CRIZOTINIB RISK MANAGEMENT PLAN

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Rationale for submitting an updated RMP: to update final completion date and final analysis dates for CRISP Study ITCC (Innovative Therapy for Children with Cancer) 053.

Summary of changes in this RMP:

- To update CRISP Study ITCC 053 final completion date to 30 January 2030 and final analysis date to 30 January 2031 in Part III and Annex 2.

Other RMP versions under evaluation: not applicable.

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QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

LIST OF ABBREVIATIONS

AE	Adverse Event
ALCL	Anaplastic Large Cell Lymphoma
ALK	Anaplastic Lymphoma Kinase
ASCO	American Society Of Clinical Oncology
AUC	Area Under The (Blood Concentration) Curve
BID	Twice Daily
BSA	Body Surface Area
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
DHPC	Direct Healthcare Professional Communication
EFS	Event Free Survival
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EML4	Echinoderm Microtubule-Associated Protein Like 4
ESMO	European Society For Medical Oncology
EU	European Union
FDA	US Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GLOBOCAN	Global Cancer Observatory
HER-1,2	Human Epidermal Growth Factor Receptor 1,2
HLT	High Level Term (Meddra)
HR	Hazard Ratio
IARC	International Agency For Research On Cancer
IDM	International Developed Market
IHC	Immunohistrochemistry
IMT	Inflammatory Myofibroblastic Tumor
IVD	In Vitro Diagnostics
LOT	Length Of Therapy
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary For Regulatory Activities
N/A	Not Applicable
NHL	Non-Hodgkin's Lymphoma
NSCLC	Non-Small Cell Lung Cancer
OAT	Organic Anion Transporter
OCT	Organic Cation Transporter
ORR	Objective Response Rate
OS	Overall Survival
PAD	Peripheral artery disease
PFS	Progression-Free Survival
P-gp	P-Glycoprotein
PK	Pharmacokinetic/Pharmacokinetics
PMA	Premarket Approval
PSUR	Periodic Safety Update Report
PT	Preferred Term (Meddra)
PVA	Pharmacovigilance Activity
PVD	Peripheral vascular disease
QD	Once Daily
QTc	QT Interval, Corrected For Heart Rate.
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
RON	Recepteur D'origine Nantais

ROS1	Ros Oncogene 1
RT	Radiation Therapy
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SEER	Surveillance Epidemiology and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardised Meddra Query
TKI	Tyrosine Kinase Inhibitor
US	United States
VATS	Video-Assisted Thoracic Surgery
VEGF	Vascular Endothelial Growth Factor

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PART.I. PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Crizotinib
Pharmacotherapeutic group(s) (ATC Code)	Anaplastic lymphoma kinase (ALK) inhibitors (L01ED01)
Marketing Authorisation Holder	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	XALKORI
Marketing authorisation procedure	centralised
Brief description of the product:	Chemical class: Protein kinase inhibitor
	Summary of mode of action: Crizotinib is a selective small-molecule inhibitor of the ALK RTK and its oncogenic variants (ie ALK fusion events and selected ALK mutations). Crizotinib is also an inhibitor of the HGFR, c-Met RTK, c-ROS1 and Recepteur d'Origine Nantais RTK. Crizotinib demonstrated concentration-dependent inhibition of the kinase activity of ALK, ROS1, and c-Met in biochemical assays and inhibited phosphorylation and modulated kinase-dependent phenotypes in cell-based assays. Crizotinib demonstrated potent and selective growth inhibitory activity and induced apoptosis in tumour cell lines exhibiting ALK fusion events (including EML4-ALK and NPM-ALK), ROS1 fusion events, or exhibiting amplification of the ALK or MET gene locus. Crizotinib demonstrated anti-tumour efficacy, including marked cytoreductive anti-tumour activity, in mice bearing tumour xenografts that expressed ALK fusion proteins. The anti-tumour efficacy of crizotinib was dose-dependent and correlated to pharmacodynamic inhibition of phosphorylation of ALK fusion proteins (including EML4-ALK and NPM-ALK) in tumours in vivo. Crizotinib also demonstrated marked antitumor 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 antitumor efficacy of crizotinib was dose-dependent and demonstrated a correlation with inhibition of ROS1 phosphorylation in vivo. In vitro studies in 2 ALCL derived cell lines (SU DHL 1 and Karpas 299, both containing NPM ALK) showed that crizotinib

	was able to induce apoptosis, and in Karpas 299 cells, crizotinib inhibited proliferation and ALK mediated signaling at clinically achievable concentrations. In vivo data obtained in a Karpas 299 model showed complete regression of the tumour at a dose of 100 mg/kg once daily.
	Important information about its composition: None
Hyperlink to the Product Information:	Module 1.3.1
Indication(s) in the EEA	Crizotinib as monotherapy is indicated for: • the first-line treatment of adults with ALK-positive advanced NSCLC. • the treatment of adults with previously treated ALK positive advanced NSCLC. • the treatment of adults with ROS1-positive advanced NSCLC. • the treatment of paediatric patients (age ≥1 to <18 years) with relapsed or refractory systemic ALK-positive ALCL. • the treatment of paediatric patients (age ≥1 to <18 years) with recurrent or refractory ALK-positive unresectable IMT.
Dosage in the EEA	**Recommended dosing in adult patients with ALK-positive or ROS1-positive advanced NSCLC:** The recommended dose schedule of crizotinib is 250 mg taken orally twice daily (500 mg daily) taken continuously. Continue treatment as long as the patient is deriving clinical benefit from therapy. Crizotinib may be taken with or without food. Capsules should be swallowed whole. If a dose of crizotinib is missed, then it should be taken as soon as the patient remembers unless it is less than 6 hours until the next dose, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.
	Recommended dosing in paediatric patients with ALK-positive ALCL or ALK-positive IMT: The recommended starting dose schedule of crizotinib in paediatric patients is based on body surface area (BSA). The recommended dosage of crizotinib for paediatric patients with ALCL or IMT is 280 mg/m^2 orally twice daily until disease progression or unacceptable toxicity. • The recommended dosage for paediatric patients with BSA ≥1.34 m^2 is provided in Table 1 of the SmPC. If needed, attain the desired dose by combining different strengths of crizotinib capsules. • For paediatric patients with BSA <1.34 m^2, the granules in capsules for opening formulation of

	crizotinib should be used. The recommended dosage for paediatric patients with BSA <1.34 m^2 is provided in Table 2 of the SmPC. Administer crizotinib to paediatric patients under adult supervision.
Pharmaceutical form(s) and strengths	Crizotinib capsules are supplied as follows: Hard capsule 200 mg White opaque and pink opaque hard capsule, with "Pfizer" imprinted on the cap and "CRZ 200" on the body. 250 mg Pink opaque hard capsule, with "Pfizer" imprinted on the cap and "CRZ 250" on the body.
	XALKORI 20 mg granules in capsules for opening Capsule consists of a light blue cap printed with "Pfizer" in black ink and a white body printed with "CRZ 20" in black ink. XALKORI 50 mg granules in capsules for opening Capsule consists of a gray cap printed with "Pfizer" in black ink and a light gray body printed with "CRZ 50" in black ink. XALKORI 150 mg granules in capsules for opening Capsule consists of a light blue cap printed with "Pfizer" in black ink and a light blue body printed with "CRZ 150" in black ink.
Is/will the product be subject to additional monitoring in the EU?	No

ALK = Anaplastic Lymphoma Kinase; EML4= Echinoderm Microtubule-Associated Protein Like 4; HGFR = Hepatocyte Growth Factor Receptor; N/A = Not Applicable; NPM = Nucleophosmin; NSCLC = Non-Small Cell Lung Cancer; ROS1 = ros Oncogene 1; RTK = Receptor Tyrosine Kinase;

PART.II. SAFETY SPECIFICATION

Module.SI. Epidemiology of the Indication(s) and Target Population (s)

Indications: XALKORI as monotherapy is indicated for:

- the first-line treatment of adults with Anaplastic Lymphoma Kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).
- the treatment of adults with previously treated ALK-positive advanced NSCLC.
- the treatment of adults with ROS1-positive advanced NSCLC.
- the treatment of paediatric patients (age ≥1 to <18 years) with relapsed or refractory systemic ALK-positive anaplastic large cell lymphoma (ALCL).
- the treatment of paediatric patients (age ≥1 to <18 years) with recurrent or refractory ALK-positive unresectable inflammatory myofibroblastic tumour (IMT).

Indication: ALK-positive and ROS1 NSCLC

ALK-positive and ROS1 are prognostic and predictive tumor markers in NSCLC. Their positivity is 2.6% and 1.3%, respectively, and patients who have mutations in both genes are extremely rare.[1] No published data that standardize the incidence or prevalence of ALK-positive NSCLC and ROS1-positive NSCLC to a general population were available to provide a regional, national, or global incidence or prevalence of ALK-positive NSCLC in the general population. However, the incidence of NSCLC and all lung cancers in the general population has been estimated at a global and, in some instances, national level.[2] Additionally, the prevalence of ALK-positive NSCLC and ROS1-positive NSCLC from retrospective studies using resected tumor samples provided insight into population-wide estimates. A number of studies reported the prevalence of the ALK rearrangement among patients with NSCLC. In unselected clinical populations worldwide, ALK rearrangements were reported to occur in approximately 3%-5% of all-type NSCLCs.[3,4]

Survival estimates were not available in the literature for general ALK-positive NSCLC populations. For patients with NSCLC overall, 1-year survival estimates range from 89% in an Italian study to 51% among US males and 60% among US females.[5,6] A Belgian study reported a 2-year survival of 30.8% and a 5-year survival of between 15%-66%; lower.[7] estimates were found among populations with higher percentages of adenocarcinomas Five-year survival estimates were longer in women (19%) than men (15%) among all patients with NSCLC. Median survival for men and women with NSCLC follow this same pattern, with longer survival observed among women (1.4 years) than among men (1 year), and median overall survival for ALK positive patients who did not receive crizotinib was 1.3 years.[6]

Epidemiological Literature Search Strategy

In 2012, the US National Library of Medicine Entrez-Pubmed database was searched for primary literature and review articles on incidence, prevalence, mortality, risk factors, and

comorbidites of ALK-positive NSCLC and ROS1-positive NSCLC[1]. When results in ALK-positive NSCLC and ROS1-positive NSCLC populations were limited these searches were expanded to include patients with NSCLC and lung cancer of any kind. Studies that reported on NSCLC adenocarcinomas specifically were also reviewed, as the literature indicates that most ALK-positive patients with NSCLC have adenocarcinomas. Where population-based studies were unavailable, placebo arms or therapeutic arms not involving crizotinib of randomized clinical trials among NSCLC populations or prospective studies of non-crizotinib NSCLC therapies were reviewed and summarized.

On April 14, 2021, an additional search was conducted in PubMed for articles on ALK-positive NSCLC and ROS1-positive NSCLC. The following filters were applied: meta-analysis, review, systematic review, published in the last 10 years, adult 19+ years, English, humans[2]. This search yielded 43 titles and 4 additional articles via citation matching. Five articles were selected for inclusion.

Incidence:

No published data on the incidence of ALK-positive NSCLC and ROS1-positive NSCLC in general populations are available. Retrospective tissue bank studies have suggested that the incidence of ALK-rearrangement is 3%-5% within NSCLC, with no differences by ethnicity.[8] The incidence of lung cancer, NSCLC, as well as the subset of adenocarcinoma, are briefly summarized below.

Among European men, incidence for all lung cancer was 46.6 per 100,000 in 2012 and has declined over the last decade according to estimates from the GLOBOCAN project, with an age-standardized rate of 43.6 per 100,000 in 2020.[9] However this continent-wide trend has not been observed in every country. Overall lung cancer incidence remained stable in Norway, Sweden, Austria, Switzerland, Croatia, Spain, and Lithuania between the early 1990s and 2000s.[10] However, in past decade incidence has further declined in these countries. In men, lung cancer incidence was higher in Eastern Europe than in Western

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[1] Footnote: Search terms: (carcinoma*, non small cell lung OR carcinoma*, non-small-cell lung OR lung carcinoma*, non-small-cell OR non-small-cell lung carcinoma* OR non small cell lung carcinoma* OR carcinoma*, non-small cell lung) AND (ALK OR anaplastic lymphoma kinase OR adenoma* OR adenocarcinoma*) AND (incidence OR prevalence OR mortality OR morbidity OR rate OR epidemiology) ALK[All Fields] AND (("carcinoma, non-small-cell lung"[MeSH Terms] OR ("carcinoma"[All Fields] AND "non-small-cell"[All Fields] AND "lung"[All Fields]) OR "non-small-cell lung carcinoma"[All Fields] OR "nsclc"[All Fields]) OR ("lung"[MeSH Terms] OR "lung"[All Fields]))

[2] Footnote: Search terms: ("ALK"[All Fields] OR ("ALK"[All Fields] AND ("positive"[All Fields] OR "positively"[All Fields] OR "positiveness"[All Fields] OR "positives"[All Fields] OR "positivities"[All Fields] OR "positivity"[All Fields])) OR "ROS1"[All Fields] OR ("ROS1"[All Fields] AND ("positive"[All Fields] OR "positively"[All Fields] OR "positiveness"[All Fields] OR "positives"[All Fields] OR "positivities"[All Fields] OR "positivity"[All Fields]))) AND ("carcinoma, non small cell lung"[MeSH Terms] OR ("carcinoma"[All Fields] AND "non small cell"[All Fields] AND "lung"[All Fields]) OR "non-small-cell lung carcinoma"[All Fields] OR "nsclc"[All Fields] OR "nsclc s"[All Fields] OR "nsclcs"[All Fields]) AND ("humans"[MeSH Terms] AND "english"[Language] AND "adult"[MeSH Terms] AND 2011/01/01:2021/12/31[Date - Publication] AND y_10[Filter] AND (meta-analysis[Filter] OR review[Filter] OR systematicreview[Filter])

Europe. In 2020, the highest age standardized lung cancer incidence was in Serbia (68 per 100,00); incidence was also high in Hungary (66.6 per 100,000), Bosnia Herzegovina (64.7 per 100,000), Montenegro (61.2 per 100,000), Slovakia (54.3 per 100,000), Romania (53.1 per 100,000) Belarus (53 per 100,000), and Poland (51.5 per 100,000). The lowest rate among men was in Sweden (17.2 per 100,000. **Refer to** Table 1.[9,11]

In women, the incidence of lung cancer has increased and was higher in Western Europe than in Eastern Europe. According to GLOBOCAN estimates, continent wide lung cancer incidence was 18.1 per 100,000 in 2020. Age-adjusted lung cancer incidence in women was highest in Hungary (38.1 per 100,000), Denmark (36.8 per 100,000), the Netherlands (33.5 per 100,000), and Ireland (32.9 per 100,000). Female lung cancer incidence was lowest in Belarus (4.9 per 100,000), the Ukraine (5.9 per 100,000), and Albania (7.4 per 100,000, [9,12]).

Table 1. Lung Cancer by Country in Europe for 2020 from GLOBOCAN

Country	Men			Women		
	Number	Unadjusted	Age-Standardized	Number	Unadjusted	Age-Standardized
Austria	2992	67.4	32.4	2264	49.6	22.0
Belgium	6425	111.8	51.7	3221	55.1	27.0
Bulgaria	3357	99.5	49.7	943	26.4	12.0
Croatia	2276	115.0	54.2	959	45.1	19.0
Cyprus	445	73.7	43.6	126	20.9	11.3
Czechia	4146	78.6	36.7	2414	44.4	17.6
Denmark	2399	83.3	36.9	2648	90.9	36.8
Estonia	578	92.0	47.9	231	33.1	12.5
Finland	1822	66.7	26.2	1113	39.6	13.7
France	31941	101.1	49.1	16358	48.6	22.7
Germany	38436	92.8	39.2	26368	62.2	25.7
Greece	6786	132.6	56.3	2174	41.0	16.6
Hungary	5812	126.4	66.6	4462	88.1	38.1
Ireland	1643	67.0	36.6	1628	65.5	32.9
Italy	28369	96.4	36.0	13584	43.8	16.4
Latvia	888	102.1	51.4	317	31.2	10.7
Lithuania	1110	88.1	45.0	390	26.7	9.4
Luxembourg	238	75.2	40.8	113	36.5	18.5
Malta	200	90.3	34.1	58	26.3	11.3
Poland	18277	99.7	51.5	11232	57.6	24.6
Portugal	3933	81.5	35.4	1482	27.6	10.8
Romania	9030	96.5	53.1	3092	31.3	14.0
Slovakia	2531	95.2	54.3	785	28.0	13.3
Slovenia	931	89.9	41.6	545	52.2	21.9
Spain	21480	93.5	44.4	7708	32.4	15.4
Sweden	2158	42.7	17.2	2409	47.8	18.5
Switzerland	2525	58.8	26.0	2015	46.2	19.6
The Netherlands	7050	82.6	34.3	6450	75.0	33.5
United Kingdom	26943	79.8	44.5	25040	72.9	29.9

Adapted from Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2020). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed 16 April 2021.[11,12]
Incidence per 100,000 people

NSCLC represents between 80% and 85% of all lung cancer cases. In 2010, the European Society for Medical Oncology (ESMO) working group reported that the incidence of NSCLC ranged from 22-63 per 100,000 men, and from 5-33 per 100,000 women across Europe. Despite higher NSCLC incidence in men than women, the difference between the incidence in men and women was decreasing particularly in Northwestern Europe. The ESMO working group noted a rise in the proportions of adenocarcinomas which may be linked to greater availability of "light" cigarettes that were inhaled more deeply than other varieties.[13]

A study of NSCLC adenocarcinoma patients which used data from 16 countries in the European cancer incidence and mortality (EUROCIM) database found that the trend toward a higher incidence in men than women for all NSCLC also held for men and women with adenocarcinoma NSCLC. In the 16-country study, incidence of NSCLC adenocarcinoma increased over time, though these increases were often not large. Among males, incidences ranged from 3.5-26 per 100,000, and among females, incidences ranged from 1.1-18 per 100,000.[14]

Prevalence:

A prevalence of ALK-positive tumors among all NSCLC of 3%-5% has been suggested after an examination of prevalence reports from Europe, the US, and Asia.[3,4] However, in selected NSCLC patient populations, the prevalence of ALK positivity have ranged from 1.3%-18% of NSCLC tumors.[15,16]

Variation in prevalence reports has been attributed to variable prescreening practices that may enrich the study populations with ALK-positive patients. In addition, 3 testing methods for the ALK rearrangement based on immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and reverse transcriptase-polymerase chain reaction (RT-PCR) have differed in sensitivity and specificity which may affect prevalence estimates.[17] Heterogeneity of the ALK-positivity prevalence in the broader populations may have explained some prevalence variation. The ALK rearrangement has also been associated with the adenocarcinoma histology, young age, not or light smoking and variation in these risk factors could affect prevalence.[18,19,20,21]

ROS1-positive NSCLC occurs in approximately 1-2% of patients with NSCLC.[22,23] Of the estimated 1.5 million new cases of NSCLC worldwide each year, approximately 15,000 may be driven by oncogenic ROS1 fusions. ROS1 rearrangements are more commonly found in patients who have never smoked or have a history of light smoking and who have histologic features of adenocarcinoma.[23,24] The genetic level, ALK and ROS1 rearrangements rarely occur in the same tumor, with each defining a unique molecular subgroup of NSCLC.[24] The prevalence of ALK rearrangement ranged from 2.6%-10.5% among European NSCLC populations when FISH was used. In studies that only examined NSCLC adenocarcinomas,

with FISH the range between high and low prevalence estimates was lower (2.6%-5.8%) than was the range among all NSCLC (**Refer to** Table 2).

