceration; Mucosal Inflammation; Oral Pain; Oropharyngeal Pain; Oropharyngeal Discomfort; Stomatitis.

Grade 3 and 4 All-Causality and Treatment-Related AEs

Table 30: Most Common (≥2%) Treatment-Emergent Grade 3 or 4 AEs in Decreasing Order of All-Causality Grade 3 Frequency (All-Causality and Treatment-Related, All Cycles, ROS1-Positive NSCLC) - Safety Analysis Population

MedDRA Preferred Term or Clustered Term	ROS1-positive NSCLC, 250 mg BID (N=53)			
	All-Causality		Treatment-Related	
	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hypophosphataemia	8 (15.1)	0	7 (13.2)	0
NEUTROPENIA	5 (9.4)	0	5 (9.4)	0
Headache	4 (7.5)	0	0	0
DYSPNOEA	3 (5.7)	0	0	0
Syncope	3 (5.7)	0	0	0
Vomiting	3 (5.7)	0	1 (1.9)	0
Electrocardiogram QT prolonged	2 (3.8)	0	1 (1.9)	0
ELEVATED TRANSAMINASES	2 (3.8)	0	2 (3.8)	0
Pneumonia	2 (3.8)	0	0	0
PULMONARY EMBOLISM	0	6 (11.3)	0	0

Source: Section 14.3, Tables 14.3.1.2.11.ros and 14.3.1.3.11.ros.
MedDRA version 17.1 coding dictionary applied.
Abbreviations: BID=twice daily; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer.

Adverse Events of Special Interest

Based on their clinical significance or frequency of observation in previous clinical studies, and potential attribution to crizotinib treatment, the following list of AEs of special interest was pre-defined:

Elevated transaminases	Hepatotoxicity	Interstitial lung disease
Electrocardiogram QT prolonged	Bradycardia	Vision disorder
Gastrointestinal events: constipation, diarrhoea, nausea, vomiting	Renal cyst	Oedema
Blood creatinine increased	Syncope	Abdominal pain*
Dizziness*	Dysgeusia*	Dyspnoea*
Hypokalaemia*	Leukopenia*	Neuropathy*
Neutropenia*	Pulmonary embolism*	Upper respiratory infection*

*upon further clinical review, these preferred terms or clustered terms were only included within the source tables and not further discussed by the applicant.

All AEs of special interest were analysed for time to first onset, duration, and prevalence, except for prevalence of Electrocardiogram QT prolonged since ECGs were only required for the first 2 cycles of crizotinib treatment.

Elevated transaminases and hepatotoxicity

All-causality elevated transaminases were reported for 19 (35.8%) patients, including 2 (3.8%) patients with Grade 3 event. No Grade 4 or 5 AEs were reported. There were no AEs of hepatotoxicity.

Treatment-related elevated transaminases events were reported for 16 (30.2%) patients, including 2 (3.8%) patients Grade 3. There were no SAEs treatment-related. The median time to first onset was 17.5 days (range: 7 to 442 days), with a median duration of 99 days (range: 7 to 1088 days). The prevalence of treatment-related elevated transaminases was highest during the Weeks 1 to 4 interval (17.0%) and then remained relatively constant during all subsequent 4-week intervals through Week 24 (10.9% to 15.4% of patients).

Based on laboratory measurements, shifts from Grade ≤2 to Grade 3/4 were seen for 3 (5.7%) patients for ALT and 2 (3.8%) patients for AST. Treatment-related elevated transaminases were associated with dose reduction for 2 (3.8%) patients, one of whom also had temporary treatment discontinuation. There was no permanent treatment discontinuation and no potential Hy's Law cases were identified.

Interstitial lung disease

All-causality event Grade 1 (not serious) was reported in 1 (1.9) patient. This event was considered treatment-related. Time to onset was 112 days, with a duration of 8 days. This event was associated with temporary treatment discontinuation for 7 days, but was not associated with dose reduction or permanent treatment discontinuation.

Across studies in patients with either ALK-positive or ROS1-positive NSCLC (N=1722), 50 (3%) patients treated with crizotinib had any grade all-causality ILD, including 18 (1%) patients with Grade 3 or 4, and 8 (<1%) patients with fatal cases. According to an independent review committee (IRC) assessment of patients with ALK-positive NSCLC (N=1669), 20 (1.2%) patients had ILD/pneumonitis, including 10 (<1%) patients with fatal cases. These cases generally occurred within 3 months after the initiation of treatment.

Electrocardiogram QT Prolonged

All-causality event was reported for 2 (3.8%) patients, both of which were Grade 3 in severity. One of these (1.9%) was considered treatment-related. Time to onset was 15 days and duration was 1 day. This event was associated with a dose reduction, but was not associated with temporary or permanent treatment discontinuation.

Across studies in patients with either ALK-positive or ROS1-positive advanced NSCLC, QTcF (corrected QT by the Fridericia method) ⩾500 msec was recorded in 34 (2.1%) of 1619 patients with at least 1 postbaseline ECG assessment and a maximum increase from baseline in QTcF ⩾60 msec was observed in 79 (5.0%) of 1585 patients with a baseline and at least 1 postbaseline ECG assessment. All-causality Grade 3 or 4 Electrocardiogram QT prolonged was reported in 27 (1.6%) out of 1722 patients (see sections 4.2, 4.4, 4.5 and 5.2 of the SmPC).

Bradycardia

All-causality event was reported for 14 (26.4%) patients, none of which were Grade ≥ 3 in severity. A Grade 2 all-causality AE was reported for 1 (1.9%) patient.

Treatment-related events were reported for 11 (20.8%) patients. One (1.9%) patient had a

treatment-related SAE (Grade 2) which was associated with temporary treatment discontinuation. The median time to first onset was 29.0 days (range: 15 to 929 days), with a median duration of 581 days (range: 5 to 1226 days). The prevalence of treatment-related bradycardia was lowest during the Weeks 1 to 4 interval (9.4%) and was slightly increased in the subsequent 4-week intervals through Week 24 (13.5% to 16.3%).

A minimum on-study pulse rate of <50 bpm was reported for 13/52 (25.0%) patients and a maximum decrease in pulse rate from baseline ≤30 bpm was reported for 19/52 (36.5%) patients. No patients had treatment-related bradycardia associated with dose reduction or permanent treatment discontinuation. There were no additional patients with temporary treatment discontinuation other than the SAE noted above.

Across all studies with crizotinib in patients with either ALK-positive or ROS1-positive advanced NSCLC, all-causality bradycardia was experienced by 219 (13%) of 1722 patients treated with crizotinib. Most events were mild in severity. A total of 259 (16%) of 1666 patients with at least 1 postbaseline vital sign assessment had a pulse rate <50 bpm.

Vision disorder

All-causality event was reported for 46 (86.8%) patients, none of which were Grade ≥ 3 in severity. A Grade 2 all-causality AE was reported for 1 (1.9%) patient.

Events were considered treatment-related for 45 (84.9%) patients, and in 44 of them events were Grade 1 in severity. No SAEs were registered. Of note, there were no AEs associated with severe visual loss. The median time to first onset was 8 days (range: 1 to 465 days), with a median duration was 297 days (range: 7 to 1486 days). The prevalence of treatment-related vision disorder was highest during the Weeks 1 to 4 interval (71.7%) and then gradually decreased over each 4-week interval through Week 24 (from 65.4% to 54.3% of patients).

Most patients did not have new findings/worsening of findings when ophthalmologic examinations were performed on-treatment; the most common (≥5%) new findings/worsening of findings were reported for biomicroscopic examination of the lens (15.1% of patients for both eyes), fundoscopic examination of the vitreous body (11.3% for both eyes), and fundoscopic examination of the fundus (5.3% for the left eye). There was no temporary treatment discontinuation, dose reduction, or permanent treatment discontinuation.