The prevalence of ROS1 rearrangement ranged from 0.7%-1.9% among European NSCLC populations.[25,26,27,28,29,30,18,31]

Table 2. ALK Positive Prevalence in Europe

Publication	Total	Diagnostic Test	ALK Positive (n)	%	Patient Characteristics
Conde et al. 2012	86	FISH	9	10.5	All histologies
Grioux Leprieur et al. 2013	147	IHC	4	2.7	All histologies
Martelli et al. 2009	120	Multiple	9	7.5	All histologies
Martinez et al. 2013	99	FISH	7	7.1	All histologies
Perner et al. 2008[a]	603	FISH	16	2.7	All histologies
Salido et al. 2011	107	FISH	3	2.8	All histologies
	107	IHC	2	1.9	All histologies
Hofman et al. 2012	154	FISH	4	2.6	Adenocarcinomas
Llie et al. 2012	87	FISH	5	5.8	Adenocarcinomas
Martelli et al. 2009	63	Multiple	3	4.8	Adenocarcinomas
McLeer-Florin et al. 2012	441	IHC	29	6.6	Adenocarcinomas

a. Patient population from both Switzerland and the US
FISH= Fluorescence In Situ Hybridization; IHC=Immunohistochemistry

Demographics of the population:

Female patients with NSCLC are more likely to present with adenocarcinoma than males, although the majority of patients with NSCLC overall are male.[32] African Americans have a higher incidence of NSCLC compared to whites in the US.[33] However, a meta-analysis found that patients with ALK rearrangement were younger even across subgroups by race.[34] Similarly, never smokers were more likely to have ALK rearrangement across races.[35,36] ALK rearrangement is more common in younger, female, non-smoking patients with NSCLC whose tumors contain adenocarcinoma components.[34,35,36] Elderly patients with ALK+ disease are likely underrepresented in clinical trials due to having more comorbidities than younger patients.[37]

Risk factors for NSCLC, such as tobacco smoking and air pollution, are part of the social and physical environment, and their persistence underscores the need for novel, effective therapies against all NSCLC including ALK-positive NSCLC. Tobacco smoking has driven NSCLC rates since the early 20th century, and the distribution of NSCLC is expected to continue to follow smoking patterns into at least the middle of the 21st century.[2]

Since the 1980s, it has been clear that second-hand smoke contributes appreciably to NSCLC rates.[38,7] Occupational exposures, such as asbestos and radon as well as air pollution, have also been closely linked to NSCLC.[39] A growing awareness of the distinct characteristics of non-tobacco related NSCLC has had implications for treatment. Gefitinib, erlotinib, and crizotinib have been particularly effective against non-tobacco-related types of NSCLC.[2,3]

Aggregation studies first identified clusters of NSCLC within families suggesting that NSCLC had a genetic component.[3] More recently, numerous genetic markers that interact with smoking[2] and other exposures[4] to cause NSCLC have been identified. In smokers and non-smokers, germline mutations to the P53 gene increase the risk of all lung cancers including NSCLC by 3-fold.[4] The oncogenes BRAF, KRAS, MET, HERS-2, and EGFR, also show associations with NSCLC. The EGFR mutation is associated with NSCLC in never and former smokers.[40,41,2] In addition to genomic variation, potentially reversible epigenetic changes involving methylation of tumor suppressor genes may be related to NSCLC and the epigenetic effect may differ by smoking status.[31,2,5]

An association with adenocarcinomas, younger age, and low smoking rates has been supported by 2 studies in the US[19,20] and 1 study in Japan with more than 1,000 participants (Takeuchi 2012). Much of the clinical information on ALK-positive NSCLC comes from Asian populations and some evidence suggests that the ALK mutation in NSCLC may be more common in Asia than in Europe or the US.[42]

In 2007, a large-scale phosphoproteomic screen for tyrosine kinase activity in lung cancer identified an ROS1 fusion. ROS1 gene rearrangements can be found in a variety of human malignancies. ROS1-positive NSCLC identifies a molecularly defined patient group whose clinico-pathological characteristics resemble those of patients harbouring the ALK gene rearrangement: young age, never/light-smoking history, and adenocarcinoma histology.[2,3,4] Likewise, ROS1 rearrangements do not seem to overlap with other mutations, such as ALK, EGFR or KRAS.[2]

The main existing treatment options:

Surgery is curative in some patients (~30%) with NSCLC that is diagnosed in early, in Stage I or II. However, the majority of patients with NSCLC receives a diagnosis in later stages and relies on chemotherapies and radiation therapy (RT) with poor survival rates.[14] For patients who can withstand surgical resection, surgery can greatly improve survival if the cancer is diagnosed at Tumor, Nodes, Metastasis (TNM) Stages I or II and has not metastasized. Mortality from thoracic surgery remains high (2%-5%) particularly when full pneumonectomy is required.[38]

Following resected early-stage NSCLC, patients often undergo adjuvant therapy to delay or prevent relapse.[43,44] Even after some pneumonectomies, paclitaxel/gemcitabine/vinorelbine adjuvant therapy can reduce the hazard of death by 40%-50%.[45]

Patients with NSCLC benefit from current chemotherapies, but many including Molina et al. argue that, "the use of traditional chemotherapeutic agents has reached a therapeutic plateau." On the other hand, molecularly-targeted agents such as osimertinib, gefitinib, erlotinib, and afatinib, dacomitinib for EGFR mutations and crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib for ALK rearrangements provide novel, personalized therapeutic options.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Data on mortality and morbidity in ALK-positive NSCLC populations without exposure to crizotinib has recently become available. Results were mixed as to whether the morbidity and mortality of patients with ALK rearrangements were different from that in general patients with NSCLC. These studies were further complicated by the rarity of ALK arrangements in NSCLC populations (3%-5%), which made it difficult to adjust for potential confounding factors such as age and use of different chemotherapy. Patients with NSCLC that received a positive test for the ALK rearrangement were likely to have received crizotinib and tended to be younger and less likely to smoke than ALK negative patients which improved survival in the ALK-positive patients.[46] Therefore, the confounding effect of crizotinib use, age and smoking might have artificially biased the survival estimates for ALK-positive patients toward the appearance of longer survival. Data on mortality in ROS1-positive NSCLC populations without exposure to crizotinib was not available. Like patients with ALK positive NSCLC, patients with ROS1-positive NSCLC tend to be younger and less likely to smoke comparing with ROS1-negative NSCLC patients.

In European populations, deaths from all lung cancers are declining for men but rising for women. Patients with NSCLC tend to have better survival rates at 1 year following diagnosis and at younger ages. These trends are fairly stable over time except among those 70 and older, whose survival rates have increased steadily over calendar time. Two studies reporting 1- through 5-year survival among European patients with NSCLC differ, with an Italian study reporting 89%, 76%, and 66%, for 1-, 3-, and 5-year survival, respectively, and a Belgian study reporting 36.6% and 20.8% for 2- and 5-year survival, respectively. Lower survival rates were reported for exclusively NSCLC adenocarcinoma patients in the Netherlands, for whom 1-year survival ranges from 45%-59% over time, and 5-year survival ranges from 18%-28% over time.[47,5]

Data from the Eindhoven Cancer Registry covering the southern part of the Netherlands (~2 million inhabitants, only general hospitals) was used to determine changes in relative survival of patients with NSCLC from 1970 to 1997. Survival rates decrease over time since diagnosis and with age but tended to remain stable over calendar time. The exception to this appears to be 3- and 5-year survival among those 70 and over at diagnosis, which has shown steady, if small, increases over time.[48] From the same Eindhoven Cancer registry in the southern Netherlands, there were 7,273 patients diagnosed with NSCLC during 1975-1994. Overall, relative 1-year survival among all NSCLC cases was 48%, 47%, 48%, and 47% in the periods 1975-79, 1980-84, 1985-89, and 1990-92, respectively; 5-year survival was 15%, 15%, and 17% during the periods 1975-79, 1980-84, and 1985-89, respectively. Among the 1,287 adenocarcinoma cases, relative 1-year survival was 59%, 49%, 46%, and 45% in the periods during 1975-79, 1980-84, 1985-89, and 1990-92, respectively; relative 5-year survival was 28%, 24%, and 18% during 1975-79, 1980-84, and 1985-89, respectively.[48]

In a retrospective review of 140 cases of N2 NSCLC (mean age 61 years; 25% [35/140] with adenocarcinoma) who underwent surgical resection at a single Hospital in Belgium between 1985 and 1993, median survival time was 14 months, and 2- and 5-year survival rates were 36.6% and 20.8%, respectively. Among the subset of 35 adenocarcinoma cases, median

survival time was 14 months, and 2- and 5-year survival rates were 30.8% and 18.1%, respectively.[48]

Important co-morbidities[3]:

- Chronic Respiratory Disease:
- Peripheral Vascular Disease:
- Cardiovascular Events:
- Diabetes Mellitus:

Indication: paediatric patients (age ≥1 to <18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK) positive anaplastic large cell lymphoma (ALCL).

Epidemiologic Literature Search Strategy:

The US National Library of Medicine PubMed database was searched for primary literature and review articles on incidence, prevalence, mortality, risk factors, and comorbidities of relapsed or refractory ALK-positive ALCL.[4]

Articles with abstracts that were available in English and reported human populations were included. A total of 284 titles and abstracts were screened for relevance. Articles were

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[3] Footnote: Comorbidities search terms: (comorbidity* OR co-morbidit* OR Charlson OR heart disease* OR cardiac disease* OR cardiovascular death OR non-fatal myocardial infarction OR non-fatal mi OR myocardial infarction OR myocardial infarct OR MI OR non-fatal stroke OR stroke OR non-fatal cerebral stroke OR cerebral stroke OR non-fatal vascular accident OR vascular accident OR not fetal brain vascular accident OR brain vascular accident OR non-fatal cerebrovascular apoplexy OR cerebrovascular apoplexy OR non-fatal cerebrovascular stroke OR cerebrovascular stroke OR nonfatal cerebrovascular accident OR cerebrovascular accident OR non-fatal apoplexy OR apoplexy OR congestive heart failure OR cardiac failure OR myocardial failure OR heart decompensation OR diabetes OR chronic bronchitis OR HPV OR human papillomavirus OR COPD OR chronic obstructive pulmonary disease OR COAD OR chronic obstructive airway disease OR chronic obstructive lung disease OR chronic airflow obstruction* OR peripheral vascular disease* OR peripheral angiopath* OR peripheral arterial disease* OR periphery artery disease* OR peripheral artery occlusive disease OR PVD OR PAD OR PAOD)

[4] Footnote: Search terms: ("anaplastic lymphoma kinase"[MeSH Terms] OR ("anaplastic"[All Fields] AND "lymphoma"[All Fields] AND "kinase"[All Fields]) OR "anaplastic lymphoma kinase"[All Fields] OR "alk"[All Fields]) **AND** ("lymphoma, large cell, anaplastic"[MeSH Terms] OR ("lymphoma"[All Fields] AND "large cell"[All Fields] AND "anaplastic"[All Fields]) OR "anaplastic large-cell lymphoma"[All Fields] OR ("anaplastic"[All Fields] AND "large"[All Fields] AND "cell"[All Fields] AND "lymphoma"[All Fields]) OR "anaplastic large cell lymphoma"[All Fields] OR "alcl"[All Fields]) **AND** (("unresectability"[All Fields] OR "unresectable"[All Fields] OR "unresected"[All Fields] OR ("recurrance"[All Fields] OR "recurrence"[MeSH Terms] OR "recurrence"[All Fields] OR "recurrences"[All Fields] OR "recurrencies"[All Fields] OR "recurrency"[All Fields] OR "recurrent"[All Fields] OR "recurrently"[All Fields] OR "recurrents"[All Fields]) OR ("refractories"[All Fields] OR "refractoriness"[All Fields] OR "refractory"[All Fields]) OR ("relapse"[All Fields] OR "relapses"[All Fields] OR "relapsing"[All Fields] OR "relapsed"[All Fields] OR "relapser"[All Fields] OR "relapsers"[All Fields])) **AND** ("hasabstract"[All Fields] AND "humans"[MeSH Terms] AND "english"[Language]))

excluded if they reported on in vitro studies, clinical trials, case reports or case series, or small population sizes with specified ages. Reference lists of included studies were also scanned, and articles that cited included studies were also reviewed for relevance. There were 39 articles retained for full-text review, with 18 included.

Incidence:

There is very little information available on the incidence of paediatric anaplastic lymphoma kinase-positive (ALK-positive) anaplastic large cell lymphoma (ALCL) specifically or of paediatric ALCL generally.[49] One U.S. publication[50] reported on data from 1975–1995, reporting an ALCL incidence of 4.3 and 7.8 cases per million in males 10–14 and 15-19 years old, respectively. Meanwhile, the comparative incidence was 2.8 and 3.4 cases per million in females 10–14 and 15–19, respectively. However, these incidence estimates may be out of date and may not apply to European populations.

Another approach for generating an approximate estimate of paediatric ALK-positive ALCL would be based upon estimates of the incidence of paediatric non-Hodgkin lymphoma (NHL). Studies suggest that ALCL accounts for 10-15% of paediatric NHL, and that the large majority (90–95%) of paediatric ALCL is ALK+.[49,51,52,53,54,55,56,57,58] Using an assumed range of 10–15% of NHL being due to ALCL, with 90% of paediatric ALCL being ALK-positive, incidence estimates can be generated.

One study[59] suggested that the age-adjusted incidence rate for NHL among children under 15 years of age between 1988–1997 was 9.4 per million (with an average annual increase of 0.9% over the past 20 years); the incidence rate for adolescents 15–19 years of age over the same period was 15.9 per million (with an average annual increase of 1.7% over the past 20 years). These figures would suggest an incidence rate of approximately 0.85–1.27 and 1.43–2.15 cases of ALK-positive ALCL per million children 0–14 and 15–19 years of age, respectively.

The International Agency for Research on Cancer (IARC) estimated a similar incidence of NHL in Europe in 2020, reporting an age-standardized rate of 10 per million for individuals 0–19 years of age, 13 per million among males 0–19 years of age, and 7.5 per million among females 0–19 years of age.[60,61,62] This would translate to an incidence rate for ALK+ ALCL of 0.90–1.34 per million, 1.17–1.76 per million, and 0.68–1.01 per million for those 0–19 years of age from both sexes, males, and females, respectively.

Incidence rates for relapsed or recurrent ALCL were not available, though studies suggest that relapse occurs in 25–35% of children with ALCL, usually within six months of treatment (Damm-Welk 2014; Eyre 2014; Strullu 2015).

Prevalence:

Little information on the prevalence of paediatric ALCL was available. As mentioned above, most studies reported that ALCL accounted for 10–15% of paediatric NHL, which can be used to estimate the prevalence of ALCL in children.[49,51-58] IARC estimated a 1-year prevalence of NHL among Europeans 0–19 years old of 8.9 per million in Europe, which would translate to a 1-year prevalence of paediatric ALK-positive ALCL of 0.8–1.2 per

million.[63] IARC estimated a 1-year prevalence of NHL of 11 per million among males 0–19 years old in Europe, and 6.6 per million among females 0–19 years old.[64,65,66] This would translate to a 1-year prevalence of 1.0–1.5 and 0.59–0.89 per million for males and females, respectively.

Meanwhile, IARC estimated a 5-year prevalence of NHL among individuals 0–19 years of age in Europe of 35, 45, and 25 per million among both sexes, males, and females, respectively.[67,68,69] This would translate to a 5-year prevalence of ALK-positive ALCL among the same population of approximately 3.2–4.7, 4.1–6.1, and 2.3–3.4 per million among both sexes, males, and females, respectively.

Demographics of the population:

Given the small sample sizes included in studies of paediatric ALCL patients, demographic comparisons are generally limited to age and gender. However, a literature review of the entire ALCL population (paediatric and adult) by Shustov and colleagues (2019) reported that ALK-positive ALCL was quite uncommon in Hispanic, Asian, and Pacific Islander populations, and is more frequently diagnosed in Blacks than non-Hispanic Whites. Results from the paediatric literature, described below, suggest that the median age at diagnosis is between 10 and 12 years of age, and that paediatric ALCL is more common in males than females.

Among 34 French children who had undergone treatment for relapsed/progressive ALK+ ALCL, 28 had at least one relapse that triggered treatment while 6 were treated for progressive disease. The median age at initial diagnosis was 7.4 years (range 1.1–17 years), with 47% male; 6 (17.7%) of the 34 patients relapsed during a median follow-up of 6 years (Strullu 2015). Another study of 82 children in France newly diagnosed with ALCL (93% ALK-positive) reported a median age of 10 years at diagnosis (range 17 months to 17 years), with 56% male; 21 (25.6%) patients relapsed a median of 10 months after diagnosis (range 7–49 months).[52] A study of 119 German children with ALK-positive ALCL reported a median age at diagnosis of 12.0 years (range 0.3–17.8 years), with 58% male.[70] An Italian study of 52 patients with ALCL (90% ALK-positive) — 11 (21.1%) of whom relapsed — reported a median age of 9.8 years (range 1.4–17.4 years), with 67.3% male (Mussolin 2005). A study of 23 ALCL patients under 18 years of age in Turkey (66% ALK-positive among 21 with data available) reported a median age of 11.4 years (range 3.6–17.8 years), with 60.9% male; 7 of the patients (30%) relapsed during follow-up.[49]

Outside of Europe, a study of 90 Taiwanese children with ALCL (93% ALK-positive) — 20 (22.2%) of whom were patients with relapsed or refractory disease — reported a median age at initial diagnosis of 11.7 years (range 2.3–17.9 years), with 56.7% male.[55] A U.S. cohort study of 86 children with ALCL (90% ALK-positive) reported that 56% were male; 21 (24.4%) patients were relapsed cases, including 17 relapses within 2 years of diagnosis.[55] A Japanese study of 31 children with ALCL (88% ALK+) — 9 (26.5%) of whom were relapsed cases — reported a median age of 11 years (range 2-18 years), with 61% male.[71]

A South Korean study of 28 paediatric ALCL cases (68% male, median age 10.8) observed 8 relapses a median of 12.5 months after diagnosis.[72]

The main existing treatment options: Currently, there are no approved therapies for the treatment of relapsed or refractory pediatric ALCL. Standard of care has not been established for the 25-35% of children who develop recurrent disease, and all current treatment options for pediatric patients in the relapsed setting are associated with significant toxicity, including transplant-related morbidity and mortality, the potential for permanent adverse effects, and the risk of secondary malignancies. With relapse, patients can undergo high-dose chemotherapy. Induction therapy (including with multiagent regimens such as CCNU, and Ara-C or vindesine, dexamethasone, Ara-C, and etoposide) followed by high-dose chemotherapy and autologous or allogeneic hematopoetic stem cell transplant (HSCT). After achieving a second remission, many patients undergo autologous or allogeneic HSCT, as a "consolidation" strategy after chemotherapy.[69]

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Paediatric ALK positive ALCL is categorized in four stages of severity, with Stage I being the least advanced and Stage IV being most advanced. The St. Jude (Murphy's) classification[52,53] is commonly used to determine disease stage, with full staging criteria available in a report by Feinberg and colleagues (2007). The Ann Arbor classification system is also used to stage paediatric ALCL, again with four stages of increasing severity.[54] Higher disease stages are associated with multiple tumors, distributed tumor location, unresectable disease, and initial central nervous system or bone marrow involvement.[73]

Generally, more than 70% of children with ALCL present for care at an advanced stage (Stage III–IV).[51,54] For example, Brugières and colleagues (1998) reported that 28% of paediatric ALCL patients identified had Stage I–II disease, while 72% had Stage III–IV disease. Similarly, Chen and colleagues (2019) reported that 30% of Taiwanese paediatric ALCL patients identified had Stage I–II disease, while 70% had stage III–IV disease.