All-causality, all grade, vision disorder, most commonly visual impairment, photopsia, vision blurred, and vitreous floaters, was experienced by 1084 (63%) of 1722 patients treated with crizotinib. Of the 1084 patients who experienced vision disorder, 95% had events that were mild in severity (see SmPC section 4.8).

Gastrointestinal events

Gastrointestinal events, including Nausea, Vomiting, Diarrhoea, and Constipation, were among the most common all-causality and treatment-related AEs reported for patients with ROS1-positive NSCLC in Study 1001. The treatment-related AEs were primarily Grade 1 in severity.

- Nausea

All-causality event was reported for 31 (58.5%) patients, none of which were Grade 4 or 5 in severity. A Grade 3 all-causality AE was reported for 1 (1.9%) patient.

Treatment-related event was reported for 26 (49.1%) patients. There was no treatment-related Grade ≥ 3 events and SAEs. The median time to first onset was 2.5 days (range: 1 to 932 days), with a median duration of 87 days (range:1 to 1228 days). The prevalence of treatment-related Nausea was highest the Weeks 1 to 4 interval (39.6%) and decreased over the subsequent three 4-week interval through Week 16

(to 18.8% of patients) and remained constant for the next two 4-week intervals through Week 24 (19.6% of patients). There was no temporary treatment discontinuation or crizotinib dose reduction. In 1 (1.9%) patient the treatment-related Nausea (Grade 2) was associated with permanent treatment discontinuation.

- Diarrhoea

All-causality event was reported for 24 (45.3%) patients, none of which were Grade 4 or 5 in severity. A Grade 3 all-causality AE of Diarrhoea was reported for 1 (1.9%) patient.

Treatment-related event was reported for 22 (41.5%) patients. There were no Grade ≥ 3 events and no SAEs. The median time to first onset was 15 days (range: 1 to 145 days), with a median duration of 361 days (range: 40 to 1237 days). The prevalence remained relatively constant over the 4-week intervals through Week 24 (27.1% to 32.7% of patients). Treatment-related Diarrhoea was associated with temporary treatment discontinuation in 1 (1.9%) patient (Section 14.3, Table 14.3.1.1.3.3.ros).

- Vomiting

All-causality event was reported for 27 (50.9%) patients. There were no Grade 4 or 5 events. A Grade 3 all-causality AE of Vomiting was reported for 3 (5.7%) patients

Treatment-related events, including 1 (1.9%) Grade 3, were reported for 20 (37.7%) patients. No SAEs were reported. The median time to first onset was 8 days (range: 1 to 490 days), with a median duration of 37 days (range: 1 to 814 days). The prevalence of the event was highest during the Weeks 1 to 4 interval (20.8%) and remained relatively constant during the subsequent 4-week intervals through Week 24 (10.4% to 15.2%). Treatment-related Vomiting was associated with temporary treatment discontinuation for 3 (5.7%) patients.

- Constipation

All-causality event was reported for 23 (43.4%) patients, none of which Grade ≥3. A Grade 2 all- Causality AE of Constipation was reported for 4 (7.5%) patients.

Treatment-related event was reported for 18 (34.0%) patients. No SAEs were reported. The median time to first onset was 10.5 days (range: 1 to 407 days), with a median duration of 404 days (range: 29 to 1240 days). The prevalence of event remained relatively constant across the 4-week intervals through Week 24 (22.6% to 28.6% of patients). No patients had treatment-related Constipation associated with temporary treatment discontinuation, dose reduction, or permanent treatment discontinuation.

Renal cyst

All-causality event was reported for 2 (3.8%) patients, both Grade 1 in severity.

Treatment-related event was reported for 1 (1.9%) patient. Time to onset was 490 days and duration was 245 days. This event was not associated with temporary treatment discontinuation, dose reduction, or permanent treatment discontinuation.

Oedema

All-causality event was reported for 29 (54.7%) patients, none of which were Grade ≥ 3 in severity. Grade 2 all-causality AEs were reported for 9 (17.0%) patients.

Treatment-related event was reported for 24 (45.3%) patients. No SAEs were reported. The median time to first onset was 55 days (range: 7 to 644 days), with a median duration of 601 days (range: 57 to 1308 days). The prevalence of the event was lowest during the Weeks 1 to 4 interval (13.2%) and gradually increased over each 4-week interval through Week 24 (to 30.4% of patients at the Week 21 to 24 interval). Treatment-related EDEMA was associated with temporary treatment discontinuation in 1 (1.9%) patient.

Blood creatinine increased

All-causality event was reported for 6 (11.3%) patients, none of which were Grade ≥ 3 in severity. A Grade 2 all-causality AE was reported for 1 (1.9%) patient.

Treatment-related event was reported for 2 (3.8%) patients, 1 Grade 1 and 1 Grade 2. No SAEs were reported. The median time to first onset was 134 days (range: 15 to 253 days), with a median duration of 50 days (range: 29 to 71 days). Based on laboratory measurements, no patients had a shift from Grade ≤2 to Grade 3/4 for creatinine.

Syncope

All-causality event was reported for 3 (5.7%) patients, all of which were Grade 3 in severity. None of them was considered treatment-related.

Table 31: Time to First Onset of Treatment-Emergent AE of Special Interest (Treatment-Related, All Cycles, ROS1-Positive NSCLC) - Safety Analysis Population

MedDRA Preferred Term or Clustered Term	ROS1-positive NSCLC, 250 mg BID (N=53)			
	Time to First Onset (Days)			
	n	Mean (SD)	Median	Range
BLOOD CREATININE INCREASED	2	134.0 (168.29)	134.0	15-253
BRADYCARDIA	11	184.4 (302.50)	29.0	15-929
Constipation	18	39.3 (93.65)	10.5	1-407
Diarrhoea	22	31.5 (44.96)	15.0	1-145
EDEMA	24	130.1 (176.31)	55.0	7-644
Electrocardiogram QT prolonged	1	15.0 (NA)	15.0	15-15
ELEVATED TRANSAMINASES	16	81.0 (133.30)	17.5	7-442
INTERSTITIAL LUNG DISEASE	1	112.0 (NA)	112.0	112-112
Nausea	26	56.0 (184.41)	2.5	1-932
RENAL CYST	1	490.0 (NA)	490.0	490-490
VISION DISORDER	45	30.8 (93.05)	8.0	1-465
Vomiting	20	77.2 (128.34)	8.0	1-490

Source: Section 14.3, Table 14.3.1.6.3.2.ros and Appendix 16.2, Table 16.2.7.1.ros.
Time to first onset = (AE start date - first dose date + 1). First dose date is the Cycle 1 Day 1 dose. Descriptive statistics are presented for patients who had the AE.
MedDRA version 17.1 coding dictionary applied.
Abbreviations: AE=adverse event; BID=twice daily; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with data; N=total number of patients in population; NA=not applicable; NSCLC=non-small cell lung cancer; SD=standard deviation.

Table 32: Duration of Treatment-Emergent AEs of Special Interest (Treatment-Related, All Cycles, ROS1-Positive NSCLC) - Safety Analysis Population

MedDRA Preferred Term or Clustered Term	ROS1-positive NSCLC, 250 mg BID (N=53)			
	Duration (Days)[a]			
	n	Mean (SD)	Median	Range
BLOOD CREATININE INCREASED	2	50.0 (29.70)	50.0	29-71
BRADYCARDIA	11	546.6 (468.73)	581.0	5-1226
Constipation	18	435.1 (334.69)	404.0	29-1240
Diarrhoea	22	405.8 (336.33)	360.5	40-1237
EDEMA	24	627.2 (348.31)	601.0	57-1308
Electrocardiogram QT prolonged	1	1.0 (NA)	1.0	1-1
ELEVATED TRANSAMINASES	16	252.6 (310.14)	99.0	7-1088
INTERSTITIAL LUNG DISEASE	1	8.0 (NA)	8.0	8-8
Nausea	26	258.5 (331.45)	87.0	1-1228
RENAL CYST	1	245.0 (NA)	245.0	245-245
VISION DISORDER	45	425.5 (402.14)	297.0	7-1486
Vomiting	20	130.3 (205.48)	37.0	1-814

Source: Section 14.3, Table 14.3.1.6.2.2.ros and Appendix 16.2, Table 16.2.7.1.ros.
MedDRA version 17.1 coding dictionary applied.
Abbreviations: AE=adverse event; BID=twice daily; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with data; N=total number of patients in population; NA=not applicable; NSCLC=non-small cell lung cancer; SD=standard deviation.
a Duration = (AE end date - AE start date + 1) per episode. If a patient had multiple episodes of an AE, cumulative duration across all episodes was used adjusting for any overlap. If a patient had an AE that was ongoing at the time of analysis, the time was censored at the last available on-treatment visit date.

Table 33: Prevalence of Treatment-Emergent AEs of Special Interest by Weeks (Treatment-Related, All Cycles, ROS1-Positive NSCLC) - Safety Analysis Population

MedDRA Preferred Term or Clustered Term	ROS1-positive NSCLC, 250 mg BID					
	Weeks 1-4 (N=53) n (%)	Weeks 5-8 (N=52) n (%)	Weeks 9-12 (N=49) n (%)	Weeks 13-16 (N=48) n (%)	Weeks 17-20 (N=46) n (%)	Weeks 21-24 (N=46) n (%)
BLOOD CREATININE INCREASED	1 (1.9)	1 (1.9)	1 (2.0)	1 (2.1)	0	0
BRADYCARDIA	5 (9.4)	7 (13.5)	8 (16.3)	7 (14.6)	7 (15.2)	7 (15.2)
Constipation	12 (22.6)	14 (26.9)	14 (28.6)	13 (27.1)	12 (26.1)	12 (26.1)
Diarrhoea	16 (30.2)	16 (30.8)	16 (32.7)	13 (27.1)	14 (30.4)	15 (32.6)
EDEMA	7 (13.2)	9 (17.3)	11 (22.4)	11 (22.9)	12 (26.1)	14 (30.4)
ELEVATED TRANSAMINASES	9 (17.0)	8 (15.4)	6 (12.2)	6 (12.5)	5 (10.9)	5 (10.9)
Nausea	21 (39.6)	16 (30.8)	11 (22.4)	9 (18.8)	9 (19.6)	9 (19.6)
VISION DISORDER	38 (71.7)	34 (65.4)	31 (63.3)	30 (62.5)	27 (58.7)	25 (54.3)
Vomiting	11 (20.8)	6 (11.5)	7 (14.3)	5 (10.4)	7 (15.2)	5 (10.9)

Source: Section 14.3, Tables 14.3.1.8.1.1.ros, 14.3.1.8.1.2.ros, 14.3.1.8.1.3.ros, 14.3.1.8.1.4.ros, 14.3.1.8.1.5.ros, and 14.3.1.8.1.6.ros.
MedDRA version 17.1 coding dictionary applied.
AE prevalence was defined as the number of patients with an AE in a particular time period (including both new cases with an onset date during the specified time period AND cases with an AE continued from a previous time period) divided by the number of patients at risk during the specified time period.
Abbreviations: AE=adverse event; BID=twice daily; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with data; N=total number of patients in population actively receiving treatment at the beginning of the reporting interval; NSCLC=non-small cell lung cancer.

Adverse Drug Reactions (ADRs)

Table 34: Crizotinib ADRs by SOC and Severity Frequency of All-Causality AEs in Patients with ROS1-Positive NSCLC in Study 1001 - Safety Analysis Population

SOC Adverse Reaction	Frequency[a]	Number (%) of Patients Crizotinib (N=53) All Grades	 Grade 3[b]
Blood and Lymphatic System Disorders			
Neutropenia[c]	Very Common	9 (17.0)	5 (9.4)
Leukopenia[c]	Common	3 (5.7)	0
Metabolism and Nutritional Disorders			
Decreased appetite	Very Common	13 (24.5)	1 (1.9)
Nervous System Disorders			
Dysgeusia	Very Common	12 (22.6)	0
Neuropathy[c]	Very Common	16 (30.2)	0
Dizziness[c]	Very Common	21 (39.6)	0
Eye Disorders			
Vision Disorder[c]	Very Common	46 (86.8)	0
Cardiac Disorders			
Bradycardia[c]	Very Common	14 (26.4)	0
Electrocardiogram QT prolonged	Common	2 (3.8)	2 (3.8)
Syncope	Common	3 (5.7)	3 (5.7)
Respiratory, Thoracic and Mediastinal Disorders			
Interstitial Lung Disease[c]	Common	1 (1.9)	0
Gastrointestinal Disorders			
Diarrhoea	Very Common	24 (45.3)	1 (1.9)
Nausea	Very Common	31 (58.5)	1 (1.9)
Vomiting	Very Common	27 (50.9)	3 (5.7)
Constipation	Very Common	23 (43.4)	0
Dyspepsia	Very Common	6 (11.3)	0
Hepatobiliary Disorders			
Elevated Transaminases[c]	Very Common	19 (35.8)	2 (3.8)
Blood alkaline phosphatase increased	Common	2 (3.8)	0
Hepatic failure	NA[e]	0	0
Skin and Subcutaneous Tissue Disorders			
Rash	Very Common	14 (26.4)	0
Renal and Urinary Disorders			
Renal Cyst[c]	Common	2 (3.8)	0
Blood creatinine increased[c,d]	Very common	6 (11.3)	0
General Disorders and Administration Site Conditions			
Edema[c]	Very Common	29 (54.7)	0
Fatigue	Very Common	17 (32.1)	0

Source: Study 1001 ROS1 CSR, Tables 14.3.1.2.11.ros and Table 14.3.1.2.10.ros
CTCAE v3.0 was used and MedDRA (v17.1) coding dictionary applied.
Abbreviations: ADR=adverse drug reaction; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; NA=not applicable; NSCLC=non-small cell lung cancer; SOC=System Organ Class; v=version.

a. Frequencies are provided for events of all grades and defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), or very rare (<1/10,000).
b. There were no Grade 4 events.
c. Includes Preferred Terms reported within the clustered terms.
d. Blood creatinine increased was added to the ADR list after the Study 1014 supplemental submission.
e. There were no cases of Hepatic failure among patients with ROS1-positive NSCLC in Study 1001; across clinical trials with crizotinib, Hepatic failure was uncommonly (<1%) observed.