Among 34 French children receiving treatment for relapsed or progressive ALK-positive ALCL, 5-year event-free (EFS) and overall survival (OS) were 58% and 70%, respectively.[56] A study that was not specifically restricted to paediatric populations noted that several small retrospective studies have reported that patients experiencing an ALK-positive ALCL relapse have a 50–60% chance of survival; it should be noted that ALK-positive ALCL is generally observed in younger populations, so this likely applies to the population of interest.[57,58]

Studies not specifically related to relapsed cases reported higher survival rates. A study of 14 Turkish paediatric ALK-positive ALCL cases reported an EFS and OS of 34.9% and 91.7%, respectively, at 3 years.[49] A study of 82 French paediatric ALCL cases (92.5% ALK-positive) reported an EFS and OS of 66% and 83%, respectively, at 3 years.[52] Outside of Europe, a U.S. study of 86 children with ALCL (90% ALK-positive) reported a 5-year EFS and OS of 68% (95% CI 57–78%) and 80% (95% CI 69–87%), respectively.[55] A Japanese study of 31 paediatric ALCL cases (88% ALK-positive) reported 5-year EFS and OS of 66.7% and 71.2%, respectively.[71]

Important co-morbidities:

Due to the rarity of paediatric ALCL, the studies available on paediatric ALCL generally and ALK-positive ALCL or relapsed ALCL specifically — are characterized by small population sizes, with most studies characterizing populations of less than 30 patients. As such, information on important co-morbidities was unavailable, and could not be inferred from a paediatric population (i.e., compared to elderly populations with more established comorbidities).

Paediatric patients (age ≥1 to <18 years) with recurrent or refractory anaplastic lymphoma kinase (ALK) positive unresectable inflammatory myofibroblastic tumour (IMT).

Accurate data regarding the epidemiology of IMT are difficult to obtain, partly due to the rarity of the disease (nearly every article was a case report or case series) and partly due to often being conflated over time with other terms, such as "inflammatory pseudotumour," "inflammatory fibroscaroma," and many others.[74,75]

No study was found that focused on the target population specifically (paediatric patients with unresectable, recurrent, or refractory ALK-positive IMT), nor on paediatric patients with ALK-positive IMT.

Epidemiologic Literature Search Strategy:

The National Library of Medicine Pubmed database was searched for primary literature and review articles on incidence, prevalence, mortality, risk factors, and comorbidities of relapsed or refractory ALK-positive IMT.[5]

Articles with abstracts that were available in English and reported human populations were included. A total of 142 titles and abstracts were screened for relevance. Articles were excluded if they reported on in vitro studies, clinical trials or case reports. Reference lists of included studies, articles that cited included studies, and additional iterative PubMed

[5] Footnote: Search terms: ("anaplastic lymphoma kinase"[MeSH Terms] OR ("anaplastic"[All Fields] AND "lymphoma"[All Fields] AND "kinase"[All Fields]) OR "anaplastic lymphoma kinase"[All Fields] OR "alk"[All Fields]) **AND** ("granuloma, plasma cell"[MeSH Terms] OR ("granuloma"[All Fields] AND "plasma"[All Fields] AND "cell"[All Fields]) OR "plasma cell granuloma"[All Fields] OR ("inflammatory"[All Fields] AND "myofibroblastic"[All Fields] AND "tumor"[All Fields]) OR "inflammatory myofibroblastic tumor"[All Fields] OR ("granuloma, plasma cell"[MeSH Terms] OR ("granuloma"[All Fields] AND "plasma"[All Fields] AND "cell"[All Fields]) OR "plasma cell granuloma"[All Fields] OR ("inflammatory"[All Fields] AND "myofibroblastic"[All Fields] AND "tumour"[All Fields]) OR "inflammatory myofibroblastic tumour"[All Fields]) OR "imt"[All Fields]) **AND** (("unresectability"[All Fields] OR "unresectable"[All Fields] OR "unresected"[All Fields] OR ("recurrance"[All Fields] OR "recurrence"[MeSH Terms] OR "recurrence"[All Fields] OR "recurrences"[All Fields] OR "recurrencies"[All Fields] OR "recurrency"[All Fields] OR "recurrent"[All Fields] OR "recurrently"[All Fields] OR "recurrents"[All Fields]) OR ("refractories"[All Fields] OR "refractoriness"[All Fields] OR "refractory"[All Fields]) OR ("relapse"[All Fields] OR "relapses"[All Fields] OR "relapsing"[All Fields] OR "relapsed"[All Fields] OR "relapser"[All Fields] OR "relapsers"[All Fields])) **AND** ("hasabstract"[All Fields] AND "humans"[MeSH Terms] AND "english"[Language]))

searches were also reviewed for relevance. There were 30 articles retained inclusion in this review.

Incidence:

IMT is very rare and occurs in less than one in one million people. An estimated 150-200 people are diagnosed in the US annually.[76,77,78] The majority of patients are pediatric. Case reports and case series suggest that between 1/3 and 2/3 or IMT involve ALK gene rearrangements.[79,80,81,82,83,84,85] The proportion of IMTs that are unresectable, recurrent, or refractory is around 20-30% of patients.[79,80,85]

Taken together, if IMT occurs in 1 per million people, the majority of which are children, half of which are ALK+, and 30% are unresectable, recurrent, or refractory, then the annual incidence of pediatric ALK+ IMT that is unresectable, recurrent or refractory is on the order of 0.2 per million.

Prevalence:

IMTs account for 0.04% to 0.2% of thoracic surgical procedures.[86,87] They are more common in children and are the most common pediatric primary lung lesion accounting for 16%-38% of primary lung tumors evaluated at single centers.[88,89,90,91]

Demographics of the population:

Children and young adults form the majority of IMT patient population (mean age at diagnosis 10 years), and the lesions affect females more frequently than males.[92,93,94]

The main existing treatment options:

Surgical resection is the mainstay of treatment for IMT, but due to close proximity to vital structures, a complete surgical resection may not always be an option. There are no approved therapies for patients with unresectable, recurrent, or refractory IMT. However, as a mesenchymal tumor admixed with an inflammatory component, IMTs may respond initially to systemic corticosteroid therapy or non-steroidal anti-inflammatory drugs.[69]

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

IMT forms in mucosal surfaces (such as eyes, nose, mouth, digestive tract, lungs, and genital and urinary tracts) and mesentery. The most common anatomical locations are the abdominopelvic region, lung, and retroperitoneum,[95] but virtually any site may be involved, including the bladder, uterus, larynx, stomach, liver, intestine, bone, or central nervous system.[96,74]

While some researchers believe IMT is a true neoplasm, others believe that it represents an immunologic response to an infectious or noninfectious agent.[97] The clinical behaviour of IMTs may be unpredictable. In most cases, they are benign lesions; however, occasionally, they are regarded as true neoplasms with a tendency for local recurrence and sometimes

metastases.[93] Recurrence does sometimes occur, even after complete surgical resection of the primary tumor.[79,98]

As surgical resection has been considered as the standard treatment;[84] the majority (80% to 100%) of IMT patients undergo resection.[79,99,100,101] Local recurrence may occur after initial surgery, ranging from 0% to 25% from study to study.[79,99,101,102,103] The reported incidence of local recurrence in children with mesentery and retroperitoneal tumours is between 15% and 37%.[79,98]

The overall prognosis for IMT is good, even for initially unresectable disease and in ALK– cases (Casanova 2020). In general, those with IMT that is completely removed by surgery do very well and most people survive past 10 years.[78] However, conclusive data regarding the prognosis are lacking due to the absence of routine and standardized follow-up.[104] Precise removal with adequate margins has great prognostic significance, and the recurrence rate is <10 % when complete resection is achieved.[106,103] In some studies, complete resection was considered curative in most patients.[106] Clinical and radiological follow-up is required to detect recurrence.[84,106]

Patients with unresectable tumours had a variable clinical course—some underwent resection of recurrences with durable benefit, while others with multicentric disease died with metastases.[80]

In Italy, among 26 children with IMT (27% ALK-positive) that were retrospectively observed, 21 of them underwent complete excision, and 5 received chemotherapy. After a median follow-up of 6.6 years, 24 patients were in complete remission, and 2 patients died of disease. The 5-year and 10-year EFS rates were 87.4% and 72.8%, respectively.[79]

Among 60 IMT patients (age <25 years) registered from 9 European countries, 40 of them were ALK+ (66.7%). Treated by surgery and systemic therapy, the five-year EFS and OS were 82.9% and 98.1%, respectively.[85]

Important co-morbidities:

Due to the rarity of paediatric IMT, the studies available on paediatric IMT generally — and ALK+ IMT or relapsed IMT specifically — are characterized by small population sizes, with most studies characterizing populations of less than 30 patients. As such, information on important co-morbidities was unavailable, and could not be inferred from a paediatric population (i.e. compared to elderly populations with more established comorbidities).

Module.SII. Non-Clinical Part of the Safety Specification

Non-clinical in vitro and in vivo safety studies have been conducted with crizotinib to support clinical studies. These non-clinical studies were primarily conducted in rats and dogs based on the similarity of metabolic profiles to human and suitable pharmacokinetic profiles. The majority of in vivo studies were conducted with oral dosing, the intended route of administration in humans. Study types included safety pharmacology, repeat-dose toxicity (up to 3 months duration), reproductive and developmental toxicity, genetic toxicity, and phototoxicity studies.

Based on the non-clinical studies conducted with crizotinib, the primary toxicities were observed in the gastrointestinal tract, haematopoietic system, cardiovascular, hepatic (transaminase elevation), and reproductive organs. Additional findings identified following crizotinib administration included an effect on retinal function, phospholipidosis in multiple organs without correlated toxicities, an effect on actively growing long bones, potential for embryofetal development effects, and aneugenicity. Other findings of uncertain risk to humans included decreased cellularity in lymphoid organs, potential for phototoxicity, and effects on salivary glands.

Additional details on the non-clinical safety findings are provided in Module 2, Non-clinical Overview; Section 2.4.4.10 (Target Organ Toxicity).

Table 3 describes the non-clinical safety findings that have potential relevance to human use.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Gastrointestinal Gastrointestinal effects were primarily observed as clinical signs of emesis and/or abnormal faeces in rats, dogs, and monkeys. At severely toxic doses, microscopic changes in the stomach or intestines (eg focal oedema of the gastric submucosa; mucosal and submucosal congestion of intestines; cecal erosion and ulceration) accompanied the clinical signs. (Non-clinical Overview: Section 2.4.4.10.1)	Crizotinib has the potential to cause gastrointestinal perforation in humans. For more information see Section SVII.3.1.6. Crizotinib has the potential to cause other gastrointestinal ADRs of nausea, vomiting, and diarrhea in humans. These effects are not included as safety concerns because they are known to health professionals and do not require additional pharmacovigilance activities or risk minimization measures.
Haematopoietic Haematopoietic effects that affected both myeloid (primarily neutrophils and lymphocytes) and erythroid parameters were observed in rats, dogs, and monkeys. Bone marrow hypocellularity (myeloid and erythroid) observed in the rat and monkey correlated to the peripheral haematological changes. (Non-clinical Overview: Section 2.4.4.10.2)	Crizotinib has the potential to cause leukopenia in humans. This effect is not included as a safety concern because it is known to health professionals and does not require additional pharmacovigilance activities or risk minimization measures.
Cardiovascular Decreases in heart rate, diastolic blood pressure, and myocardial contractility were observed in an anaesthetised cardiovascular dog study. Increases in left ventricular end diastolic pressure, PR, and QRS interval prolongation, and decreased myocardial contractility were also observed. Crizotinib is a mixed ion channel blocker with human ether-à-go-go related gene potassium channel and calcium channel inhibition. As such, crizotinib is considered to have the potential to cause QT interval prolongation; however, QT interval prolongation observed in an anaesthetised dog study was considered secondary to decreased heart rate observed at those doses. (Non-clinical Overview: Section 2.4.4.10.3)	Crizotinib has the potential to cause QTc prolongation, bradycardia, and cardiac failure in humans. For more information see Section SVII.3.1.3.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Despite the effect on cardiac function in the anaesthetised dog study, there has been no evidence of cardiac toxicity from rat or dog general toxicity studies of up to 3 months duration. The effect on cardiac function therefore appears to occur in the absence of structural damage to the heart. There is therefore no additional non-clinical safety data on cardiotoxicity risk of crizotinib.	
Liver An elevation of liver enzymes (ALT, AST, and/or GGT) presented without a histological correlate in rats, dogs, and monkeys in studies up to 3 months in duration. (Non-clinical Overview: Section 2.4.4.10.4)	Crizotinib has the potential to cause hepatotoxicity in humans. For more information see Section SVII.3.1.1.
Reproductive Toxicity Effects on male and female reproductive organs were observed in the rat and dog following repeat-dose administration of crizotinib. Testicular pachytene spermatocyte degeneration and single cell necrosis of ovarian follicles was identified in rats given crizotinib for 1 month or 3 days, respectively. (Non-clinical Overview: Section 2.4.4.10.5).	Crizotinib has the potential to impair reproductive function and adversely affect fertility in humans including pregnant and lactating women. For more information see Section SVII.3.1.8.
Developmental Toxicity Crizotinib administration was associated with reduced foetal body weights in rat and rabbit embryofoetal development studies, but did not cause teratogenic effects (Non-clinical Overview: Section 2.4.4.10.12).	Crizotinib has the potential to adversely affect embryo-fetal development in humans. For more information see Section SVII.3.1.8.
Vision Disorder A delay in dark adaptation was observed following 2 and 4 weeks of dosing in a rat electroretinography study (Non-clinical Overview: Section 2.4.4.10.6). No ocular toxicity was observed in general toxicity studies of up to 3 months duration in the mouse, rat, dog, or monkey, which suggests that the effect on retinal function is not associated with a morphological insult.	Crizotinib has the potential to cause a severe vision loss or sight threatening events in humans. For more information see Section SVII.3.1.9.
Phototoxicity Crizotinib was evaluated for its phototoxic potential in a 3T3 fibroblast Neutral Red Uptake assay. Photo irritation factor and mean photo effect values were 3.4 and 0.1, respectively. Under the conditions of this experiment, crizotinib showed probable evidence of phototoxicity. (Non-clinical Overview: Section 2.6.6.8.2)	Crizotinib has the potential to cause photosensitivity. It is not included as a safety concern because it occurs at a low frequency that is considered to be acceptable in relation to the severity of the indications treated.
Bone Growth A decrease in bone formation at the primary spongiosa of growing long bones was observed in immature rats following 28 days of dosing. (Non-clinical Overview: Section 2.4.4.10.8)	Based on clinical data from a study (CRZ-NBALCL) designed to evaluate bone toxicity and impaired bone growth in paediatric and young adult patients, there was no evidence of bone toxicity associated with crizotinib.
Genotoxicity Crizotinib was aneugenic in an in vitro micronucleus assay in Chinese Hamster Ovary cells and in an in vitro human lymphocyte chromosome aberration assay.	There is currently insufficient evidence to determine if crizotinib has the potential to cause other potential effects resulting from aneugenicity.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Small increases of structural chromosomal aberrations at cytotoxic concentrations were seen in human lymphocytes that are believed to be secondary to the aneugenic activity of the compound. (Non-clinical Overview: Section 2.4.4.10.11)	
Renal Cysts Published literature suggests a potential role for HGF in the kidney and potential factors of this pathway that may contribute to cyst formation. There were no renal cysts observed in vivo in rats or dogs in toxicity studies up to 3 months in duration.	Crizotinib has the potential to cause renal cysts. For more information see Section SVII.3.1.5.

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GGT = Gamma glutamyl transpeptidase; QTc = QT interval, Corrected for Heart Rate.

Module.SIII. Clinical Trial Exposure

ALK-positive advanced NSCLC and ROS1-positive advanced NSCLC

A total of 1669 patients had locally advanced or metastatic ALK-positive NSCLC (in this document referred to as "ALK-positive advanced NSCLC") and received crizotinib 250 mg orally twice daily in Studies A8081001 (patients with ALK-positive NSCLC RP2D cohort only), A8081005, A8081007 and A8081014 (crizotinib arm and patients crossing over from the chemotherapy arm to receive crizotinib) in the target population. The exposure includes pooled data for first and second line patients through 30 November 2013. Exposure for these 1669 patients is summarised in Table 4, Table 5 and Table 6.

A total of 53 patients had locally advanced or metastatic ROS1-positive advanced NSCLC (in the document referred to as 'ROS1-positive advanced NSCLC") and received crizotinib at a starting dose of 250 mg orally twice daily in Study A8081001. The exposure includes ROS1-positive NSCLC through 30 November 2014. Exposure for these 53 patients is summarised in Table 7, Table 8 and Table 9.Pooled exposure (1669 patients + 53 patients) for the 1722 patients is summarised in Table 10, Table 11 and Table 12.

Table 4. Crizotinib: Duration Of Exposure In All Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Patients

Duration of Exposure[a]	Crizotinib	
	Persons	Person-Time (Months)
<1 month	117[b]	64.5[d]
≥1 month	1552[c]	21636.4[e]
≥3 months	1340	21232.3
≥6 months	1102	20137.7
≥12 months	733	16893.8
≥18 months	495	13394.3
≥24 months	289	9084.1
≥36 months	55	2317.6
Total[f]	1669	21700.8

Source: Table 14.4.1.10.1.6 Date of Table Generation: 25 August 2014. Includes Protocols: A8081001 (ALK-positive NSCLC RP2D cohort only), A8081005, A8081007 (crizotinib only) and A8081014 (crizotinib only, including patients who crossed over from chemotherapy to receive crizotinib).
ALK = Anaplastic Lymphoma Kinase; NSCLC = Non-Small Cell Lung Cancer; RP2D = Recommended Phase 2 Dose.
a. Duration excludes time of temporary treatment discontinuation; 1 month is defined as 30.44 days.
b. Represents the number of patients with duration of exposure <1 month.
c. Represents the number of patients with duration of exposure ≥1 month; additional rows follow the same pattern.
d. Represents total number of person-months of exposure for patients with a duration of exposure <1 month.
e. Represents total number of person-months of exposure for patients with duration of exposure ≥1 month; additional rows follow the same pattern.
f. Represents total exposure for all patients who received ≥1 dose of study treatment.