Table 35: Crizotinib Adverse Drug Reactions (All-Causality Events by Decreasing Frequency in Patients with ROS1-Positive NSCLC) by Patient Population

Number of Patients (%)	ROS1-Positive NSCLC N=53		ALK-Positive NSCLC N=1669	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Vision Disorder[a]	46 (86.8)	0	1038 (62.2)	6 (0.4)
Nausea	31 (58.5)	1 (1.9)	943 (56.5)	37 (2.2)
Edema[a]	29 (54.7)	0	814 (48.8)	36 (2.2)
Vomiting	27 (50.9)	3 (5.7)	847 (50.7)	31 (1.9)
Diarrhoea	24 (45.3)	1 (1.9)	906 (54.3)	20 (1.2)
Constipation	23 (43.4)	0	720 (43.1)	15 (0.9)
Dizziness[a]	21 (39.6)	0	421 (25.2)	9 (0.5)
Elevated Transaminases[a]	19 (35.8)	2 (3.8)	534 (32.0)	176 (10.5)
Fatigue	17 (32.1)	0	497 (29.8)	56 (3.4)
Neuropathy[a]	16 (30.2)	0	419 (25.1)	22 (1.3)
Bradycardia[a]	14 (26.4)	0	205 (12.3)	7 (0.4)
Rash	14 (26.4)	0	213 (12.8)	5 (0.3)
Decreased appetite	13 (24.5)	1 (1.9)	498 (29.8)	29 (1.7)
Dysgeusia	12 (22.6)	0	352 (21.1)	0
Neutropenia[a]	9 (17.0)	5 (9.4)	365 (21.9)	207 (12.4)
Dyspepsia	6 (11.3)	0	137 (8.2)	0
Blood creatinine increased[a, b]	6 (11.3)	0	132 (7.9)	4 (0.2)
Leukopenia[a]	3 (5.7)	0	247 (14.8)	48 (2.9)
Syncope	3 (5.7)	3 (5.7)	41 (2.5)	39 (2.3)
Electrocardiogram QT prolonged	2 (3.8)	2 (3.8)	62 (3.7)	25 (1.5)
Blood alkaline phosphatase increased	2 (3.8)	0	110 (6.6)	16 (1.0)
Renal Cyst[a]	2 (3.8)	0	50 (3.0)	10 (0.6)
Interstitial Lung Disease[a]	1 (1.9)	0	49 (2.9)	18 (1.1)
Hepatic failure	0	0	5 (0.3)	4 (0.2)

Source: Study 1001 ROS1 CSR Appendix 1 Tables 14.3.1.2.11.1 and 14.3.1.3.9.1.1.
Data presented for patients with ROS1-positive NSCLC: CTCAE v3.0 was used and MedDRA (v17.1) coding dictionary was applied. Data presented for patients with ALK-positive NSCLC: CTCAE v4.0 was used and MedDRA (v16.1) coding dictionary applied. Data cutoff dates were 30 Nov 2014 and 30 Nov 2013 for patients with ROS1-positive NSCLC and patients with ALK-positive NSCLC, respectively.
ALK-positive NSCLC includes Studies 1014 (crizotinib only, including patients crossed over to crizotinib), 1007 (crizotinib only), 1005, and 1001 (RP2D, ALK-positive NSCLC).
Abbreviations: ADR=adverse drug reaction; ALK=anaplastic lymphoma kinase; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; NSCLC=non-small cell lung cancer; RP2D=recommended Phase 2 dose; v=version.
a. Includes Preferred Terms reported within the clustered terms.
b. Blood creatinine was added to the ADR list after the Study 1014 supplemental submission.

Serious adverse event / deaths / other significant events

All-causality SAEs were reported in 22 (41.5%) patients, and the most common (≥ 2 patients) events were, in decreasing order, Disease Progression (9 patients, 19%), Pneumonia (3 patients, 5.7%), Headache (2 patients, 3.8%) and Nausea (2 patients, 3.8%).

Treatment-related SAEs were bradycardia and Gastrointestinal amyloidosis, each reported in 1 (1.9%) patient.

Regarding the Gastrointestinal amyloidosis SAE, the condition may have been present prior to treatment start. The symptoms were resolved by supportive therapy and did not recur after crizotinib was re-administered. The investigator assessed the causality between the event and crizotinib as 'unknown'. The MAH considers there is no sufficient evidence to suggest a causal relationship between crizotinib and Gastrointestinal amyloidosis in this patient.

Deaths

At the data cut-off date, 16 deaths were reported, including 7 patients who died 28 days after the last crizotinib dose.

Table 36: Deaths in Patients with ROS1-Positive NSCLC in Study 1001 - Safety Analysis Population

	Crizotinib (N=53) n (%)
Deaths from all causes:	16 (30.2)
Within 28 days of last dose of study drug	9 (17.0)
More than 28 days after last dose of study drug	7 (13.2)
Cause of death[a]:	
Disease under study	15 (28.3)
Unknown[b]	1 (1.9)

Source: Study 1001 ROS1 CSR Table 14.3.2.1.2.2.ros.
Summary of death data are based on the 'Patient Survival' case report form.
Abbreviations: n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer.
a More than 1 cause of death may be reported.
b Unknown cause of death includes Not reported. Patient 10021130 died more than 8 months after their last dose of crizotinib (Study 1001 ROS1 CSR, Tables 16.2.5.1.4.ros and 16.2.6.10.ros).

All the 9 deaths occurred within 28 days of last treatment dose were due to disease under study. No death was considered related to crizotinib by either the investigator or the MAH.

Laboratory findings

Haematology

Shifts from Grade ≤2 to Grade 3/4 were observed for absolute neutrophils (9.4% of patients), absolute lymphocytes (7.5%), and white blood cells (1.9%).

Table 37: Shift Table of Haematology Laboratory Results From Grade ≤2 to Grade 3/4 (All Cycles, ROS1-Positive NSCLC) - Safety Analysis Population

	ROS1-positive NSCLC, 250 mg BID (N=53)	
Patients with shift from Grade ≤2 at Baseline to Grade 3/4:	**N***	**n (%)**
Hemoglobin	53	0
Lymphocytes (absolute)	53	4 (7.5)
Neutrophils (absolute)	53	5 (9.4)
Platelets	53	0
White blood cells	53	1 (1.9)

Source: Section 14.3, Table 14.3.4.1.5.6.4.ros.
CTCAE version 3.0 criteria have been used.
Abbreviations: BID=twice daily; CTCAE=Common Terminology Criteria for Adverse Events; n=number of patients whose laboratory results met the CTCAE grade criteria; N=total number of patients in population; N*=number of patients with at least 1 postbaseline value; NSCLC=non-small cell lung cancer.

Across studies in patients with either ALK-positive or ROS1-positive advanced NSCLC (N=1722), Grade 3 or 4 neutropenia was observed in 212 (12%) patients treated with crizotinib. Median time to onset of any grade neutropenia was 89 days. Neutropenia was associated with dose reduction or permanent treatment discontinuation for 3% and <1% of patients, respectively (see section 4.8 of the SmPC).

Chemistry

The most common (≥2% of patients) shifts from Grade ≤2 to Grade 3/4 were observed for hypophosphatemia (15.1% of patients), ALT (5.7%), AST (3.8%), and hyponatremia (3.8%).

Table 38: Shift Table of Clinical Chemistry Laboratory Results From Grade ≤2 to Grade 3/4 (All Cycles, ROS1-Positive NSCLC) - Safety Analysis Population

	ROS1-positive NSCLC, 250 mg BID (N=53)	
Patients with shift from Grade ≤2 at Baseline to Grade 3/4:	**N***	**n (%)**
Alanine aminotransferase (ALT)	53	3 (5.7)
Alkaline phosphatase	53	0
Aspartate aminotransferase (AST)	53	2 (3.8)
Bicarbonate	53	0
Bilirubin (total)	53	0
Creatinine	53	0
Hypercalcemia	53	0
Hyperglycemia	53	1 (1.9)
Hyperkalemia	53	1 (1.9)
Hypernatremia	53	0
Hypoalbuminemia	53	1 (1.9)
Hypocalcemia	53	1 (1.9)
Hypoglycemia	53	1 (1.9)
Hypokalemia	53	0
Hyponatremia	53	2 (3.8)
Hypophosphatemia	53	8 (15.1)

Source: Section 14.3, Table 14.3.4.1.6.6.4.ros.
CTCAE version 3.0 criteria have been used.
Abbreviations: BID=twice daily; CTCAE=Common Terminology Criteria for Adverse Events; n=number of patients whose laboratory results met the CTCAE grade criteria; N=total number of patients in population; N*=number of patients with at least 1 postbaseline value; NSCLC=non-small cell lung cancer.

Safety in special populations

Age

Table 39: Most Common (≥10%) Treatment-Emergent AEs By Age Group in Decreasing Order of Frequency For <65 Years Group (Treatment-Related, All Cycles, ROS1-Positive NSCLC) - Safety Analysis Population

MedDRA Preferred Term or Clustered Term	ROS1-positive NSCLC, 250 mg BID					
	<65 years (N=38)			≥65 years (N=15)		
	Total n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	Grade 3 n (%)	Grade 4 n (%)
VISION DISORDER	33 (86.8)	0	0	12 (80.0)	0	0
Diarrhoea	19 (50.0)	0	0	3 (20.0)	0	0
EDEMA	19 (50.0)	0	0	5 (33.3)	0	0
Nausea	16 (42.1)	0	0	10 (66.7)	0	0
Vomiting	16 (42.1)	1 (2.6)	0	4 (26.7)	0	0
ELEVATED TRANSAMINASES	14 (36.8)	2 (5.3)	0	2 (13.3)	0	0
Constipation	12 (31.6)	0	0	6 (40.0)	0	0
BRADYCARDIA	7 (18.4)	0	0	4 (26.7)	0	0
DIZZINESS	7 (18.4)	0	0	3 (20.0)	0	0
Fatigue	7 (18.4)	0	0	3 (20.0)	0	0
Hypophosphataemia	7 (18.4)	6 (15.8)	0	1 (6.7)	1 (6.7)	0
NEUTROPENIA	7 (18.4)	5 (13.2)	0	0	0	0
Dysgeusia	5 (13.2)	0	0	5 (33.3)	0	0
NEUROPATHY	5 (13.2)	0	0	0	0	0
Rash	5 (13.2)	0	0	2 (13.3)	0	0
Decreased appetite	4 (10.5)	1 (2.6)	0	2 (13.3)	0	0
Dyspepsia	2 (5.3)	0	0	3 (20.0)	0	0
Weight increased	1 (2.6)	0	0	2 (13.3)	0	0

Source: Section 14.3, Table 14.3.1.4.1.2.ros.
MedDRA version 17.1 coding dictionary applied.
Abbreviations: BID=twice daily; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer.

Gender

Table 40: Most Common (≥10%) Treatment-Emergent AEs By Gender in Decreasing Order of Frequency For Male Group (Treatment-Related, All Cycles, ROS1-Positive NSCLC) - Safety Analysis Population

MedDRA Preferred Term or Clustered Term	ROS1-positive NSCLC, 250 mg BID					
	Male (N=23)			Female (N=30)		
	Total n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	Grade 3 n (%)	Grade 4 n (%)
VISION DISORDER	19 (82.6)	0	0	26 (86.7)	0	0
Diarrhoea	11 (47.8)	0	0	11 (36.7)	0	0
EDEMA	9 (39.1)	0	0	15 (50.0)	0	0
Nausea	9 (39.1)	0	0	17 (56.7)	0	0
ELEVATED TRANSAMINASES	8 (34.8)	1 (4.3)	0	8 (26.7)	1 (3.3)	0
Constipation	7 (30.4)	0	0	11 (36.7)	0	0
Fatigue	6 (26.1)	0	0	4 (13.3)	0	0
Hypophosphataemia	6 (26.1)	5 (21.7)	0	2 (6.7)	2 (6.7)	0
Vomiting	5 (21.7)	0	0	15 (50.0)	1 (3.3)	0
BRADYCARDIA	4 (17.4)	0	0	7 (23.3)	0	0
Dysgeusia	4 (17.4)	0	0	6 (20.0)	0	0
HYPOGONADISM	3 (13.0)	0	0	0	0	0
Rash	3 (13.0)	0	0	4 (13.3)	0	0
DIZZINESS	2 (8.7)	0	0	8 (26.7)	0	0
NEUROPATHY	2 (8.7)	0	0	3 (10.0)	0	0
Dyspepsia	1 (4.3)	0	0	4 (13.3)	0	0
NEUTROPENIA	0	0	0	7 (23.3)	5 (16.7)	0
Decreased appetite	0	0	0	6 (20.0)	1 (3.3)	0
Pruritus	0	0	0	3 (10.0)	0	0

Source: Section 14.3, Table 14.3.1.4.3.2.ros.
MedDRA version 17.1 coding dictionary applied.
Abbreviations: BID=twice daily; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer.

Race

Table 41: Most Common (≥10%) Treatment-Emergent AEs By Race Group in Decreasing Order of Frequency For Asian Group (Treatment-Related, All Cycles, ROS1-Positive NSCLC) - Safety Analysis Population

MedDRA Preferred Term or Clustered Term	ROS1-positive NSCLC, 250 mg BID					
	Asian (N=21)			Non-Asian (N=32)		
	Total n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	Grade 3 n (%)	Grade 4 n (%)
VISION DISORDER	19 (90.5)	0	0	26 (81.3)	0	0
Nausea	16 (76.2)	0	0	10 (31.3)	0	0
Vomiting	13 (61.9)	1 (4.8)	0	7 (21.9)	0	0
Constipation	12 (57.1)	0	0	6 (18.8)	0	0
Diarrhoea	12 (57.1)	0	0	10 (31.3)	0	0
EDEMA	10 (47.6)	0	0	14 (43.8)	0	0
DIZZINESS	8 (38.1)	0	0	2 (6.3)	0	0
ELEVATED TRANSAMINASES	6 (28.6)	1 (4.8)	0	10 (31.3)	1 (3.1)	0
NEUTROPENIA	6 (28.6)	5 (23.8)	0	1 (3.1)	0	0
Decreased appetite	5 (23.8)	1 (4.8)	0	1 (3.1)	0	0
Dysgeusia	4 (19.0)	0	0	6 (18.8)	0	0
Rash	4 (19.0)	0	0	3 (9.4)	0	0
BRADYCARDIA	3 (14.3)	0	0	8 (25.0)	0	0
Fatigue	3 (14.3)	0	0	7 (21.9)	0	0
NEUROPATHY	3 (14.3)	0	0	2 (6.3)	0	0
Pruritus	3 (14.3)	0	0	0	0	0
Hypophosphataemia	2 (9.5)	2 (9.5)	0	6 (18.8)	5 (15.6)	0

Source: Section 14.3, Table 14.3.1.4.2.2.ros.
MedDRA version 17.1 coding dictionary applied.
Abbreviations: BID=twice daily; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer.

Discontinuation due to adverse events

All-causality AEs associated with permanent treatment discontinuation were Disease progression (2 patients, 3.8%), Nausea (1 patient, 1.9%) and Pericardial effusion (1 patient, 1.9%). Among these events, the only considered treatment-related was Nausea.

All-causality SAEs leading to permanent crizotinib discontinuation were Disease progression (2 patients, 3.8%) and Pericardial effusion (1 patient, 1.9%). None of these was considered treatment-related.

A temporary treatment discontinuation was requested in 24 (45.3%) patients due to all-causality AEs, and in 13 (24.5%) patients due to treatment-related AEs.

Table 42: Most Common (≥2%) Treatment-Emergent AEs Associated With Temporary Treatment Discontinuation (All-Causality and Treatment-Related) Patients with ROS1-Positive NSCLC in Study 1001 - Safety Analysis Population

MedDRA Preferred Term or Clustered Term	Crizotinib (N=53) n (%)	
	All-Causality n (%)	Treatment-Related n (%)
Vomiting	5 (9.4)	3 (5.7)
NEUTROPENIA	4 (7.5)	4 (7.5)
Nausea	3 (5.7)	0
Cataract	2 (3.8)	0
Decreased appetite	2 (3.8)	1 (1.9)
Diarrhoea	2 (3.8)	1 (1.9)
ELEVATED TRANSAMINASES	2 (3.8)	1 (1.9)
Headache	2 (3.8)	0
Hypoxia	2 (3.8)	0
Pneumonia	2 (3.8)	0

Source: Study 1001 ROS1 CSR, Tables 14.3.1.1.3.2.ros and 14.3.1.1.3.3.ros.
MedDRA version 17.1 coding dictionary applied.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer.