Table 5. Crizotinib: Duration Of Exposure By Age Group And Gender In All Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Patients

Age Group	Crizotinib (N = 1669)			
	Male		Female	
	Persons	Person-Time (Months)	Persons	Person-Time (Months)
≤65 years[a]	610	7972.8	789	10691.9
≥65 years	107	1273.2	163	1763.0
Total	717	9246.0	952	12454.9

Source: Table 14.4.1.10.3.6 Date of Table Generation: 09 June 2014. Includes Protocols: A8081001 (ALK-positive NSCLC RP2D cohort only), A8081005, A8081007 (crizotinib only) and A8081014 (crizotinib only, including patients who crossed over from chemotherapy to receive crizotinib).
ALK = Anaplastic Lymphoma Kinase; N = Total Number of Patients; NSCLC = Non-Small Cell Lung Cancer; RP2D = Recommended Phase 2 Dose.
a. There is no paediatric exposure (<18 years of age) data in the clinical database.

Table 6. Crizotinib: Duration Of Exposure By Ethnic Origin In All Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Patients

Race	Crizotinib (N = 1669)	
	Persons	Person-Time (Months)
White	853	10789.2
Black	28	367.9
Asian	753	9996.9
Racial Designation for Asian		
Japanese	162	1903.1
Korean	236	3818.5
Chinese	322	3908.5
Other	33	366.8
Other	35	546.8
Total	1669	21700.8

Source: Table 14.4.1.10.4.6 Date of Table Generation: 09 June 2014. Includes Protocols: A8081001 (ALK-positive NSCLC RP2D cohort only), A8081005, A8081007 (crizotinib only) and A8081014 (crizotinib only, including patients who crossed over from chemotherapy to receive crizotinib).
ALK = Anaplastic Lymphoma Kinase; N = Total Number of Patients; NSCLC = Non-Small Cell Lung Cancer; RP2D = Recommended Phase 2 Dose.

Table 7. Crizotinib: Duration of Exposure in ROS1-Positive Advanced Non-Small Cell Lung Cancer Patients in Study A8081001

Duration of Exposure[a]	Crizotinib	
	Persons	Person-time (Months)
< 1 month	1[b]	0.5[d]
≥ 1 month	52[c]	1004.3[e]
≥ 3 months	47	994.8
≥ 6 months	42	971.4
≥ 12 months	36	917.7
≥ 18 months	27	781.9
≥ 24 months	16	546.7
≥ 36 months	7	289.9
Total[f]	53	1004.8

a. Duration excludes time of temporary treatment discontinuation; 1 month is defined as 30.44 days.
b. Represents the number of patients with a duration of exposure < 1 month.
c. Represents the number of patients with a duration of exposure ≥ 1 month; additional rows follow the same pattern.
d. Represents total number of person-months of exposure for patients with a duration of exposure <1 month.
e. Represents total number of person-months of exposure for patients with a duration of exposure ≥ month; additional rows follow the same pattern
f. Represents total exposure for all patients who received ≥ 1 dose of study treatment.
Source: Table 14.4.1.10.1.1 Date of Table Generation: 24 September 2015. Includes Protocol: A8081001 (ROS1-Positive NSCLC patients).

Table 8. Crizotinib: Duration of Exposure by Age Group and Gender in ROS1-Positive Advanced Non-Small Cell Lung Cancer Patients in Study A8081001

Age Group	Crizotinib (N = 53)			
	Male		Female	
	Person	Person-time (Months)	Person	Person-time (Months)
< 65 years[a]	17	395.8	21	371.3
>=65 years	6	85.3	9	152.3
Total	23	481.2	30	523.6

Source: Table 14.4.1.10.3.1 Date of Table Generation: 14 September 2015. Includes Protocol: A8081001 (ROS1-positive NSCLC patients).
N = Total Number of Subjects Participated in Study; NSCLC = Non-Small Cell Lung Cancer; ROS1 = Ros Oncogene 1.
a. There is no paediatric exposure (<18 years of age) data in the clinical database.

Table 9. Crizotinib: Duration of Exposure by Ethnic Origin in ROS1-Positive Advanced Non-Small Cell Lung Cancer Patients in Study A8081001

Race	Crizotinib (N = 53)	
	Persons	Person-time (Months)
White	30	533.4
Black	2	63.7
Asian	21	407.7
Racial Designation for Asian		
Korean	13	223.3
Chinese	4	89.3
Other	4	95.1
Total	53	1004.8

Source: Table 14.4.1.10.4.1 Date of Table Generation: 14 September 2015. Includes Protocol: A8081001 (ROS1-positive NSCLC patients).
N = Total Number of Subjects Participated in Study; NSCLC = Non-Small Cell Lung Cancer; ROS1 = Ros Oncogene 1.

Table 10. Crizotinib: Duration of Exposure ROS1-Positive Advanced Non-Small Cell Lung Cancer And In All Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Patients In All Studies

Duration of Exposure[a]	Crizotinib	
	Persons	Person-time (Months)
< 1 month	118[b]	65.0[d]
≥ 1 month	1604[c]	22640.6[e]
≥ 3 months	1387	22227.1
≥ 6 months	1144	21109.1
≥ 12 months	769	17811.5
≥ 18 months	522	14176.2
≥24 months	305	9630.8
≥ 36 months	62	2607.5
Total[f]	1722	22705.6

Source: Table 14.4.1.10.1.2 Date of Table Generation: 24 September 2015. Includes Protocols: A8081001 (RP2D, NSCLC, ALK-Positive), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1-Positive NSCLC patients).
ALK = anaplastic lymphoma kinase; NSCLC = Non-Small Cell Lung Cancer; ROS1 = Ros Oncogene 1; RP2D = Recommended Phase 2 Dose.
a. Duration excludes time of temporary treatment discontinuation; 1 month is defined as 30.44 days.
b. Represents the number of patients with a duration of exposure < 1 month.
c. Represents total number of person-months of exposure for patients with a duration of exposure <1 month.
d. Represents the number of patients with a duration of exposure ≥ 1 month; additional rows follow the same pattern.
e. Represents total number of person-months of exposure for patients with a duration of exposure ≥ month; additional rows follow the same pattern.
f. Represents total exposure for all patients who received ≥ 1 dose of study treatment.

Table 11. Crizotinib: Duration of Exposure by Age Group and Gender in ROS1-Positive Non-Small Cell Lung Cancer And In All Anaplastic Lymphoma Kinase Positive Advanced Non-Small Cell Lung Cancer Patients In All Studies

Age Group	Crizotinib (N = 1722)			
	Male		Female	
	Person	Person-time (Months)	Person	Person-time (Months)
< 65 years[a]	627	8368.6	810	11063.2
≥65 years	113	1358.5	172	1915.3
Total	740	9727.1	982	12978.5

Source: Table 14.4.1.10.3.2 Date of Table Generation: 14 September 2015. Includes Protocol: A8081001 (RP2D, NSCLC, ALK-Positive), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1-Positive NSCLC patients).
ALK = Anaplastic Lymphoma Kinase; N = Total Number of Subjects Participated in Study; NSCLC = Non-Small Cell Lung Cancer; ROS1 = Ros Oncogene 1; RP2D = Recommended Phase 2 Dose.
a. There is no paediatric exposure (<18 years of age) data in the clinical database.

Table 12. Crizotinib: Duration of Exposure by Ethnic Origin in ROS1-Positive Non-Small Cell Lung Cancer And In All Anaplastic Lymphoma Kinase Positive Advanced Non-Small Cell Lung Cancer Patients In All Studies

Race	Crizotinib (N = 1722)	
	Persons	Person-time (Months)
White	883	11322.6
Black	30	431.6
Asian	774	10404.6
Racial Designation for Asian		
Japanese	162	1903.1
Korean	249	4041.7
Chinese	326	3997.8
Other	37	462
Other	35	546.8
Total	1722	22705.6

Source: Table 14.4.1.10.4.2 Date of Table Generation: 24 September 2015. Include Protocols: A8081001 (RP2D, NSCLC, ALK-Positive), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1-Positive NSCLC patients).
ALK = Anaplastic Lymphoma Kinase; N = Total Number of Subjects Participated in Study; NSCLC = Non-Small Cell Lung Cancer; ROS1 = Ros Oncogene 1; RP2D = Recommended Phase 2 Dose.

ALCL and IMT in the Paediatric Population

A total of 41 paediatric patients with relapsed or refractory systemic ALK positive ALCL or with recurrent or refractory ALK positive unresectable IMT received crizotinib as a single agent.

With reference to ALK-positive ALCL, a total of 25 patients (22 patients from Study ADVL0912 and 3 patients from Study A8081013) received at least 1 dose of crizotinib. Of the 22 patients in Study ADVL0912, 16 received crizotinib at a starting dose of 280 mg/m^2 BID. In Study A8081013, the 3 patients received crizotinib at a starting dose of 250 mg BID in Study A8081013.

With reference to ALK-positive IMT, a total of 16 patients (14 patients from Study ADVL0912 and 2 patients from Study A8081013) received at least 1 dose of crizotinib. Of the 14 patients in Study ADVL0912, 12 received crizotinib at a starting dose of 280 mg/m^2 BID. In Study A8081013, the 2 patients received crizotinib at a starting dose of 250 mg BID.

Exposure for these 41 patients is summarised in Table 13, Table 14, Table 15, and Table 16.

Table 13. Crizotinib: Duration of Exposure by Tumor Type (ALCL or IMT) in the paediatric population (age < 18 years)

	Crizotinib					
	ALCL		IMT		ALCL + IMT	
Duration of Exposure [a]	Persons [b]	Person-Time (Months) [c]	Persons [b]	Person-Time (Months) [c]	Persons [b]	Person-Time (Months) [c]
< 1 month	0	0	0	0	0	0
≥ 1 month	25	507.5	16	495.3	41	1002.7
≥ 3 months	17	490.3	15	492.5	32	982.8
≥ 6 months	11	463.2	14	487.9	25	951.1
≥ 12 months	7	431.9	12	471.4	19	903.3
≥ 18 months	5	400.2	9	418.7	14	819
≥ 24 months	5	400.2	7	377.1	12	777.4
≥ 36 months	5	400.2	4	297.3	9	697.6
Total [d]	25	507.5	16	495.3	41	1002.7

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08 January 2021)
[a]Duration is dosing days on which study drug was actually administered; 1 month is defined as 30.4375 days.
[b] Represents the number of patients with a duration of exposure.
[c] Represents total number of person-months of exposure for patients with a duration of exposure.
[d] Represents total exposure for all patients who received ≥ 1 dose of study treatment
Date of Generation: 23FEB2021

Table 14. Crizotinib: Duration of Exposure by Age Group in ALCL or IMT paediatric population (age < 18 years)

	Crizotinib					
	ALCL		IMT		ALCL + IMT	
Age group	Persons [a]	Person-Time (Months) [b]	Persons [a]	Person-Time (Months) [b]	Persons [a]	Person-Time (Months) [b]
< 2 years	0	0	0	0	0	0
2 - < 6 years	4	166.9	4	115.7	8	282.6
6 - < 12 years	11	65.6	8	173.7	19	239.3
12 - < 18 years	10	275	4	205.8	14	480.8
Total [c]	25	507.5	16	495.3	41	1002.7

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08 January 2021)
Note: Duration is dosing days on which study drug was actually administered; 1 month is defined as 30.4375 days.
[a] Represents the number of patients with a duration of exposure.
[b] Represents total number of person-months of exposure for patients with a duration of exposure.
[c] Represents total exposure for all patients who received ≥ 1 dose of study treatment.
Date of Generation: 23FEB2021

Table 15. Crizotinib: Duration of Exposure by Gender in ALCL or IMT paediatric population (age < 18 years)

	Crizotinib					
	ALCL		IMT		ALCL + IMT	
Gender	Persons [a]	Person-Time (Months) [b]	Persons [a]	Person-Time (Months) [b]	Persons [a]	Person-Time (Months) [b]
Male	19	297.6	6	183.8	25	481.4
Female	6	209.9	10	311.5	16	521.3
Total [c]	25	507.5	16	495.3	41	1002.7

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08 January 2021)
Note: Duration is dosing days on which study drug was actually administered; 1 month is defined as 30.4375 days.
[a] Represents the number of patients with a duration of exposure.
[b] Represents total number of person-months of exposure for patients with a duration of exposure.
[c] Represents total exposure for all patients who received ≥ 1 dose of study treatment.
Date of Generation: 23FEB2021

Table 16. Crizotinib: Duration of Exposure by Ethnic Origin in ALCL or IMT paediatric population (age < 18 years)

	Crizotinib					
	ALCL		IMT		ALCL + IMT	
Ethnic Origin	Persons [a]	Person-Time (Months) [b]	Persons [a]	Person-Time (Months) [b]	Persons [a]	Person-Time (Months) [b]
White	12	342.6	10	221.9	22	564.5
Black or African American	5	27	1	17.9	6	44.9
Asian	4	121.1	2	182.5	6	303.6
Unknown	4	16.8	3	73	7	89.7
Total [c]	25	507.5	16	495.3	41	1002.7

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08 January 2021)
Note: Duration is dosing days on which study drug was actually administered; 1 month is defined as 30.4375 days.
[a] Represents the number of patients with a duration of exposure.
[b] Represents total number of person-months of exposure for patients with a duration of exposure.
[c] Represents total exposure for all patients who received ≥ 1 dose of study treatment.
Date of Generation: 23FEB2021

Module.SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

There has been limited exposure in special populations to crizotinib and no epidemiologic studies have been conducted in pregnant/lactating women, and specific subpopulations that were excluded from the CT development programme.

The following is the important exclusion criterion across the crizotinib development program:

Hypersensitivity to crizotinib or to any of the excipients

Reason for exclusion**:** Unknown risk but standard wording for the administration of an exogenous substance.

Is it considered to be included as missing information? No

Rationale**:** there is no anticipated use of crizotinib where a patient has a known hypersensitivity reaction to crizotinib or excipients.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 17. Exposure of special populations included or not in clinical trial development programmes[a]

Type of special population	Exposure
Patients with relevant comorbidities: • Patients with hepatic impairment	Crizotinib is extensively metabolised in the liver. Treatment with crizotinib should be used with caution in patients with hepatic impairment. A clinical study was conducted in patients with advanced cancer and varying degrees of hepatic impairment (Study A8081012). No starting dose adjustment of crizotinib is recommended for patients with mild hepatic impairment (either AST > ULN and total bilirubin ≤ULN or any AST and total bilirubin >ULN but ≤1.5×ULN). The starting crizotinib dose for patients with moderate hepatic impairment (any AST and total bilirubin >1.5×ULN and ≤3×ULN) is recommended to be 200 mg twice daily. The starting crizotinib dose for patients with severe hepatic impairment (any AST and total bilirubin >3×ULN) is recommended to be 250 mg once daily, as crizotinib doses greater than 250 mg once daily have not

Table 17. Exposure of special populations included or not in clinical trial development programmes[a]

Type of special population	Exposure
	been studied in patients with severe hepatic impairment and may result in increases of systemic crizotinib exposure to supra-therapeutic levels.
• Patients with renal impairment	Crizotinib has been studied in patients with severe renal impairment as part of a Post-Marketing Requirement study in the US and Post-Authorisation Measure in the EU in Study A8081020. Based on these results, an adjustment in the starting dose of crizotinib to 250 mg QD for patients with severe renal impairment is recommended. No starting dose adjustment is recommended for patients with mild (60≤CrCL<90 mL/min) and moderate (30≤CrCL<60 mL/min) renal impairment since no clinically meaningful changes in steady state crizotinib plasma trough concentrations were observed in single-arm Studies A8081001 and A8081005 for those patients with mild or moderate renal impairment.
P-Glycoprotein Substrates	There is limited experience with crizotinib in patients taking P-glycoprotein substrates. There is currently no study planned to study the effects of P-glycoprotein substrates.
Patients Undergoing Long-term Treatment with Crizotinib	There are cases of adult and paediatric patients who have received crizotinib long term, however a formal evaluation of crizotinib long-term treatment has not been conducted..

ADR = Adverse Drug Reaction; AE = Adverse Event; ALCL = Anaplastic Large Cell Lymphoma; ALK = Anaplastic Lymphoma Kinase; ALT = Alanine Transaminase; AST = Aspartate Aminotransferase; AUC = Area Under the Curve; BID = Twice Daily; CI = Confidence Interval; C_{max} = Peak serum concentration; COG = Children's Oncology Group; CrCL = Creatinine Clearance; CYP = Cytochrome P450; DDI = Drug-Drug Interaction; EU = European Union; N = Total Number of Subjects Participated in Study; NCI = National Cancer Institute; NSCLC = Non-Small Cell Lung Cancer; PK = Pharmacokinetic; QD = Once Daily; $t_{½}$ = Terminal Phase Half-Life; TEAE = Treatment-emergent Adverse Event; T_{max} = Time o Peak Serum Concentration; ULN = Upper Limit of Normal.

a. Although not all special populations included or not in the adult CT development programmes have been observed or not in the CTs of paediatric patients, the same should be considered for paediatric populations.

Module.SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

Cumulatively, as of the data lock point (15 July 2024) of this report, it was estimated that **124,843** patients had been exposed to crizotinib commercially from launch to 15th July 2024.

As per the updated methodology for crizotinib, we have leveraged the actual mg Sales from 01 July 2012 to 31 August 2021 from the Midas Database. Further which is converted to patients using the AVDOS as 159,700. This exposure is added to the exposure calculated from the Shipments data from 01 September 2021 to 15 July 2024. We have leveraged the actual mg sales from 01 July 2012 to 31 August 2021 from the Midas data source and we

have leveraged the actual mg sales from 01 September 2021 to 15 July 2024 from the Shipments data.

Exposure from shipments data is calculated by using the following methodology:

- multiplied the API 1 Strength and the pack size to get the total strength of 1 pack in mg.
- Then, divide the total mg sales by the AVDOS (159,700) to calculate the total patients.

Further, we add the patients calculated from the Midas data source and from the shipments data source to get the total patients in the cumulative period which equates to 124,843 patients for the cumulative period since launch to 15 July 2024.