In 6 (11.3%) patients the crizotinib dose was reduced due to AEs:

Table 43: Treatment-Emergent AEs Associated With Dose Reduction (All-Causality and Treatment-Related) Patients with ROS1-Positive NSCLC in Study 1001 - Safety Analysis Population

MedDRA Preferred Term or Clustered Term	Crizotinib (N=53) n (%)	
	All-Causality n (%)	Treatment-Related n (%)
ELEVATED TRANSAMINASES	2 (3.8)	2 (3.8)
CHEST PAIN	1 (1.9)	0
Decreased appetite	1 (1.9)	1 (1.9)
Electrocardiogram QT prolonged	1 (1.9)	1 (1.9)
Fatigue	1 (1.9)	1 (1.9)
NEUTROPENIA	1 (1.9)	1 (1.9)
VIth nerve paralysis	1 (1.9)	1 (1.9)

Source: Study 1001 ROS1 CSR, Tables 14.3.1.1.3.4.ros and 14.3.1.1.3.5.ros.
MedDRA version 17.1 coding dictionary applied.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer.

Post marketing experience

No post-marketing data in ROS1-positive NSCLC patients have been submitted (crizotinib received the FDA approval after the submission of this extension of indication application).

Based on the most recent PSUR (#7), cumulatively through 25 August 2015, it is estimated that 2835 patients participated in the crizotinib clinical development program, including 2151 that were exposed to crizotinib as a single agent, 139 treated with crizotinib as part of a combination or crossover regimen, 205 that received blinded-therapy, and 340 that received active comparator drugs. It is estimated from post marketing experience that 18,689 patients have received crizotinib.

Signals reviewed for crizotinib during the reporting interval included cardiac failure and renal toxicity. A retrospective investigation of the possible effect of crizotinib on renal function was completed and based on this review, it was determined that blood creatinine increased is an ADR of crizotinib. After the database for this PSUR was locked, cardiac failure was added as an ADR and as an important identified risk for crizotinib in the EU as per PRAC request.

Important identified risks for crizotinib at the beginning of the reporting period were hepatotoxicity, pneumonitis/interstitial lung disease, QTc prolongation, bradycardia, vision disorder, oedema, leukopenia, neuropathy, renal cyst, and gastrointestinal perforation. Gastrointestinal perforation is considered an important identified risk in the EU.

Important potential risks were reproductive toxicity, photosensitivity, and malignant melanoma.

2.5.1. Discussion on clinical safety

The crizotinib safety profile in the ROS1-positive NSCLC population is based on data from the 53 patients treated in Study 1001. Most of these patients (67.9%) received crizotinib for longer than 12 months, and the median treatment duration was 23.2 months (95% CI: 15.0, NR), with approximately half of patients (47.2%) still on treatment at the data cut-off date (30 November 2014).

Overall, similar baseline demographic characteristics in terms of gender, age and smoking behaviour were observed in patients with ROS1-positive or ALK-positive NSCLC.

No new safety concerns were raised by data from these additional 53 patients. The known crizotinib safety profile, mainly characterized by Vision disorder, Gastrointestinal disorders (nausea, diarrhoea, vomiting, constipation), and General disorders (oedema and fatigue) was confirmed in ROS1-positive patients.

Hypophosphataemia and Neutropaenia were the most common Grade 3 treatment-related AEs (13.2% and 9.4%, respectively). No Grade 4 treatment-related AEs as well as death considered related to crizotinib treatment were registered. Treatment-related SAEs were bradycardia and gastrointestinal amyloidosis, each reported by 1 (1.9%) patient.

Toxicities experienced by ROS1-positive NSCLC patients were mostly manageable by short (<1 week) dose interruption and crizotinib dose reduction. Only in one patient treatment was permanently discontinued due to drug-related AE.

In ROS1-positive NSCLC patients, some crizotinib ADRs, such as Vision disorder, Dizziness, Bradycardia and Rash, were observed at an increased frequency with a difference of ≥10% in comparison to ALK-positive NSCLC patients. However, the limited number of the ROS1-positive subgroup does not allow to draw any meaningful conclusion.

Some differences in frequencies of individual ADRs are observed between the ROS1-positive and ALK-positive NSCLC populations. Of note, vision disorder, dizziness, bradycardia, and Rash were reported with higher frequency (difference of ≥10%) for patients with ROS1-positive NSCLC than for patients with ALK-positive NSCLC.

In total 15 ROS1-positive NSCLC patients older than 65 years were included in Study 1001. No major differences in the frequency of toxicities can be observed compared to the group of younger patients, except for a most common treatment-related Dysgeusia (33.3% vs13.2%) and Nausea (66.7% vs 42.1%).

As expected, in general, treatment-related events, in particular Nausea, Vomiting, Constipation, Diarrhoea, Dizziness, Neutropenia and Decreased appetite were most commonly observed in Asian than in non-Asian patients.

2.5.2. Conclusions on clinical safety

No new safety signals were identified from patients with ROS1-positive NSCLC, as reported AEs and laboratory abnormalities were consistent with the established safety profile as described in the current Pfizer reference product label information for crizotinib. The safety profile of crizotinib in the 53 patients with ROS1-positive NSCLC in Study 1001 was consistent with the known overall crizotinib safety profile.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP):

The PRAC considered that the RMP version 7.0 (dated 19 January 2016) could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur Updated assessment report (AR) dated 13 May 2016, and in the PRAC Rapporteur Revised AR dated 19 May 2016.

The CHMP endorsed this advice.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the RMP version 7.1 (dated 13 June 2016) with the following content:

Safety concerns

Table 44 – Summary of the safety concerns

Important identified risks	• Hepatotoxicity • Pneumonitis/Interstitial lung disease • QTc Prolongation • Bradycardia • Vision Disorder • Renal Cyst • Oedema • Leukopenia • Neuropathy • Gastrointestinal perforation (*a.) • Cardiac failure (*b.)
Important potential risks	• Reproductive Toxicity (including pregnant and lactating women) • Photosensitivity • Malignant melanoma
Missing information	• Patients with severe hepatic impairment • Pediatric patients • Drug interaction with strong CYP3A inhibitors, strong CYP3A4 inducers, CYP3A4 substrates with narrow therapeutic indices, or P-glycoprotein substrates • Patients undergoing long-term treatment
*a. Considered as an important identified risk in the EU only *b. Considered as an important identified risk in the EU, Japan, and Switzerland only and other ex-US countries	

Pharmacovigilance plan

Table 45 – Table of Ongoing and Planned Additional PV Studies / Activities in the Pharmacovigilance Plan

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)
Update of the OS status of Study A8081007 and of the final efficacy and safety data. Category 2	To provide mature overall survival data to confirm the benefit/risk of crizotinib.	Updated safety and overall survival data from Study 1007 to support the efficacy and safety results from the originally submitted report.	Started	30 June 2016
Study A8081038 A Multinational Active Safety Surveillance Study of Crizotinib in Europe and in the United States. It is a non-interventional, active safety surveillance study using existing health care data sources in Europe to evaluate safety outcomes among lung cancer patients. Existing health care data sources in Denmark, Finland, the Netherlands, Sweden and the United States will be used to evaluate safety outcomes among lung cancer patients receiving crizotinib prescriptions over a 3-year period under real-world conditions. To contextualize the findings, the study will also obtain data among lung cancer patients receiving prescriptions of erlotinib or gefitinib in the same data sources during the study period. Category 3	To estimate the incidence rate and incidence proportion over a 3-year period of observation for hepatotoxicity, pneumonitis/ILD, cardiac failure, QTc prolongation related events, bradycardia, visual disorders, renal cysts, oedema, leukopenia, neuropathy, GI perforation, photosensitivity, and malignant melanoma among lung cancer patients receiving crizotinib dispensation.	Hepatotoxicity, Pneumonitis/ ILD, Cardiac failure, QTc prolongation, Bradycardia, Vision disorder, Renal cysts, Oedema, Leukopenia, Neuropathy, GI perforation, Photosensitivity, Malignant melanoma, Patients with hepatic impairment, Patients with renal impairment, Patients undergoing long term treatment.	Started	30 June 2018
Study A8081012 A Phase 1 study to evaluate the effect of hepatic impairment on the pharmacokinetics and safety of crizotinib in advanced cancer patients. Category 3	To evaluate the effect of hepatic impairment on the steady state pharmacokinetics and safety of crizotinib in advanced cancer patients.	Patients with hepatic impairment.	Started	30 October 2017
Study A8081001 (Amendment #20 Itraconazole sub-study) Category 3	Evaluate the effect of itraconazole (a strong inhibitor of CYP3A) on multiple-dose PK of crizotinib in advanced cancer patients.	Drug interaction with CYP3A inhibitors.	Started	31 December 2016

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)
Study A8081049 XALKORI Physician Survey Study Category 3	Evaluate the effectiveness of crizotinib educational materials.	Hepatotoxicity, ILD/ Pneumonitis, QTc prolongation, Bradycardia, Vision disorder, Leukopenia	Started	30 March 2017
Study A8081050 XALKORI Patient Survey Study Category 3	Evaluate the effectiveness of crizotinib educational materials.	Hepatotoxicity, ILD/ Pneumonitis, QTc prolongation, Bradycardia, Vision disorder, Leukopenia	Started	30 March 2017
Study A8081062 A descriptive study of potential sight threatening events and severe visual loss following exposure to Xalkori (crizotinib) Category 3	Evaluate the frequency of risk factors for and sequelae of potential sight threatening events and severe visual loss among patients being treated with crizotinib.	Severe visual loss during Crizotinib treatment	Started	31 December 2021

Risk minimisation measures

Table 46 - Summary Table of Risk Minimisation Measures

Safety Concern	*Routine Risk Minimisation Measures*	*Additional Risk Minimisation Measures*
Important Identified Risk		
Hepatotoxicity	Wording in SmPC Section 4.2, 4.3, 4.4, and 4.8	Educational Materials: therapeutic management guide and patient information brochure.
Pneumonitis/ Interstitial lung disease	Wording in SmPC Section 4.2, 4.4, and 4.8.	Educational Materials: therapeutic management guide and patient information brochure.
QTc prolongation	Wording in SmPC Section 4.2, 4.4, 4.8, and 5.2.	Educational Materials: therapeutic management guide and patient information brochure.

Safety Concern	***Routine Risk Minimisation Measures***	***Additional Risk Minimisation Measures***
Bradycardia	Wording in SmPC Section 4.2, 4.4, 4.5, 4.8.	Educational Materials: therapeutic management guide and patient information brochure.
Vision disorder	Wording in SmPC Section 4.2, 4.4, 4.7, and 4.8.	Educational Materials: therapeutic management guide and patient information brochure.
Renal cyst	Wording in SmPC Section 4.8.	Educational Materials: therapeutic management guide and patient information brochure.
Oedema	Wording in SmPC Section 4.8.	Educational Materials: therapeutic management guide and patient information brochure.
Leukopenia	Wording in SmPC Section 4.2, 4.4, and 4.8.	Educational Materials: therapeutic management guide and patient information brochure.
Neuropathy	Wording in SmPC Section 4.8.	Educational Materials: therapeutic management guide and patient information brochure.
Gastrointestinal perforation (EU only)	Wording in SmPC Section 4.4, and 4.8.	Educational Materials: therapeutic management guide and patient information brochure.
Cardiac failure (EU, Japan, and Switzerland, and other ex-US Countries only)	Wording in SmPC Section 4.4, and 4.8.	Educational Materials: therapeutic management guide and patient information brochure.
Important Potential Risks		
Reproductive Toxicity (including pregnant and lactating women)	Wording in SmPC Section 4.6, and 5.3.	Educational Materials: therapeutic management guide and patient information brochure.
Photosensitivity	Wording in SmPC Section 5.3.	None
Malignant Melanoma	None proposed	None

Safety Concern	*Routine Risk Minimisation Measures*	*Additional Risk Minimisation Measures*
Missing Information		
Patients with severe hepatic impairment	Wording in SmPC Section 4.2, 4.3, 4.4, and 4.8.	None
Paediatric patients	Wording in SmPC Section 4.2.	None
Drug interaction with strong CYP3A inhibitors, strong CYP3A4 inducers, substrates with narrow therapeutic indices, or Pglycoprotein substrates.	Wording in SmPC Section 4.4, 4.5, and 5.2.	Educational Materials: therapeutic management guide and patient information brochure.
Patients undergoing long-term treatment	None proposed	None

The CHMP, having considered the data submitted in the application was of the opinion that the RMP version 7.1 (dated 13 June 2016) is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Annex II.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable due to the limited proposed changes to the PI that do not significantly alter the readability of the approved document.

3. Benefit-Risk Balance

An extension of crizotinib indication for the treatment of patients with ROS1-positive advanced NSCLC is requested by the MAH based on efficacy data from 53 patients enrolled in the open-label, phase I study 1001, including 46 previously treated and 7 untreated.

Similarly to what observed for NSCLC ALK-positive patients, ROS-1 positive NSCLC patients are typically young, non-smokers and with adenocarcinoma histology. More than half of the patients enrolled in study 1001 were female.

Benefits

Beneficial effects

An outstanding benefit in terms of ORR (69.8%, 95%CI 55.7, 81.7), supported by a meaningful duration of response, was observed. Six out the 7 previously untreated patients achieved an objective response.

These data favourably compare with response to prior therapy for ROS-1 positive NSCLC patients enrolled in the study 1001. The ORR was 21.7% for prior first-line chemotherapy (29.4% with pemetrexed), 16.7% for prior second-line chemotherapy (30.8% with pemetrexed), and 23.7% for any line therapy with pemetrexed. A statistical analysis was also provided in which TTP on crizotinib was compared with TTP on last prior therapy: the median TTP with crizotinib vs last prior therapy was 19.8 vs 8.1 months (HR=0.59, 95% CI: 0.31, 1.13). Supportive published data from Investigator-Initiated Research studies were provided by the MAH.

Uncertainty in the knowledge about the beneficial effects

Data on previously untreated ROS-1 NSCLC patients are very limited. However, pre-clinical and clinical ancillary data show efficacy both in ROS1 and ALK mutated patients including in first line setting

Data on the prognostic value of ROS-1 positivity are sparse and difficult to interpret. Similarly, data from independent retrospective studies, are difficult to interpret, due to the heterogeneity in type of regimen and agents used, but seem to show an ORR to prior treatment similar or even higher than in study 1001.

Risks

Unfavourable effects

No new safety concerns were raised by data from these additional 53 patients. The known crizotinib safety profile, mainly characterized by Vision disorder, Gastrointestinal disorders (nausea, diarrhoea, vomiting, constipation), and General disorders (oedema and fatigue) was confirmed in ROS1-positive patients.

Toxicities experienced by ROS1-positive NSCLC patients were mostly manageable by short (<1 week) dose interruption and crizotinib dose reduction. Only in one patient treatment was permanently discontinued due to drug-related AE.