Cumulative estimated exposure based on total MG sales since launch through 15 July 2024, are summarized in Table 18

Table 18. Cumulative Estimated Exposure for Crizotinib (IBD through 15 July 2024)

Country	Total Patients
Algeria	68
Argentina	555
Australia	812
Austria	462
Bahrain	9
Belarus	50
Belgium	497
Bosnia	0
Brazil	1280
Bulgaria	31
Canada	1375
Chile	805
China	57573
Colombia	542
Croatia	25
Czech Republic	225
Denmark	292
Ecuador	2
Egypt	85
Estonia	1
Finland	220
France	5987
Georgia	1
Germany	4659
Greece	85
Hong Kong	1334
Hungary	266

Table 18. Cumulative Estimated Exposure for Crizotinib (IBD through 15 July 2024)

India	6788
Indonesia	15
Iraq	10
Ireland	188
Israel	90
Italy	3144
Japan	5747
Jordan	7
Kazakhstan	83
Kuwait	14
Latvia	0
Lebanon	135
Libya	0
Lithuania	3
Macedonia	2
Malaysia	462
Mexico	232
Montenegro	1
Morocco	35
Netherlands	300
New Zealand	7
Norway	209
Oman	23
Panama	36
Paraguay	1
Peru	36
Philippines	57
Poland	408
Portugal	740
Puerto Rico	11
Qatar	21
Romania	467
Russia	1414
Saudi Arabia	182
Serbia	5
Singapore	428
Slovakia	47
Slovenia	38
South Africa	36
South Korea	2712
Spain	1817
Sweden	522

Table 18. Cumulative Estimated Exposure for Crizotinib (IBD through 15 July 2024)

Switzerland	690
Taiwan	1495
Thailand	330
Transatlantic Accord	1
Tunisia	15
Turkiye	2838
Ukraine	36
United Kingdom	1569
United States	14093
Uruguay	2
Utd.Arab.Emir.	63

Module.SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

The potential for misuse is considered to be very low given crizotinib does not have characteristics which would make it attractive for use for illegal purposes. In addition, given the age of the target patient population, crizotinib will initiated and managed under the oversight of the prescribing physician as described in the SmPC. It is not considered that there is a high risk of potential for intentional overdose in the treated population with crizotinib or potential for major dose-related toxicity.

Module.SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

The safety concerns in the initial RMP are listed below:

Table 19. Summary of Safety Concerns in the Initial RMP

Summary of Safety Concerns	
Important identified risks	• Hepatotoxicity • Pneumonitis • QTc Prolongation • Bradycardia • Vision Disorder
Important potential risks	• Renal Cyst • Oedema • Leukopenia • Neuropathy • Reproductive Toxicity • Photosensitivity
Missing information	• patients with hepatic impairment

Table 19. Summary of Safety Concerns in the Initial RMP

Summary of Safety Concerns	
	• patients with renal impairment • elderly patients • pediatric patients • pregnant and lactating women andwomen of childbearing potential • patients taking CYP3A inhibitors, inducers, P-glycoprotein substrates, proton pump inhibitors, or H2 antagonists • Patients undergoing long-term treatment

Crizotinib EU-RMP dated 14 December 2012

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP**:**

None.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Not applicable.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers:

Vision disorder, Oedema, Leukopenia, Neuropathy, Nausea, Vomiting. Diarrhoea

Known risks that do not impact the risk-benefit profile:

Not applicable

Other reasons for considering the risks not important[6]:

Photosensitivity, Malignant melanoma

[6] Potential risks with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Adult indications:

The identified and potential risks for crizotinib are characterised based on pooled safety data from 1669 adult patients in 4 clinical trials (Studies A8081001 [ALK-positive NSCLC RP2D cohort only], A8081005, A8081007 [crizotinib only] and A8081014 [crizotinib only, including patients who crossed over from chemotherapy to receive crizotinib]) and from 53 patients with ROS1-positive NSCLC in clinical trial A8081001.

Paediatric indications:

For relapsed or refractory systemic ALK-positive ALCL and with recurrent or refractory ALK-positive unresectable IMT the identified and potential risks for crizotinib are based on pooled safety data from 2 single-arm studies, Study ADVL0912 and Study A8081013 in paediatric populations. The identified and potential risks for crizotinib are characterised based on pooled safety data from 41 paediatric patients in 2 clinical trials (ADVL0912, A8081013). Twenty-five (25) patients with ALCL and 16 patients with IMT.

Important Identified Risks:

Hepatotoxicity
Adult: All-causality AEs suggestive of hepatotoxicity occurred with a frequency of 33.4% (95% CI: 31.16, 35.67).

Paediatric: The frequency of hepatotoxicity with crizotinib treatment is 87.8 % (CI: 86.28, 100.00) and 68.8% (41.34, 88.98) in ALCL and IMT respectively.

Risk-benefit impact: Adverse events associated with Hepatotoxicity include Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased and Gamma glutamyl transferase increased. Drug-induced liver injury and Hepatic failure have been reported. There were no Grade 4 or 5 events.

Hepatotoxicity may have an impact the overall risk-benefit balance of crizotinib. The impact on individual patients is determined by loss of clinical benefit (tumour response) in patients in which crizotinib was discontinued (which is particularly significant in situations where hepatotoxicity is in fact not drug-related as suspected) as well as by the potential for a fatal outcome.

Pneumonitis/Interstitial lung disease
Adult: All-causality AEs suggestive of pneumonitis occurred with frequency of 3.4% (95% CI: 2.62, 4.40).

Paediatric: The frequency of pneumonitis with crizotinib treatment is 4.0 % (CI: 0.10, 20.35) and 0.0% (0.00, 0.00) in ALCL and IMT respectively.

Risk-benefit impact: ILD involves pulmonary fibrosis and patients can experience shortness of breath. ILD may have an impact on individual patients is determined by loss of clinical

benefit (tumour response) in patients in which crizotinib was discontinued as well as by the potential for a fatal outcome.

QTc Prolongation
Adult: All-causality AEs suggestive of QTc prolongation occurred with a frequency of 6.6% (95% CI: 5.49, 7.90).

Paediatric: The frequency of QTc Prolongation with crizotinib treatment is 8.0 % (CI: 0.98, 26.03) and 6.3% (0.16, 30.23) in ALCL and IMT respectively.

Risk-benefit impact: QTc prolongation can be an asymptomatic finding on ECG, but can lead to syncope or cardiac arrest. QTc prolongation may have an impact on individual patients is determined by loss of clinical benefit (tumour response) in patients in which crizotinib requires permanent discontinuation as well as by the potential for a fatal outcome.

Bradycardia
Adult: All-causality AEs suggestive of bradycardia occurred with a frequency of 12.7% (95% CI: 11.18, 14.38).

Paediatric: The frequency of bradycardia with crizotinib treatment is 20.0% (CI: 6.83, 40.70) and 12.5% (1.55, 38.35) in ALCL and IMT respectively.

Risk-benefit impact: Bradycardia may be asymptomatic but some cases may require medical intervention. Bradycardia may have an impact on individual patients is determined by loss of clinical benefit (tumour response) in patients in which crizotinib was discontinued (which is particularly significant in situations where bradycardia is in fact not drug-related as suspected) as well as by the potential for a fatal outcome.

Renal Cyst
Adult: All-causality AEs suggestive of renal cyst occurred with a frequency of 3.0% (95% CI: 2.26, 3.94).

Paediatric: No AEs suggestive of renal cyst were reported with crizotinib treatment in the paediatric CTs.

Risk-benefit impact: Simple and complex renal cysts have been reported. Renal cysts may have an impact on individual patients is determined by loss of clinical benefit (tumour response) in patients in which crizotinib was discontinued (which is particularly significant in situations where renal cyst is in fact not drug-related).

Gastrointestinal perforation
Adult: All-causality AEs suggestive of gastrointestinal perforation occurred with a frequency of 0.2% (95% CI: 0.06, 0.59).

Paediatric: No AEs suggestive of gastrointestinal perforation were reported with crizotinib treatment in the paediatric CTs.

Risk-benefit impact: Gastrointestinal perforation has also been reported with abdominal abscess and peritonitis. Gastrointestinal perforation may have an impact on individual patients is determined by loss of clinical benefit (tumour response) in patients in which crizotinib was discontinued (which is particularly significant in situations where GI perforation is in fact not drug-related) as well as by the potential for a fatal outcome.

Cardiac failure
Adult: All-causality AEs suggestive of cardiac failure occurred with a frequency of 1.1% (95% CI: 0.67, 1.72).

Paediatric: The frequency of cardiac failure with crizotinib treatment is 0.0 % (CI: 0.00, 0.00) and 6.3% (0.16, 30.23) in ALCL and IMT respectively

Risk-benefit impact: Cardiac failure can include ejection fraction decreased, left ventricular failure and pulmonary oedema. Cardiac failure may have an impact on individual patients is determined by loss of clinical benefit (tumour response) in patients in which crizotinib was discontinued (which is particularly significant in situations where cardiac failure is in fact not drug-related) as well as by the potential for a fatal outcome.

Important Potential Risks:

Reproductive Toxicity (including pregnant and lactating women)
Adult: All-causality AEs suggestive of reproductive toxicity (including pregnant and lactating women) occurred with a frequency of 0.6% (95% CI: 0.32, 1.14).

Paediatric: No AEs suggestive of reproductive toxicity (including pregnant and lactating women) were reported with crizotinib treatment.

Risk-benefit impact: Currently, the impact to the overall risk-benefit is not known because the relationship of reproductive and developmental toxicity to crizotinib treatment has not been identified.

If reproductive and developmental toxicity is established as related to crizotinib treatment, it may have the potential to affect the risk-benefit profile of crizotinib.

Severe Vision Loss/Potential Sight Threatening Event
Adult: All-causality AEs suggestive of Vision Disorder occurred with a frequency of 64.5% (95% CI: 62.21, 66.78). Vision disorder could lead to severe vision loss/potential sight threatening event which is considered an important potential risk.

Paediatric: The overall frequency of Vision Disorder[7] with crizotinib treatment is 72.0 % (CI: 50.61, 87.93) and 50.0% (24.65, 75.35) in ALK positive ALCL and IMT respectively. The PTs Vision blurred, Visual impairment, Photopsia, Vitreous floaters, Photophobia, Dyschromotopsia and Visual acuity reduced were reported. The frequency of these AEs with

[7] The search strategy for the new important potential risk, severe vision loss/potential sight threatening events is the same as the important identified risk Vision disorder that was removed.

crizotinib treatment is 20.0 % (CI: 6.83,40.70) and 12.5% (1.55,38.35) in ALK positive ALCL and IMT respectively. Vision disorder could lead to severe vision loss/potential sight threatening event which is considered an important potential risk.

Risk-benefit impact: Currently there is no known impact of severe vision loss/potential sight threatening event on the overall risk-benefit of crizotinib because the relationship to crizotinib treatment has not been identified. Although vision disorder is an identified risk of crizotinib treatment, it is unknown if there is risk of severe vision loss.

If severe vision loss/potential sight threatening event is established as related to crizotinib treatment, it may have the potential to affect the risk-benefit profile of crizotinib.

Missing information:

Patients undergoing long-term treatment

A formal crizotinib long-term treatment study has not been conducted.

Risk-benefit impact: Currently, the impact to the overall risk-benefit balance is not known. There are cases of adult and paediatric patients who have received crizotinib long term.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Study CRZ-NBALCL was included as category 3 additional pharmacovigilance to address the safety concern of bone toxicity and impaired bone growth in paediatric patients. This additional pharmacovigilance activity was completed with the submission of the final analysis on the 30 September 2024 as part of procedure EMEA/H/C/002489/II/0084. Study CRZ-NBALCL included 18 patients with recurrent/refractory ALK positive ALCL or ALK-positive recurrent/refractory neuroblastoma. Baseline assessments and on-treatment were conducted for tibial growth plate assessments. Of note, 12 patients with open tibial growth plates at screening, 2 permanently discontinued crizotinib treatment prior to an on-treatment assessment. Based on the data from the study, and that from the totality of the post-marketing data provided to the EMA during the assessment of procedure EMEA/H/C/002489/II/0084 the MAH considers that the important potential risk of bone toxicity and impaired bone growth in the paediatric population has been adequately assessed and can be removed from the list of the safety concerns in the RMP. Bone toxicity will continue to be monitored the risk through routine PV activities.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Similar to SVII.1.2, the identified and potential risks for crizotinib are characterized based on ALK positive and ROS1 positive NSCLC in the adult population and ALK positive ALCL and ALK positive IMT in the paediatric population.

Note: Although not all important identified and important potential risks in the adult population have been observed in clinical trials of paediatric patients, the same should be considered for the paediatric population.

SVII.3.1.1 Important Identified Risk-Hepatotoxicity

SVII.3.1.1.1. Potential Mechanisms

Hepatic CYP3A is the primary pathway of crizotinib metabolism. Elevated liver enzymes (ALT, AST, and/or GGT) without a histologic correlate were observed in rat, dog, and monkey given crizotinib for up to 3 months. Reversibility of the liver enzyme elevation observed with crizotinib was demonstrated in the rat and dog.

SVII.3.1.1.2. Evidence Source and Strength of Evidence

Evidence source: All non-clinical and all company-sponsored clinical studies; and post-marketing reports.

Strength of Evidence: There have been reports of hepatotoxic adverse reactions in patients receiving crizotinib for treatment of NSCLC and ALCL/IMT.

SVII.3.1.1.3. Characterisation of the Risk

Seriousness/Outcomes

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies

Risk Category	Preferred Term	Total[a] (N = 1722) n (%)	Serious Events[b] n (%)	Fatal* n (%)	Recovered[c] n (%)	Not Recovered[c] n (%)	Unk n (%)
Hepatotoxicity	Alanine aminotransferase increased	495 (28.8)	12 (2.4)	0	387 (78.2)	105 (21.2)	3 (0.6)
	Aspartate aminotransferase increased	383 (22.2)	7 (1.8)	0	304 (79.4)	79 (20.6)	0
	Blood bilirubin increased	27 (1.6)	1 (3.7)	0	19 (70.4)	8 (29.6)	0
	Drug-induced liver injury	6 (0.4)	6 (100.0)	1 (16.7)	4 (66.7)	2 (33.3)	0
	Hepatic encephalopathy	2 (0.1)	0	0	0	2 (100.0)	0
	Hepatic enzyme increased	2 (0.1)	1 (50.0)	0	2 (100.0)	0	0
	Hepatic failure	5 (0.3)	3 (60.0)	1 (20.0)	2 (40.0)	3 (60.0)	0
	Hepatic function abnormal	11 (0.6)	0	0	7 (63.6)	4 (36.4)	0
	Hepatic steatosis	5 (0.3)	0	0	1 (20.0)	4 (80.0)	0
	Hepatitis	2 (0.1)	2 (100.0)	0	2 (100.0)	0	0
	Hepatomegaly	1 (0.1)	0	0	1 (100.0)	0	0
	Hepatotoxicity	6 (0.4)	3 (50.0)	0	5 (83.3)	1 (16.7)	0
	Hyperbilirubinaemia	7 (0.4)	0	0	7 (100.0)	0	0

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies							
Risk Category	**Preferred Term**	**Total[a] (N = 1722) n (%)**	**Serious Events[b] n (%)**	**Fatal* n (%)**	**Recovered[c] n (%)**	**Not Recovered[c] n (%)**	**Unk n (%)**
	Liver disorder	8 (0.5)	0	0	7 (87.5)	1 (12.5)	0
	Liver function test abnormal	3 (0.2)	0	0	1 (33.3)	2 (66.7)	0
	Liver injury	3 (0.2)	0	0	3 (100.0)	0	0
	Transaminases increased	18 (1.1)	1 (5.6)	0	16 (88.9)	2 (11.1)	0

ALK = anaplastic lymphoma kinase; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes Protocols: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.
a. Total patients with specific Preferred Term
b. Patients with Specific SAE for Preferred Term
c. For all patients (i.e not only those with SAE)
* Patients with AEGRADE = 5 for preferred Term.
Source: Table 14.3.1.13.1.2 Date of Table Generation: 24 September 2015.

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ALK-positive ALCL and ALK-positive IMT Paediatric Patients					
Risk Category	**Preferred Term**	**Total (N = 41) n (%) [a]**	**Fatal n (%) [b]**	**Recovered n (%) [c]**	**Not Recovered n (%) [c]**
Hepatotoxicity	Alanine aminotransferase increased	32 (78.0)	0	16 (50.0)	16 (50.0)
	Aspartate aminotransferase increased	28 (68.3)	0	16 (57.1)	12 (42.9)
	Blood bilirubin increased	4 (9.8)	0	4 (100.0)	0
	Gamma-glutamyltransferase increased	3 (7.3)	0	1 (33.3)	2 (66.7)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08JAN2021)
N= total number of patients with ALCL or IMT in the safety analysis population.
[a] Total patients with specific preferred term.
[b] Patients with any event of CTCAE grade 5.
[c] For patients from ADVL0912, recovered patient has a non-missing resolution date for preferred term, and not recovered patient has a missing resolution date for preferred term. For patients from A8081013, adverse event outcome was collected on CRF.
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.
MedDRA v23.1 coding dictionary applied.

Severity and Nature of Risk

Number (%) of All-Causality Adverse Events compatible with possible Hepatotoxicity in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies						
Preferred Term	**Crizotinib (N = 1722)**					
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any AEs[a]	295 (17.1)	89 (5.2)	157 (9.1)	32 (1.9)	2 (0.1)	575 (33.4)
Alanine aminotransferase increased	262 (15.2)	80 (4.6)	127 (7.4)	26 (1.5)	0	495 (28.7)
Aspartate aminotransferase increased	263 (15.3)	48 (2.8)	63 (3.7)	9 (0.5)	0	383 (22.2)
Blood bilirubin increased	15 (0.9)	4 (0.2)	6 (0.3)	2 (0.1)	0	27 (1.6)
Drug-induced liver injury	0	1 (0.1)	2 (0.1)	2 (0.1)	1 (0.1)	6 (0.3)
Hepatic encephalopathy	0	0	2 (0.1)	0	0	2 (0.1)
Hepatic enzyme increased	0	1 (0.1)	1 (0.1)	0	0	2 (0.1)
Hepatic failure	0	0	4 (0.2)	0	1 (0.1)	5 (0.3)
Hepatic function abnormal	5 (0.3)	2 (0.1)	4 (0.2)	0	0	11 (0.6)
Hepatic steatosis	5 (0.3)	0	0	0	0	5 (0.3)
Hepatitis	0	0	2 (0.1)	0	0	2 (0.1)
Hepatomegaly	0	0	1 (0.1)	0	0	1 (0.1)
Hepatotoxicity	1 (0.1)	0	4 (0.2)	1 (0.1)	0	6 (0.3)
Hyperbilirubinaemia	1 (0.1)	4 (0.2)	1 (0.1)	1 (0.1)	0	7 (0.4)
Liver disorder	6 (0.3)	1 (0.1)	1 (0.1)	0	0	8 (0.5)
Liver function test abnormal	1 (0.1)	0	2 (0.1)	0	0	3 (0.2)
Liver injury	1 (0.1)	1 (0.1)	1 (0.1)	0	0	3 (0.2)
Transaminases increased	10 (0.6)	2 (0.1)	5 (0.3)	1 (0.1)	0	18 (1.0)

AE = adverse event; ALK = anaplastic lymphoma kinase; CTCAE = Common Toxicty Criteria for Adverse Events; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.

Includes protocols: A8081001(RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.

MedDRA (v17.1) coding dictionary applied.

a. Any AEs refers the number of subjects who had any treatment-emergent AEs indicative of the Preferred Term.

Source: Table 14.3.1.10.4.1.2 Date of Table Generation: 24 September 2015

Number (%) of All-Causality Adverse Events compatible with possible Hepatotoxicity by Tumour Type (ALK-positive ALCL or ALK-positive IMT, Age <18 years)						
Preferred Term	ALCL + IMT (N = 41)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs[a]	27 (65.9)	5 (12.2)	4 (9.8)	0	0	36 (87.8)
Alanine aminotransferase increased	25 (61.0)	6 (14.6)	1 (2.4)	0	0	32 (78.0)
Aspartate aminotransferase increased	25 (61.0)	1 (2.4)	2 (4.9)	0	0	28 (68.3)
Blood bilirubin increased	2 (4.9)	2 (4.9)	0	0	0	4 (9.8)
Gamma-glutamyltransferase increased	2 (4.9)	0	1 (2.4)	0	0	3 (7.3)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08JAN2021)

a. Any AEs refers the number of subjects who had any treatment-emergent AEs indicative of the Preferred Term. The table is summarized by maximum CTCAE grade.

Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.

MedDRA v23.1 coding dictionary applied..

Source 14.3.1.2.7.3.4 Crizotinib Date of Generation: 04MAR2021

Post-Marketing data from the MAH Safety Database

Table 20. Post-Marketing AEs Hepatotoxicity by Outcome

				Distribution of Event by Outcome* N (%)				
PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
Alanine aminotransferase increased	495 (15.3)	177 (35.8)	46 (9.3)	3 (0.6)	203 (41)	1 (0.2)	48 (9.7)	245 (49.5)
Hepatic function abnormal	462 (14.3)	170 (36.8)	94 (20.3)	0	251 (54.3)	1 (0.2)	38 (8.2)	172 (37.2)
Aspartate aminotransferase increased	373 (11.5)	134 (35.9)	39 (10.5)	2 (0.5)	162 (43.4)	0	35 (9.4)	176 (47.2)
Hepatic enzyme increased	250 (7.7)	61 (24.4)	18 (7.2)	1 (0.4)	75 (30)	1 (0.4)	23 (9.2)	150 (60)
Transaminases increased	217 (6.7)	68 (31.3)	13 (6)	0	92 (42.4)	0	14 (6.5)	112 (51.6)
Hepatotoxicity	215 (6.6)	185 (86)	33 (15.3)	1 (0.5)	91 (42.3)	2 (0.9)	12 (5.6)	110 (51.2)
Liver function test increased	194 (6)	40 (20.6)	12 (6.2)	1 (0.5)	56 (28.9)	0	16 (8.2)	121 (62.4)
Liver disorder	178 (5.5)	39 (21.9)	19 (10.7)	1 (0.6)	58 (32.6)	0	8 (4.5)	111 (62.4)
Liver function test abnormal	97 (3)	23 (23.7)	8 (8.2)	1 (1)	25 (25.8)	0	13 (13.4)	58 (59.8)
Hypertransaminasaemia	91 (2.8)	39 (42.9)	11 (12.1)	0	40 (44)	0	5 (5.5)	46 (50.5)

Table 20. Post-Marketing AEs Hepatotoxicity by Outcome

				Distribution of Event by Outcome* N (%)				
PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
Drug-induced liver injury	88 (2.7)	88 (100)	39 (44.3)	2 (2.3)	58 (65.9)	0	2 (2.3)	26 (29.5)

Reporting Period: Cumulative Through 15-July-2024
Total number of hepatotoxicity AEs 3242. AEs reported ≥2% are presented in the table.
* More than 1 event outcome reported in some cases

SVII.3.1.1.4. Risk Factors and Risk Groups

No risk specific risk groups or risk factors have been identified.

SVII.3.1.1.5. Preventability

It is not known which patients may be at increased risk of developing hepatotoxicity during treatment with crizotinib. Liver function tests including ALT, AST, and total bilirubin should be monitored once a week during the first 2 months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevations. Hepatoxicity may be managed by dose reduction or dose interruption. However, in some cases of severe hepatotoxicity, discontinuation of crizotinib has not been able to avert fatal outcome.

SVII.3.1.1.6. Impact on Risk-Benefit Balance of the Product

Most patients experiencing hepatic enzyme elevation are asymptomatic, however, some patients have experienced decreased appetite, abdominal pain, and jaundice as a result of severe hepatotoxicity. Some patients have needed to discontinue crizotinib treatment due to hepatic toxicity.

SVII.3.1.1.7. Public Health Impact

Some patients may experience significant LFT elevation following exposure to crizotinib. The public health impact of crizotinib-related hepatotoxicity is predominantly determined by the frequency of required permanent dose discontinuations (precluding patients from benefiting from crizotinib) and the frequency of hospitalisations, and life-threatening or fatal cases of hepatotoxicity.

SVII.3.1.2 Important Identified Risk - Pneumonitis/ILD

SVII.3.1.2.1. Potential Mechanisms

The potential mechanism of pneumonitis/interstitial lung disease associated with crizotinib is unknown. However, foamy macrophages were observed in the lungs of rats given crizotinib for 3 months, attributed to phospholipidosis. This finding was reversible and not considered an adverse finding. There were no other respiratory effects identified from safety pharmacology or toxicity studies.

SVII.3.1.2.2. Evidence source and strength of evidence

Evidence source: All non-clinical and all company-sponsored clinical studies; and post-marketing reports.

Strength of Evidence: There have been reports of pneumonitis/ILD adverse reactions in patients receiving crizotinib for treatment of NSCLC.

SVII.3.1.2.3. Characterisation of the Risk

Seriousness/Outcomes

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies

Risk Category	Preferred Term	Total[a] (N = 1722) n (%)	Serious Events[b] n (%)	Fatal* n (%)	Recovered[c] n (%)	Not Recovered[c] n (%)	Unk n (%)
Pneumonitis/ interstitial lung disease	Acute respiratory distress syndrome	4 (0.2)	2 (50.0)	1 (25.0)	4 (100.0)	0	0
	Bronchiolitis	1 (0.1)	0	0	1 (100.0)	0	0
	Interstitial lung disease	8 (0.5)	7 (87.5)	3 (37.5)	7 (87.5)	1 (12.5)	0
	Lung infiltration	2 (0.1)	1 (50.0)	0	1 (50.0)	1 (50.0)	0
	Pneumonitis	37 (2.2)	19 (51.4)	4 (10.8)	30 (81.1)	7 (18.9)	0
	Radiation pneumonitis	9 (0.5)	1 (11.1)	0	5 (55.6)	4 (44.4)	0

ALK = anaplastic lymphoma kinase; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes Protocols: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.

a. Total patients with specific Preferred Term
b. Patients with Specific SAE for Preferred Term
c. For all patients (i.e not only those with SAE)

* Patients with AEGRADE = 5 for preferred Term.
Source: Table 14.3.1.13.1.2 Date of Table Generation: 24 September 2015.

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ALK-positive ALCL and ALK-positive IMT Paediatric Patients					
Risk Category	**Preferred Term**	**Total (N = 41) n (%) [a]**	**Fatal n (%) [b]**	**Recovered n (%) [c]**	**Not Recovered n (%) [c]**
Pneumonitis/ interstitial lung disease	Lung opacity	1 (2.4)	0	1 (100.0)	0

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08JAN2021)
N= total number of patients with ALCL or IMT in the safety analysis population.
[a] Total patients with specific preferred term.
[b] Patients with any event of CTCAE grade 5.
[c] For patients from ADVL0912, recovered patient has a non-missing resolution date for preferred term, and not recovered patient has a missing resolution date for preferred term. For patients from A8081013, adverse event outcome was collected on CRF.
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.
MedDRA v23.1 coding dictionary applied.
Source Table 14.3.1.2.7.2.1 Date of Generation: 05MAR2021

Severity and Nature of Risk

Number (%) of All-Causality Adverse Events compatible with possible Pneumonitis/Interstitial Lung Disease by Severity (CTCAE Grade) in n ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies						
Prefered Term	**Crizotinib (N=1722)**					
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any AEs[a]	17 (1.0)	16 (0.9)	13 (0.8)	5 (0.3)	8 (0.5)	59 (3.4)
Acute respiratory distress syndrome	0	0	2 (0.1)	1 (0.1)	1 (0.1)	4 (0.2)
Bronchiolitis	1 (0.1)	0	0	0	0	1 (0.1)
Interstitial lung disease	3 (0.2)	1 (0.1)	1 (0.1)	0	3 (0.2)	8 (0.5)
Lung infiltration	1 (0.1)	0	1 (0.1)	0	0	2 (0.1)
Pneumonitis	10 (0.6)	10 (0.6)	9 (0.5)	4 (0.2)	4 (0.2)	37 (2.1)
Radiation pneumonitis	4 (0.2)	5 (0.3)	0	0	0	9 (0.5)

AE = adverse event; ALK = anaplastic lymphoma kinase; CTCAE = Common Toxicty Criteria for Adverse Events; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes Protocols: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.
MedDRA (v17.1) coding dictionary applied.
a. Any AEs refers the number of subjects who had any treatment-emergent AEs indicative of the Preferred Term.
Source: Table 14.3.1.10.1.1.2 Date of Table Generation: 24 September 2015.

Number (%) of All-Causality Adverse Events compatible with possible Pneumonitis/ILD ALK-positive ALCL and ALK-positive IMT Paediatric Patients						
Preferred Term	ALCL + IMT (N = 41)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs[a]	1 (2.4)	0	0	0	0	1 (2.4)
Lung opacity	1 (2.4)	0	0	0	0	1 (2.4)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08JAN2021)

a. Any AEs refers the number of subjects who had any treatment-emergent AEs indicative of the Preferred Term.

The table is summarized by maximum CTCAE grade.

Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.

MedDRA v23.1 coding dictionary applied.

Source Table 14.3.1.2.7.3.12 Crizotinib Date of Generation: 04MAR2021

Post-Marketing data from the MAH Safety Database

Table 21. Post-Marketing AEs Pneumonitis/Interstitial Lung Disease by Outcome

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
Interstitial lung disease	337 (49.6)	337 (100)	130 (38.6)	54 (16)	160 (47.5)	7 (2.1)	24 (7.1)	93 (27.6)
Pneumonitis	238 (35.1)	134 (56.3)	59 (24.8)	23 (9.7)	60 (25.2)	5 (2.1)	14 (5.9)	137 (57.6)
Pulmonary fibrosis	21 (3.1)	21 (100)	6 (28.6)	1 (4.8)	0	2 (9.5)	2 (9.5)	16 (76.2)
Acute respiratory distress syndrome	14 (2.1)	14 (100)	7 (50)	9 (64.3)	1 (7.1)	1 (7.1)	1 (7.1)	2 (14.3)

Reporting Period: Cumulative Through 15-July-2024

Total number of pneumonitis/ILD AEs 679. AEs reported ≥2% are presented in the table.

* More than 1 event outcome reported in some cases

SVII.3.1.2.4. Risk Factors and Risk Groups

There are currently no known risk groups or risk factors for the development of pneumonitis/interstitial lung disease in patients receiving crizotinib. Factors that could potentially be associated with an increased risk of developing pneumonitis/interstitial lung disease under ongoing treatment with crizotinib include a history of pre-existing pulmonary disease, prior or concomitant treatment with medications with known pulmonary toxicity: antibiotics (nitrofurantoin, amphotericin B, minocycline); chemotherapy (bleomycin, methotrexate, cyclophosphamide); antiarrhythmics (amiodarone), radiation therapy, immune suppression resulting in pneumonia (bacterial, viral, fungal, or protozoal), a predisoposition to allergic pulmonary disease, autoimmune diseases (SLE, rheumatoid arthritis, etc.), occupational exposure (smoke, dust, silicone, asbestos), and other factors. Further, the underlying malignancy, particularly lymphangiosis carcinomatosa may also increase the risk of pneumonitis and additionally confound the diagnosis.

SVII.3.1.2.5. Preventability

Since no potential mechanism of ILD associated with crizotinib treatment has been identified, this risk cannot be predicted and therefore no preventability measures can be indicated.

SVII.3.1.2.6. Impact of Benefit-Risk of the Product

Management of ILD/pneumonitis as described in the product label will minimize the risk of ILD/pneumonitis and may improve the risk-benefit profile of crizotinib. Some patients need to discontinue crizotinib due to ILD.

SVII.3.1.2.7. Public Health Impact

The public health impact of crizotinib-related Pneumonitis/ILD is predominantly determined by the frequency of required permanent dose discontinuations (precluding patients from benefiting from crizotinib) and the frequency of hospitalizations, and life-threatening or fatal cases of Pneumonitis/ILD.

SVII.3.1.3. Important Identified Risk - QTc Prolongation

SVII.3.1.3.1. Potential Mechanisms

Crizotinib inhibited hERG potassium currents with an IC_{20} and IC_{50} of 0.3 μM (135 ng/mL) and 1.1 μM (495 ng/mL), respectively. In addition to its effects on the hERG potassium channel, it was also identified as a calcium channel antagonist, suggesting that crizotinib is a mixed ion channel blocker.

Preliminary clinical pharmacokinetic data has been collected for the lactam metabolite of crizotinib (PF-06260182) from patients given the recommended human dose of 250 mg BID crizotinib. Geometric mean of steady state C_{trough} for PF-06260182 was 62 ng/mL (n=227) compared with that for crizotinib of 268 ng/mL, with a mean metabolite parent ratio of C_{trough} of 0.24. Based on this data, the lactam metabolite of crizotinib can be expected to have little contribution to the secondary pharmacology of crizotinib. In addition, given that crizotinib has mixed ion channel activity, the completion of additional in vitro assessments of ion channel activity for the lactam metabolite would not offer any additional clinical context to the identified risk for QTc prolongation. As such, no additional nonclinical work related to the lactam metabolite and possible ion channel activity is proposed.

SVII.3.1.3.2. Evidence Source and Strength of Evidence

Evidence source: All non-clinical and all company-sponsored clinical studies; and post-marketing reports.

Strength of Evidence: There have been reports of QTc prolongation adverse reactions in patients receiving crizotinib for treatment of NSCLC.

SVII.3.1.3.3. Characterisation of the Risk

Seriousness/Outcomes

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies							
Risk Category	**Preferred Term**	**Total[a] (N = 1722) n (%)**	**Serious Events[b] n (%)**	**Fatal* n (%)**	**Recovered[c] n (%)**	**Not Recovered[c] n (%)**	**Unk n (%)**
QTc prolongation	Cardiac arrest	3 (0.2)	2 (66.7)	1 (33.3)	3 (100.0)	0	0
	Electrocardiogram QT prolonged	64 (3.7)	3 (4.7)	0	55 (85.9)	9 (14.1)	0
	Loss of consciousness	3 (0.2)	1 (33.3)	0	3 (100.0)	0	0
	Sudden death	1 (0.1)	1 (100.0)	1 (100.0)	1 (100.0)	0	0
	Syncope	44 (2.6)	11 (25.0)	0	43 (97.7)	1 (2.3)	0

ALK = anaplastic lymphoma kinase; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes Protocols: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.

a. Total patients with specific Preferred Term
b. Patients with Specific SAE for Preferred Term
c. For all patients (i.e not only those with SAE)

* Patients with AEGRADE = 5 for preferred Term.
Source: Table 14.3.1.13.1.2 Date of Table Generation: 24 September 2015.

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ALK-positive ALCL and ALK-positive IMT Paediatric Patients						
Risk Category	**Preferred Term**	**Total[a] (N = 41) n (%)**	**Fatal n (%)[b]**	**Recovered[c] n (%)**	**Not Recovered[c] n (%)**	**Unk n (%)**
QTc Prolongation	Electrocardiogram QT Prolonged	3 (7.3)	0	3 (7.3)	0	0

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08JAN2021)
N= total number of patients with ALCL or IMT in the safety analysis population.
[a] Total patients with specific preferred term.
[b] Patients with any event of CTCAE grade 5.
[c] For patients from ADVL0912, recovered patient has a non-missing resolution date for preferred term, and not recovered patient has a missing resolution date for preferred term. For patients from A8081013, adverse event outcome was collected on CRF.
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.
MedDRA v23.1 coding dictionary applied.
Source Table 14.3.1.2.7.2.2 Date of Generation: 04MAR2021

Severity and Nature of Risk

Number (%) of All-Causality Adverse Events Compatible With Possible QTc prolongation in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies						
Prefered Term	**Crizotinib (N=1722)**					
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any AEs[a]	24 (1.4)	16 (0.9)	70 (4.1)	2 (0.1)	2 (0.1)	114 (6.6)
Cardiac arrest	0	0	0	2 (0.1)	1 (0.1)	3 (0.2)
Electrocardiogram QT prolonged	23 (1.3)	14 (0.8)	27 (1.6)	0	0	64 (3.7)
Loss of consciousness	0	1 (0.1)	2 (0.1)	0	0	3 (0.2)
Sudden death	0	0	0	0	1 (0.1)	1 (0.1)
Syncope	1 (0.1)	1 (0.1)	42 (2.4)	0	0	44 (2.6)

AE = adverse event; ALK = anaplastic lymphoma kinase; CTCAE = Common Toxicty Criteria for Adverse Events; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes Protocols: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.
MedDRA (v17.1) coding dictionary applied.
a. Any AEs refers the number of subjects who had any treatment-emergent AEs indicative of the Preferred Term.
Source: Table 14.3.1.10.2.1.2 Date of Table Generation: 24 September 2015.

Number (%) of All-Causality Adverse Events compatible with possible QTc prolongation in ALK-positive ALCL and ALK-positive IMT Paediatric Patients						
Preferred Term	**ALCL + IMT (N = 41)**					
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any AEs[a]	2 (4.9)	1 (2.4)	0	0	0	3 (7.3)
Electrocardiogram QT prolonged	2 (4.9)	1 (2.4)	0	0	0	3 (7.3)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08JAN2021)
a. Any AEs refers the number of subjects who had any treatment-emergent AEs indicative of the Preferred Term.
The table is summarized by maximum CTCAE grade.
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.
MedDRA v23.1 coding dictionary applied..
Source Table 14.3.1.2.7.3.2 Crizotinib Date of Generation: 04MAR2021

Post-marketing data in MAH Safety Database

Table 22. Post-Marketing AEs QTc Prolongation by Outcome

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
Electrocardiogram QT prolonged	196 (46.7)	194 (99)	23 (11.7)	0	83 (42.3)	1 (0.5)	7 (3.6)	106 (54.1)

Table 22. Post-Marketing AEs QTc Prolongation by Outcome

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
Seizure**	60 (14.3)	60 (100)	24 (40)	4 (6.7)	6 (10)	0	6 (10)	44 (73.3)
Syncope	52 (12.4)	32 (61.5)	13 (25)	0	12 (23.1)	0	1 (1.9)	39 (75)
Cardiac arrest	37 (8.8)	37 (100)	6 (16.2)	24 (64.9)	3 (8.1)	1 (2.7)	0	9 (24.3)
Loss of consciousness	37 (8.8)	35 (94.6)	4 (10.8)	3 (8.1)	6 (16.2)	1 (2.7)	2 (5.4)	25 (67.6)
Cardio-respiratory arrest	12 (2.9)	12 (100)	1 (8.3)	9 (75)	2 (16.7)	0	0	1 (8.3)
Sudden death	9 (2.1)	9 (100)	0	9 (100)	0	0	0	0
Cardiac fibrillation	4 (1)	4 (100)	0	0	2 (50)	0	0	2 (50)
Electrocardiogram QT interval abnormal	4 (1)	4 (100)	0	0	1 (25)	0	0	3 (75)
Ventricular fibrillation	4 (1)	4 (100)	3 (75)	0	3 (75)	1 (25)	0	0
Long QT syndrome	3 (0.7)	3 (100)	0	0	2 (66.7)	0	0	1 (33.3)
Ventricular arrhythmia	1 (0.2)	1 (100)	1 (100)	0	1 (100)	0	0	0
Ventricular tachycardia	1 (0.2)	1 (100)	0	0	0	0	0	1 (100)

Reporting Period: Cumulative Through 15-July-2024
Total number of QTc prolongation AEs 420.
* More than 1 event outcome reported in some cases
** Current MedDRA version is 27.0. , includes PT Seizure under Torsade de pointes/QT prolongation SMQ (narrow and broad).