In total 15 ROS1-positive NSCLC patients older than 65 years were included in Study 1001. No major differences in the frequency of toxicities can be observed compared to the group of younger patients, except for a most common treatment-related Dysgeusia (33.3% vs13.2%) and Nausea (66.7% vs 42.1%).

As expected, in general treatment-related events, in particular Nausea, Vomiting, Constipation, Diarrhoea, Dizziness, Neutropenia and Decreased appetite were most commonly observed in Asian than in non-Asian patients.

Uncertainty in the knowledge about the unfavourable effects

N/A

Effects Table

Table 47: Effects Table for Xalkori treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC) (data cut-off: 30 November 2014).

Effect	Short Description	Unit	Treatment	Uncertainties / Strength of evidence
Favourable Effects				
ORR	objective response rate	% (N)	69.8 (37)	[95% CI: 55.7, 81.7]
PFS	progression-free survival	Median in month	19.3	[95% CI: 14.8, NR]
TTR	time to response	Median in week	7.9	range: 4.3–32.0
DR	duration of response	Median in month	NR	[95% CI: 15.2, NR]
DCR	disease control rate	Week 8 Week 16	86.8 (46) 79.2 (42)	[95% CI :74.7, 94.5] at 8 week [95% CI: 65.9, 89.2] at 16 week
OS	overall survival	Median in month	NR	Probability of survival at 6 months*, % [95% CI: 90.6 [78.8, 96.0] Probability of survival at 12 months*, % [95% CI: 79.0 [65.3, 87.8]
Unfavourable Effects				
Total treatment-related AE, excl. PD permanent discontinuation Tempory discontinuation Dose reduction		N (%) 1 (1.9%) 13 (24.5%) 6 (11%))		No new safety signals were identified from patients with ROS1-positive NSCLC in Study 1001 as compared with the established safety profile for crizotinib (Crizotinib SmPC).
Total AEs treatment-related Most common treatment related (≥30%) SAE treatment-related		52 (98%) Vision disorder (85%), nausea (49%), oedema (45%), diarrhoea (42%), vomiting (38%), constipation (34%), elevated transaminases (30%) 2 (3.8%)		

*Kaplan-Meier estimate

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Advanced NSCLC remains a highly symptomatic and incurable disease requiring safer and more effective treatments in addition to those currently available. With the evolving understanding of the molecular basis of the disease, agents that target specific oncogenic driver alterations in subsets of patients have become an increasing focus of cancer drug development. ALK and ROS1 gene rearrangements rarely occur in the same tumour, with each defining a unique molecular subgroup of NSCLC (Gainor and Shaw, 2013). ROS1-positive NSCLC represents an additional molecularly-defined subgroup which may be effectively treated with a specific targeted therapy

Results from the cohort of ROS1-positive patients in Study 1001 indicate that crizotinib is an effective and safe treatment for this specific, rare subset of NSCLC. Crizotinib has shown robust and clinically meaningful antitumor activity as a single agent in patients with previously untreated and previously treated ROS1-positive NSCLC, as shown by a high ORR with responses that were rapid and durable.

Benefit-risk balance

The B/R of crizotinib as a single agent in the treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC), is considered positive.

Discussion on the Benefit-Risk Balance

The presented data from published literature regarding the natural history of ROS1-positive NSCLC suggest that ROS1 positivity is unlikely to be a favourable prognostic factor in NSCLC, similar to what has previously been shown in ALK-positive NSCLC (Shaw et al, 2009; Shaw et al, 2011).

The activity of crizotinib in ROS1-positive patients is undisputable, at least in previously treated subjects. Results taken from study 1001 show that crizotinib is associated with an ORR of 69.8% (95% CI: 55.7, 81.7), including five (9.4%) patients with a confirmed complete response. At the time of the data cutoff, the median PFS was 19.3 months (95% CI: 14.8, NR) and although the median OS had not yet been reached, the probability of survival at 12 months was 79.0% (95% CI: 65.3, 87.8).

There are limitations regarding the B/R assessment of crizotinib as a single agent in previously untreated patients mainly because of the non-comparative nature of the data and the limited sample size. However, since ROS1 positive NSCLC represents a rare, serious and life-threatening distinct molecular subset of NSCLC with no currently approved targeted therapies, pre-clinical and clinical ancillary data show efficacy both in ROS1 and ALK mutated patients (including efficacy in first line setting), a large indication including both pre-treated and non-pre-treated patient is considered acceptable.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC) based on the results of Study A8081001 (a multinational, multicenter, open-label, single-arm study of the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of crizotinib in patients with advanced cancer). Consequential changes are proposed to SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 and the Package Leaflet is proposed to be updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Annex II. An updated RMP version 7.1 was agreed during the procedure.

This CHMP recommendation is subject to the following amended conditions:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Additional risk minimisation measures**

Prior to launch of the product in each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational material with the National Competent Authority. The final wording used on the educational material should be in line with the approved product information.

The MAH should ensure that, at launch and thereafter, all Healthcare Professionals (HCPs) who are expected to use and/or prescribe XALKORI are provided with an educational pack.

The educational pack should contain the following:

1. Summary of Product Characteristics and Package Leaflet.
2. Educational material for Healthcare Professionals.
3. Patient brochure including a Patient Alert Card (text as agreed by the CHMP)

The educational material for Healthcare Professionals (HCPs) should contain the following key elements:

1. XALKORI prolongs the QTc interval which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de Pointes) or sudden death;

2. The risk of QTc prolongation may be increased in patients concomitantly taking anti-arrhythmics and in patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances (e.g., secondary to diarrhoea or vomiting);

3. XALKORI should be administered with caution to patients:
    a. Who have a history of or predisposition for QTc prolongation;
    b. Who are taking medicinal products that are known to prolong the QT interval;

4. The need for a periodic monitoring with electrocardiograms and electrolytes should be considered when using XALKORI in these patients;

5. Patients who develop a Grade 3 QTc prolongation should stop taking XALKORI until recovery to Grade ≤1, then resume at 200 mg twice daily;

6. Patients who develop a Grade 4 QTc prolongation should stop taking XALKORI permanently;

7. That XALKORI may cause vision disorders, including Grade 4 visual field defect with vision loss. However vision disorders most commonly observed were diplopia, photopsia, blurred vision, visual impairment, and vitreous floaters and were in most cases mild in severity;

8. In patients with ocular disorders, ophthalmological evaluation should be considered if vision disorder persists or worsens in severity. In the case of patients experiencing severe visual loss (best corrected visual acuity less than 6/60 in one or both eyes), XALKORI treatment should be discontinued and appropriate evaluation should be performed;

9. XALKORI may cause hepatotoxicity, symptomatic bradycardia (e.g., syncope, dizziness, hypotension), interstitial lung disease/pneumonitis, neutropenia and leukopenia, renal cyst, oedema, neuropathy, and reproductive toxicity. Recommendations on how to mitigate these risks through appropriate monitoring and management to be provided;

10. The concomitant use of XALKORI with strong CYP3A4 inhibitors/inducers and CYP3A4 substrates with narrow therapeutic indices should be avoided;

11. That XALKORI might cause gastrointestinal perforation. Hence, the product should be used with caution in patients at risk of developing gastrointestinal perforation; and discontinued in patients who experience this adverse reaction. Patients should be informed of the first signs of gastrointestinal perforations and advised to consult rapidly the treating physician in case of occurrence;

12. That XALKORI might cause severe, life-threatening or fatal cardiac failure. Hence, patients with or without pre-existing cardiac disorders, receiving crizotinib, should be monitored for signs and symptoms of heart failure. Dosing interruption, dose reduction, or discontinuation should be considered as appropriate if such symptoms are observed;

13. The need to counsel patients about risks related to the administration of XALKORI and inform them of what symptoms and signs to be aware of and the actions to take;

14. The role and use of the Patient Alert Card.