SVII.3.1.3.4. Risk Factors and Risk Groups

No specific risk factors have been identified which may predispose patients to develop symptomatic QTc prolongation as a result of treatment with crizotinib.

Based on known general risk factors for QTc prolongation, patient factors that may potentially be associated with an increased risk of developing QTc prolongation under treatment with crizotinib may include pre-existing conditions such as a Long QT Syndrome, a history of cardiac dysrhythmia, electrolyte disturbances, cardiac ischemia, and the concomitant use of medications with the potential to prolong QTc.

SVII.3.1.3.5. Preventability

Since no potential mechanism of QTc prolongation associated with crizotinib treatment has been identified, this risk cannot be predicted and therefore no preventability measures can be indicated.

SVII.3.1.3.6. Impact on the Risk-Benefit Balance of the product

Management of QTc prolongation as described in the product label will minimize the risk of QTc prolongation and may improve the risk-benefit profile of crizotinib.

SVII.3.1.3.7. Public Health Impact

Some patients may experience QTc prolongation following exposure to crizotinib. QTc prolongation may lead to severe ventricular arrhythmias (eg Torsade de Pointes), which can be fatal.

SVII.3.1.4. Important Identified Risk – Bradycardia

SVII.3.1.4.1. Potential Mechanisms

Crizotinib administration was associated with hemodynamic effects in the anesthetized cardiovascular dog study. Decreases in heart rate observed at ≥84 ng/mL (unbound; ≥2.2-fold the unbound Cmax associated with the 250 mg BID dose in humans) may be related to antagonism of the 5-HT_4 serotonin receptor. Although antagonist effects are unknown, agonists of the 5-HT_4 receptor, present on human atria, have been associated with tachycardia. The effect on heart rate may also relate to the inhibitory effect of crizotinib on the dopamine uptake transporter.

Wide ligand binding studies with crizotinib has shown affinity for a number of 5-hydroxytryptamine (5-HT) receptors (5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{4E}, and 5-HT_7) as well as at the 5-HT and dopamine uptake transporters. Functional studies undertaken to follow up on these findings showed that crizotinib had no agonist or antagonist activity at the 5-HT_{1B}, 5-HT_{2A}, or 5-HT_{2B} receptors and antagonist activity at the $5HT_{4E}$ receptor (K_B of 140 nM) and 5-HT_7 receptor (KB of 2.2 μM) and IC_{50} values at the dopamine and 5-HT uptake transporters of 630 nM and 830 nM, respectively. Given the maximal plasma concentrations at the recommended human dose of 250 mg BID is 84 nM (Cycle 1, Day 15 geometric mean unbound C_{max}), the potential for secondary (off-target) pharmacology at clinically relevant concentrations is possible at the 5-HT_{4E} receptor but not likely at the 5-HT_7 receptor and uptake transporters (to increase synaptic levels of dopamine and or 5-HT) given their lower functional activities.

All 5-HT receptors (except 5-HT_6) have been shown to be involved in cardiovascular regulation with central 5-HT_{1A}, 5-HT_3 and 5-HT_7 receptors playing a physiological part in the regulation of cardiovascular reflexes, controlling changes in parasympathetic (vagal) drive to the heart.[105] While agonist activity for 5-HT receptors and enhanced dopamine uptake might be expected to elicit bradycardia, the secondary pharmacology profile of crizotinib demonstrates antagonism not agonism at 5-HT receptors and inhibition of the transporter for dopamine uptake that potentially increases levels of dopamine, a known modulator of blood pressure regulation.[106] It is therefore considered unlikely that crizotinib mediates bradycardia in patients through its secondary pharmacology profile related to 5-HT receptors and the dopamine uptake transporter. As such, no additional wording is proposed for the RMP regarding a mechanistic relationship of 5-HT receptors and dopamine uptake transporter to bradycardia.

SVII.3.1.4.2. Evidence Source and Strength of Evidence

Evidence source: All non-clinical and all company-sponsored clinical studies; and post-marketing reports.

Strength of Evidence: There have been reports of bradycardia adverse reactions in patients receiving crizotinib for treatment of NSCLC.

SVII.3.1.4.3. Characterization of Risk

Seriousness/Outcomes

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies							
Risk Category	**Preferred Term**	**Total[a] (N = 1722) n (%)**	**Serious Events[b] n (%)**	**Fatal* n (%)**	**Recovered[c] n (%)**	**Not Recovered[c] n (%)**	**Unk n (%)**
Bradycardia	Bradycardia	148 (8.6)	3 (2.0)	0	101 (68.2)	45 (30.4)	2 (1.4)
	Heart rate decreased	2 (0.1)	0	0	1 (50.0)	1 (50.0)	0
	Sinus bradycardia	76 (4.4)	0	0	42 (55.3)	34 (44.7)	0

ALK = anaplastic lymphoma kinase; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes Protocols: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.
a Total patients with specific Preferred Term
b. Patients with Specific SAE for Preferred Term
c. For all patients (i.e not only those with SAE)
* Patients with AEGRADE = 5 for preferred Term.
Source: Table 14.3.1.13.1.2 Date of Table Generation: 24 September 2015.

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ALK-positive ALCL and ALK-positive IMT Paediatric Patients					
Risk Category	**Preferred Term**	**Total (N = 41) n (%) [a]**	**Fatal n (%) [b]**	**Recovered n (%) [c]**	**Not Recovered n (%) [c]**
Bradycardia	Bradycardia	1 (2.4)	0	0	1 (100.0)
	Sinus bradycardia	6 (14.6)	0	5 (83.3)	1 (16.7)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08JAN2021)
N= total number of patients with ALCL or IMT in the safety analysis population.
[a] Total patients with specific preferred term.
[b] Patients with any event of CTCAE grade 5.
[c] For patients from ADVL0912, recovered patient has a non-missing resolution date for preferred term, and not recovered patient has a missing resolution date for preferred term. For patients from A8081013, adverse event outcome was collected on CRF.
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.
MedDRA v23.1 coding dictionary applied.
Source Table 14.3.1.2.7.2.3 Date of Generation: 04MAR2021

Severity and Nature of Risk

Number (%) of All-Causality Adverse Events Compatible With Possible Bradycardia in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies						
	Crizotinib (N=1722)					
Prefered Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs[a]	194 (11.3)	18 (1.0)	7 (0.4)	0	0	219 (12.7)
Bradycardia	130 (7.5)	12 (0.7)	6 (0.3)	0	0	148 (8.6)
Heart rate decreased	2 (0.1)	0	0	0	0	2 (0.1)
Sinus bradycardia	68 (3.9)	7 (0.4)	1 (0.1)	0	0	76 (4.4)

AE = adverse event; ALK = anaplastic lymphoma kinase; CTCAE = Common Toxicty Criteria for Adverse Events; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes protocols: A8081001(RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.
MedDRA (v17.1) coding dictionary applied.
a. Any AEs refers the number of subjects who had any treatment-emergent AEs indicative of the Preferred Term.
Source: Table 14.3.1.10.3.1.2 Date of Table Generation: 24 September 2015.

Number (%) of All-Causality Adverse Events compatible with possible Bradycardia in ALK-positive ALCL and ALK-positive IMT Paediatric Patients						
Preferred Term	ALCL + IMT (N = 41)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs[a]	6 (14.6)	0	1 (2.4)	0	0	7 (17.1)
Bradycardia	1 (2.4)	0	0	0	0	1 (2.4)
Sinus bradycardia	5 (12.2)	0	1 (2.4)	0	0	6 (14.6)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08JAN2021)
a. Any AEs refers the number of subjects who had any treatment-emergent AEs indicative of the Preferred Term.
The table is summarized by maximum CTCAE grade.
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.
MedDRA v23.1 coding dictionary applied.
Source Table 14.3.1.2.7.3.3 Date of Generation: 04MAR2021

Post-marketing data in MAH Safety Database

Table 23. Post-Marketing AEs Bradycardia by Outcome

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
Bradycardia	334 (67.9)	271 (81.1)	30 (9)	1 (0.3)	121 (36.2)	0	33 (9.9)	179 (53.6)

Table 23. Post-Marketing AEs Bradycardia by Outcome

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
Heart rate decreased	95 (19.3)	22 (23.2)	8 (8.4)	2 (2.1)	15 (15.8)	0	10 (10.5)	68 (71.6)
Sinus bradycardia	58 (11.8)	22 (37.9)	9 (15.5)	0	23 (39.7)	0	8 (13.8)	28 (48.3)
Sinus arrest	3 (0.6)	3 (100)	1 (33.3)	0	2 (66.7)	0	0	1 (33.3)
Bradyarrhythmia	2 (0.4)	1 (50)	0	0	0	0	0	2 (100)

Reporting Period: Cumulative Through 15-July -20243
Total number of bradycardia AEs 492.
* More than 1 event outcome reported in some cases

SVII.3.1.4.4. Risk Factors and Risk Groups

No specific risk groups or risk factors have been identified that might predispose patients to the development of bradycardia. However, pre-existing bradycardia, sinus node dysfunction, atrioventricular conduction disturbances, as well as concomitant medications affecting heart rate, such as beta blockers and non-dihydropyridine calcium channel blockers may increase the risk of developing bradycardia.

SVII.3.1.4.5. Preventability

Since no potential mechanism of bradycardia associated with crizotinib treatment has been identified, this risk cannot be predicted and therefore no preventability measures can be indicated.

SVII.3.1.4.6. Impact on the Risk-Benefit Balance of the Product

Management of bradycardia as described in the product label will minimize the risk of bradycardia and may improve the risk-benefit profile of crizotinib.

SVII.3.1.4.7. Public Health Impact

The potential public health impact of patients treated with crizotinib is not known but is likely to be limited. Some patients may develop bradycardia following exposure to crizotinib; however, symptomatic bradycardia is likely to remain a relatively uncommon event.

SVII.3.1.5. Important Identified Risk – Renal Cyst

SVII.3.1.5.1. Potential Mechanisms

Several factors have been associated with the development of renal cysts.
In a cell culture model, cyclic adenosine monophosphate (cAMP) has been shown to contribute to cyst expansion in the presence of epidermal growth factor.[107] Hepatocyte growth factor (HGF) also plays a prominent role. HGF is involved in multiple biological processes, such as development, tissue regeneration, and tumor progression. HGF is a known mitogen with effects on endothelial cell, epithelial cells, and melanocytes.[108] HGF is

the product of activation of secreted pro-HGF by HGF activator (HGF-A). HGF-A is mainly, but not exclusively produced in the liver and circulates in the blood as an inactive zymogen. The zymogen may be activated by thrombin in response to tissue injury and inflammation.

In the kidney, HGF is expressed in mesenchymal cells, mesangial and interstitial stromal cells, while the HGF tyrosine kinase receptor (c-Met) is expressed in non-mesenchymal cells, such as those of the tubular epithelium. Expression of HGF and c-Met can mediate lumen formation in cultured epithelial cells,[109] and co-expression of HGF and c-Met induces mesenchymal to epithelial cell conversion.[110]

Horie et al.,[111] found HGF to be present in renal cysts in concentrations almost 10 times higher than found in blood and speculate that deranged expression of HGF and c-Met might be related to the de-differentiation and loss of polarity in tubulocystic epithelium. Further, they argue that the finding of elevated HGF concentration in cysts in combination with co-expression of HGF and c-Met in the cyst wall suggests an autocrine mechanism promoting cyst formation. Based on their findings,[111] suggested that pharmacological intervention in the HGF/c-Met signaling might offer new therapeutic modalities for the treatment of renal cysts.

Konda et al.,[112] found increased expression of HGF and c-Met in tubular cells and cystic epithelial cell in patients with acquired renal cystic disease (ARCD). HGF mRNA and protein as well as c-Met protein were found to be up-regulated in non-tumor and renal cell carcinoma (RCC) regions in ARCD associated RCC. They conclude that the HGF/c-Met pathway may contribute not only to tubular hyperplasia and cyst formation, but also to tumor transformation and RCC development. It appears that in the kidney the activity of HGF-A is physiologically curtailed by 2 types of HGF-activator–inhibitors (HAI-1 and HAI-2), which are expressed in renal tubular epithelial cells.[113] In resected RCC tissue, decreased HAI expression was observed compared to levels seen in normal kidneys suggesting that pro-HGF activation may be enhanced in RCC tissue**.**

These findings are of potential interest, since complex renal cysts can be associated with RCC, including multilocular cystic RCC (MCRCC), which may represent a subtype of RCC characterized by a multilocular cystic mass lacking a significant solid component, such as an expansile nodule, and with a regular thin cyst wall and septa. MCRCC is often incidentally diagnosed and accounts for only a small portion (1%-3%) of cases of RCC and appears to be less aggressive.[114,115]

While a dose-dependent increase in soluble c-Met has been observed under treatment with crizotinib, the precise relevance of the described potential factors contributing to cyst formation to the pathomechanism of cyst formation in patients treated with crizotinib is unclear.

SVII.3.1.5.2. Evidence Source and Strength of Evidence

Evidence source: All non-clinical and all company-sponsored clinical studies; and post-marketing reports.

Strength of Evidence: There have been reports of renal cyst adverse reactions in patients receiving crizotinib for treatment of NSCLC.

SVII.3.1.5.3. Characterization of Risk

Seriousness/Outcomes

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies							
Risk Category	**Preferred Term**	**Total[a] (N = 1722) n (%)**	**Serious Events[b] n (%)**	**Fatal* n (%)**	**Recovered[c] n (%)**	**Not Recovered[c] n (%)**	**Unk n (%)**
Renal cyst	Renal abscess	3 (0.2)	2 (66.7)	0	2 (66.7)	1 (33.3)	0
	Renal cyst	51 (3.0)	19 (37.3)	0	11 (21.6)	40 (78.4)	0

ALK = anaplastic lymphoma kinase; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes Protocols: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.
a. Total patients with specific Preferred Term
b. Patients with Specific SAE for Preferred Term
c For all patients (i.e not only those with SAE)
* Patients with AEGRADE = 5 for preferred Term.
Source: Table 14.3.1.13.1.2 Date of Table Generation: 24 September 2015.

No AEs suggestive of renal cyst were reported with crizotinib treatment in the paediatric CTs.

Severity and Nature of Risk

Number (%) of All-Causality Adverse Events Compatible With Possible Renal Cyst in ROS1-Positive NSCLC Patients and in All ALK-Positive NSCLC Patients in All Studies						
	Crizotinib (N=1722)					
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any AEs[a]	37 (2.1)	6 (0.3)	9 (0.5)	0	0	52 (3.0)
Renal abscess	0	1 (0.1)	2 (0.1)	0	0	3 (0.2)
Renal cyst	38 (2.2)	6 (0.3)	7 (0.4)	0	0	51 (3.0)

AE = adverse event; ALK = anaplastic lymphoma kinase; CTCAE = Common Toxicty Criteria for Adverse Events; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.
MedDRA (v17.1) coding dictionary applied.
a. Any AEs refers the number of subjects who had any treatment-emergent AEs indicative of the Preferred Term.
Source: Table 14.3.1.10.8.1.2 Date of Table Generation: 24 September 2015.

No AEs suggestive of renal cyst were reported with crizotinib treatment in the paediatric CTs.

Post-marketing data in MAH Safety Database

Table 24. Post-Marketing AEs Renal Cyst by Outcome

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
Renal cyst	129 (69.7)	44 (34.1)	20 (15.5)	0	54 (41.9)	0	21 (16.3)	54 (41.9)
Renal abscess	40 (21.6)	40 (100)	16 (40)	0	22 (55)	0	5 (12.5)	13 (32.5)
Renal cyst infection	9 (4.9)	9 (100)	3 (33.3)	0	5 (55.6)	0	1 (11.1)	3 (33.3)
Renal haematoma	3 (1.6)	2 (66.7)	1 (33.3)	0	1 (33.3)	0	1 (33.3)	1 (33.3)
Renal cyst haemorrhage	3 (1.6)	3 (100)	1 (33.3)	0	3 (100)	0	0	0
Renal cyst ruptured	1 (0.5)	1 (100)	1 (100)	0	1 (100)	0	0	0

Reporting Period: Cumulative Through 15-July-2024
Total number of renal cysts AEs 185.
* More than 1 event outcome reported in some cases

SVII.3.1.5.4. Risk Factors and Risk Groups

A blinded, retrospective, independent radiologic review (IRR) was performed using scans from patients on study for ≥6 months in three clinical trials; risk factors for renal cyst development were assessed. Among 255 crizotinib-treated patients, 22%, 3%, and 2% had preexisting simple cysts, complex cysts, or both, respectively. At the 6-month tumor assessment, 9% of all patients had acquired new cysts, and 2% of patients with pre-existing cysts had developed new cysts and enlargements (>50%) of preexisting simple cysts. Asians appeared to have an increased risk of developing new cysts on treatment; Koreans had 5.18 times higher odds of developing cysts than non-Asians (95% confidence interval, 1.51-17.78; P=.05). Crizotinib plasma $C_{trough,ss}$ was not found to be a significant driver of new renal cyst development based on a logistic regression model involving 193 of the 255 patients with blinded IRR imaging after adjusting for age and ethnicity, indicating that renal cyst development may not be associated with higher plasma exposure of crizotinib. In conclusion, crizotinib treatment appears to be associated with an increased risk of development and progression of renal cysts in patients. While close monitoring is recommended, dosing modification was not generally necessary, allowing patients to remain on crizotinib treatment.[116]

It is also possible that patients with pre-existing renal cysts are at increased risk of developing new (or enlarged) renal cysts under crizotinib.

SVII.3.1.5.5. Preventability

Since no potential mechanism of renal cysts associated with crizotinib treatment has been identified, this risk cannot be predicted and therefore no preventability measures can be indicated.

SVII.3.1.5.6. Impact on the Risk-Benefit Balance of the Product

Management of renal cysts as medically indicated will minimize the risk of renal cysts and may improve the risk-benefit profile of crizotinib.

SVII.3.1.5.7. Public Health Impact

There does not appear to be a significant public health impact resulting from the development of renal cysts in patients treated with crizotinib.

SVII.3.1.6. Important Identified Risk – Gastrointestinal Perforation

SVII.3.1.6.1. Potential Mechanisms

The exact mechanism of gastrointestinal perforation associated with the class of tyrosine kinase inhibitiors is unclear. Gastrointestinal changes in dog or monkey included mucosal congestion and cecal erosion and ulceration at non-tolerated doses. Another potential mechanism is that tumor lysis or shrinkage of gastrointestinal metastases may contribute to gastrointestinal perforation.

SVII.3.1.6.2. Evidence Source and Strength of Evidence

Evidence source: All non-clinical and all company-sponsored clinical studies; and post-marketing reports.

Strength of Evidence: There have been reports of gastrointestinal perforation adverse reactions in patients receiving crizotinib for treatment of NSCLC.

SVII.3.1.6.3. Characterization of Risks

Seriousness/Outcomes

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies

Risk Category	Preferred Term	Total[a] (N = 1722) n (%)	Serious Events[b] n (%)	Fatal* n (%)	Recovered[c] n (%)	Not Recovered[c] n (%)	Unk n (%)
Gastrointestinal perforation	Gastrointestinal perforation	1 (0.1)	1 (100.0)	0	1 (100.0)	0	0
	Intestinal perforation	2 (0.1)	2 (100.0)	0	2 (100.0)	0	0
	Large intestine perforation	1 (0.1)	1 (100.0)	0	1 (100.0)	0	0

ALK = anaplastic lymphoma kinase; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes Protocols: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.
a. Total patients with specific Preferred Term
b. Patients with Specific SAE for Preferred Term
c. For all patients (i.e not only those with SAE)
* Patients with AEGRADE = 5 for preferred Term.
Source: Table 14.3.1.13.1.2 Date of Table Generation: 24 September 2015.

No AEs suggestive of gastrointestinal perforation were reported with crizotinib treatment in the paediatric CTs.Severity and Nature of Risk

Number (%) of All-Causality Adverse Events Compatible With Possible Gastrointestinal perforation in ROS1-Positive NSCLC Patients and in All ALK+ NSCLC Patients in All Studies						
	Crizotinib (N=1722)					
Prefered Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs[a]	0	0	3 (0.2)	1 (0.1)	0	4 (0.2)
Gastrointestinal perforation	0	0	0	1 (0.1)	0	1 (0.1)
Intestinal perforation	0	0	2 (0.1)	0	0	2 (0.1)
Large intestine perforation	0	0	1 (0.1)	0	0	1 (0.1)

AE = adverse event; ALK = anaplastic lymphoma kinase; CTCAE = Common Toxicty Criteria for Adverse Events; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes Protocols: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.
MedDRA (v17.1) coding dictionary applied.
a. Any AEs refers the number of subjects who had any treatment-emergent AEs indicative of the Preferred Term.
Source: Table 14.3.1.10.13.1.2 Date of Table Generation: 24 September 2015.

No AEs suggestive of gastrointestinal perforation were reported with crizotinib treatment in the paediatric CTs.

Post-marketing data in MAH Safety Database

Table 25. Post-Marketing AEs Gastrointestinal Perforation by Outcome

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
Intestinal perforation	11 (21.6)	11 (100)	6 (54.5)	6 (54.5)	1 (9.1)	0	1 (9.1)	3 (27.3)
Peritonitis	8 (15.7)	8 (100)	4 (50)	3 (37.5)	3 (37.5)	0	0	2 (25)
Large intestine perforation	7 (13.7)	7 (100)	4 (57.1)	1 (14.3)	1 (14.3)	1 (14.3)	1 (14.3)	3 (42.9)
Abdominal abscess	4 (7.8)	4 (100)	2 (50)	0	2 (50)	0	1 (25)	1 (25)
Gastrointestinal perforation	1 (2)	1 (100)	1 (100)	0	1 (100)	0	0	0
Gastric perforation	3 (5.9)	3 (100)	2 (66.7)	0	0	0	1 (33.3)	2 (66.7)
Appendicitis perforated	1 (2)	1 (100)	1 (100)	0	0	0	0	1 (100)
Diverticular perforation	2 (3.9)	2 (100)	1 (50)	0	0	0	0	2 (100)
Oesophageal perforation	2 (3.9)	2 (100)	1 (50)	1 (50)	1 (50)	0	0	0

Table 25. Post-Marketing AEs Gastrointestinal Perforation by Outcome

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
Pneumoperitoneum	2 (3.9)	2 (100)	1 (50)	0	1 (50)	0	1 (50)	0
Rectal perforation	2 (3.9)	2 (100)	0	0	0	0	0	2 (100)
Small intestinal perforation	2 (3.9)	2 (100)	1 (50)	0	1 (50)	0	0	1 (50)
Small intestinal perforation	2 (3.9)	2 (100)	1 (50)	0	1 (50)	0	0	1 (50)
Abscess intestinal	1 (2)	1 (100)	0	0	0	0	0	1 (100)
Duodenal ulcer perforation	1 (2)	1 (100)	0	0	0	0	0	1 (100)
Gastric ulcer perforation	1 (2)	1 (100)	0	0	0	0	0	1 (100)
Oesophageal fistula	1 (2)	1 (100)	1 (100)	0	1 (100)	0	0	0
Oesophageal rupture	1 (2)	1 (100)	0	0	0	0	0	1 (100)
Retroperitoneal abscess	1 (2)	1 (100)	0	0	1 (100)	0	0	0

Reporting Period: Cumulative Through 15-July-2024
Total number of gastrointestinal perforation AEs 51.
* More than 1 event outcome reported in some cases

SVII.3.1.6.4. Risk Factors and Risk Groups

Patients with conditions such as history of diverticulitis, metastases to the gastrointestinal tract, or concomitant use of medications with a recognized risk of gastrointestinal perforation are predisposed to developing gastrointestinal perforation.

SVII.3.1.6.5. Preventability

Since no potential mechanism of gastrointestinal perforation associated with crizotinib treatment has been identified, this risk cannot be predicted and therefore no preventability measures can be indicated.

SVII.3.1.6.6. Impact on the Risk-Benefit Balance of the Product

Management of gastrointestinal perforation as medically indicated may improve the risk-benefit profile of crizotinib.

SVII.3.1.6.7. Public Health Impact

The public health impact of crizotinib-related gastrointestinal perforation is predominantly determined by the frequency of required permanent dose discontinuations (precluding patients from benefiting from crizotinib) and the frequency of hospitalizations, surgery and

life-threatening or fatal cases. The potential health impact is currently considered minimal due to the low rate of GI perforation observed with crizotinib.

SVII.3.1.7. Important Identified Risk – Cardiac Failure

SVII.3.1.7.1. Potential Mechanisms

Preclinical toxicology studies indicated that crizotinib administration may result in a decrease in heart rate, blood pressure, and myocardial contractility, as well as an increase in left ventricular end diastolic pressure.

SVII.3.1.7.2. Evidence Source and Strength of Evidence

Evidence source: All non-clinical and all company-sponsored clinical studies; and post-marketing reports.

Strength of Evidence: There have been reports of cardiac failure related adverse reactions in patients receiving crizotinib for treatment of NSCLC.

SVII.3.1.7.3. Characterization of Risks

Seriousness/Outcome

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies

Risk Category	Preferred Term	Total[a] (N = 1722) n (%)	Serious Events[b] n (%)	Fatal* n (%)	Recovered[c] n (%)	Not Recovered[c] n (%)	Unknown n (%)
Cardiac failure	Cardiac failure	6 (0.4)	2 (33.3)	1 (16.7)	5 (83.3)	1 (16.7)	0
	Cardiac failure congestive	3 (0.2)	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.7)	0
	Ejection fraction decreased	2 (0.1)	0	0	2 (100.0)	0	0
	Left ventricular failure	1 (0.1)	0	0	0	1 (100.0)	0
	Pulmonary oedema	7 (0.4)	1 (14.3)	1 (14.3)	5 (71.4)	2 (28.6)	0

ALK = anaplastic lymphoma kinase; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes Protocols: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.
a. Total patients with specific Preferred Term
b. Patients with Specific SAE for Preferred Term
c. For all patients (i.e not only those with SAE)
* Patients with AEGRADE = 5 for preferred Term.
Source: Table 14.3.1.13.1.2 Date of Table Generation: 24 September 2015.

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ALK-positive ALCL and ALK-positive IMT Paediatric Patients					
Risk Category	**Preferred Term**	**Total (N = 41) n (%) [a]**	**Fatal n (%) [b]**	**Recovered n (%) [c]**	**Not Recovered n (%) [c]**
Cardiac failure	Ejection fraction decreased	1 (2.4)	0	1 (100.0)	0

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08JAN2021)
N= total number of patients with ALCL or IMT in the safety analysis population.
[a] Total patients with specific preferred term.
[b] Patients with any event of CTCAE grade 5.
[c] For patients from ADVL0912, recovered patient has a non-missing resolution date for preferred term, and not recovered patient has a missing resolution date for preferred term. For patients from A8081013, adverse event outcome was collected on CRF.
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.
MedDRA v23.1 coding dictionary applied.
Source Table 14.3.1.2.7.2.7 04MAR2021

Severity and Nature of Risk

Number (%) of All-Causality Adverse Events compatible with possible Cardiac Failure in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies						
Preferred Term	**Crizotinib (N = 1722)**					
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any AEs[a]	3 (0.2)	5 (0.3)	6 (0.3)	2 (0.1)	3 (0.2)	19 (1.1)
Cardiac failure	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)	1 (0.1)	6 (0.3)
Cardiac failure congestive	1 (0.1)	1 (0.1)	0	0	1 (0.1)	3 (0.2)
Ejection fraction decreased	1 (0.1)	0	1 (0.1)	0	0	2 (0.1)
Left ventricular failure	0	1 (0.1)	0	0	0	1 (0.1)
Pulmonary oedema	0	2 (0.1)	4 (0.2)	0	1 (0.1)	7 (0.4)

AE = adverse event; ALK = anaplastic lymphoma kinase; CTCAE = Common Toxicty Criteria for Adverse Events; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes protocols: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.
MedDRA (v17.1) coding dictionary applied.
a. Any AEs refers the number of subjects who had any treatment-emergent AEs indicative of the Preferred Term.
Source: Table 14.3.1.10.14.1.2 Date of Table Generation: 24 September 2015

Number (%) of All-Causality Adverse Events compatible with possible Cardiac failure in ALK-positive ALCL and ALK-positive IMT Paediatric Patients						
Preferred Term	ALCL + IMT (N = 41)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs[a]	0	1 (2.4)	0	0	0	1 (2.4)
Ejection fraction decreased	0	1 (2.4)	0	0	0	1 (2.4)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08JAN2021)

a. Any AEs refers the number of subjects who had any treatment-emergent AEs indicative of the Preferred Term.

The table is summarized by maximum CTCAE grade.

Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.

MedDRA v23.1 coding dictionary applied..

Table 14.3.1.2.7.3.7 Date of Generation: 04MAR2021

Post-marketing data in MAH Safety Database

Table 26. Post-Marketing AEs Cardiac Failure by Outcome

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
Cardiac failure	89 (44.7)	88 (98.9)	33 (37.1)	23 (25.8)	29 (32.6)	0	9 (10.1)	29 (32.6)
Pulmonary oedema	68 (34.2)	68 (100)	25 (36.8)	6 (8.8)	10 (14.7)	1 (1.5)	7 (10.3)	44 (64.7)
Cardiac failure congestive	19 (9.5)	19 (100)	10 (52.6)	4 (21.1)	3 (15.8)	0	0	12 (63.2)
Cardiopulmonary failure	11 (5.5)	11 (100)	2 (18.2)	9 (81.8)	0	0	0	2 (18.2)
Ejection fraction decreased	4 (2)	0	0	0	0	0	1 (25)	3 (75)
Cardiac failure acute	3 (1.5)	3 (100)	3 (100)	0	3 (100)	0	0	0
Heart failure with preserved ejection fraction	1 (0.5)	1 (100)	0	0	1 (100)	0	0	0
Acute pulmonary oedema	1 (0.5)	1 (100)	0	0	0	0	0	1 (100)
Cardiogenic shock	1 (0.5)	1 (100)	0	0	0	0	0	1 (100)
Cor pulmonale acute	1 (0.5)	1 (100)	1 (100)	1 (100)	0	0	0	0
Ventricular failure	1 (0.5)	1 (100)	0	1 (100)	0	0	0	0

Reporting Period: Cumulative Through 15-July-2024

Total number of cardiac failure AEs 199. * More than 1 event outcome reported in some cases

SVII.3.1.7.4. Risk Factors and Risk Groups

No clear risk factors have been identified. It is theoretically possible that patients with a history of cardiac disease, cardiac risk factors, or prior therapy with cardiotoxic drugs have a higher risk developing ventricular dysfunction while receiving crizotinib.

SVII.3.1.7.5. Preventability

Since no potential mechanism of cardiac failure associated with crizotinib treatment has been identified, this risk cannot be predicted and therefore no preventability measures can be indicated.

SVII.3.1.7.6. Impact on the Benefit-Risk Balance of the Product

Management of cardiac failure as medically indicated may improve the risk-benefit profile of crizotinib.

SVII.3.1.7.7. Public Health Impact

Considering the incidence and severity of this risk in the sub-population of NSCLC, the impact on public health is small.

SVII.3.1.8. Important Potential Risk – Reproductive Toxicity (including pregnant and lactating women)

SVII.3.1.8.1. Potential Mechanisms

Effects on reproductive organs were observed with repeated dosing in non-clinical toxicity studies. The potential mechanism for any reproductive toxicity is not fully understood; however, c-Met is known to be expressed on human seminiferous epithelium and on immature and mature spermatozoa,[117] and ALK expression in the testis and ovary has been shown in mice.[118]

SVII.3.1.8.2. Evidence Source and Strength of Evidence

Evidence source: All non-clinical and all company-sponsored clinical studies; and post-marketing reports.

Strength of Evidence: There have been reports of reproductive-type (including pregnant and lactating women) adverse reactions in patients receiving crizotinib for treatment of NSCLC.

SVII.3.1.8.3. Characterization of Risk

Seriousness/Outcomes

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies

Risk Category	Preferred Term	Total[a] (N = 1722) n (%)	Serious Events[b] n (%)	Fatal* n (%)	Recovered[c] n (%)	Not Recovered[c] n (%)	Unk n (%)
Reproductive toxicity	Abortion spontaneous	1 (0.1)	1 (100.0)	0	1 (100.0)	0	0
	Foetal exposure during pregnancy	1 (0.1)	1 (100.0)	0	1 (100.0)	0	0
	Hypogonadism	10 (0.6)	0	0	4 (40.0)	6 (60.0)	0

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies							
Risk Category	**Preferred Term**	**Total[a] (N = 1722) n (%)**	**Serious Events[b] n (%)**	**Fatal* n (%)**	**Recovered[c] n (%)**	**Not Recovered[c] n (%)**	**Unk n (%)**

ALK = anaplastic lymphoma kinase; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes Protocols: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.
a. Total patients with specific Preferred Term
b. Patients with Specific SAE for Preferred Term
c. For all patients (i.e not only those with SAE)
* Patients with AEGRADE = 5 for preferred Term.
Source: Table 14.3.1.13.1.2 Date of Table Generation: 24 September 2015.

No AEs suggestive of reproductive toxicity (including pregnancy and lactation) were reported with crizotinib treatment in the paediatric CTs.

Severity and Nature of Risk

Number (%) of All-Causality Adverse Events compatible with possible Reproductive Toxicity by Severity (CTCAE Grade) in in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients						
Preferred Term	**Crizotinib (N = 1722)**					
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any AEs[a]	7 (0.4)	3 (0.2)	1 (0.1)	0	0	11 (0.6)
Abortion spontaneous	0	0	1 (0.1)	0	0	1 (0.1)
Foetal exposure during pregnancy	0	0	1 (0.1)	0	0	1 (0.1)
Hypogonadism	7 (0.4)	3 (0.2)	0	0	0	10 (0.6)

AE = adverse event; ALK = anaplastic lymphoma kinase; CTCAE = Common Toxicty Criteria for Adverse Events; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes Protocols: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1, NSCLC) patients.
MedDRA (v17.1) coding dictionary applied.
a. Any AEs refers the number of subjects who had any treatment-emergent AEs indicative of the Preferred Term.
Source: Table 14.3.1.10.9.1.2 Date of Table Generation: 24 September 2015

No AEs suggestive of reproductive toxicity (including pregnancy and lactation) were reported with crizotinib treatment in the paediatric CTs.

Post-marketing data in MAH Safety Database

Table 27. Post-Marketing AEs Reproductive Toxicity by Outcome

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
Maternal exposure during pregnancy	20 (22)	2 (10)	0	0	1 (5)	0	0	19 (95)
Maternal exposure timing unspecified	4 (4.4)	1 (25)	0	0	0	0	0	4 (100)
Premature baby	4 (4.4)	3 (75)	0	0	1 (25)	0	0	3 (75)
Abortion spontaneous	1 (1.1)	0	0	0	0	0	0	1 (100)
Foetal death	1 (1.1)	1 (100)	0	0	0	0	0	1 (100)
Foetal exposure during pregnancy	1 (1.1)	0	0	0	0	0	0	1 (100)
Maternal exposure before pregnancy	1 (1.1)	0	0	0	0	0	0	1 (100)

Reporting Period: Cumulative Through 15-July-2024
Total number of relevant reproductive toxicity (including pregnant and lactating women) AEs 32. * More than 1 event outcome reported in some cases

SVII.3.1.8.4. Risk Factors and Risk Groups

Risk factors and risk groups include women of childbearing potential, pregnant women, and lactating women.

SVII.3.1.8.5. Preventability

Women of childbearing potential should be advised to avoid becoming pregnant while receiving crizotinib. Women of childbearing potential who are receiving crizotinib should use adequate contraceptive methods during therapy and for at least 90 days after completing therapy.

Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in breastfed infants from exposure to crizotinib, mothers should be advised against breast-feeding while receiving this medicinal product.

SVII.3.1.8.6. Impact on the Risk-Benefit Balance of the Product

Given the known preclinical data with crizotinib and other drugs in class, crizotinib is not recommended during pregnancy, in lactating mothers, or for women of childbearing potential not using contraception.

SVII.3.1.8.7. Public Health Impact

The potential effect on public health cannot be precisely determined at this time. A low impact on public health resulting from foetal or developmental abnormalities would be expected as a result of crizotinib exposure.

SVII.3.1.9. Important Potential Risk – Severe Vision Loss/ Potential Sight Threatening Event

SVII.3.1.9.1. Potential Mechanisms

Effects on retinal function were observed during a dark adaptation study in rats. These indicated a delay in dark adaptation; however, the ability to achieve dark adaptation was not affected.

SVII.3.1.9.2. Evidence Source and Strength of Evidence

Evidence source: All non-clinical and all company-sponsored clinical studies; and post-marketing reports.

Strength of Evidence: There have been reports of severe vision loss/ potential sight threatening event adverse reactions in patients receiving crizotinib for treatment of NSCLC.

SVII.3.1.9.3. Characterization of Risk

Seriousness/Outcomes

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies

Risk Category	Preferred Term	Total[a] (N = 1722) n (%)	Serious Events[b] n (%)	Fatal* n (%)	Recovered[c] n (%)	Not Recovered[c] n (%)	Unk n (%)
Severe Vision Loss/ Potential Sight Threatening Event	Blindness	4 (0.2)	0	0	0	4 (100.0)	0
	Blindness unilateral	2 (0.1)	0	0	1 (50.0)	1 (50.0)	0
	Cystoid macular oedema	1 (0.1)	0	0	1 (100.0)	0	0
	Diabetic retinopathy	1 (0.1)	0	0	0	1 (100.0)	0
	Diplopia	35 (2.0)	0	0	22 (62.9)	12 (34.3)	1 (2.9)
	Eye disorder	21 (1.2)	0	0	16 (76.2)	4 (19.1)	1 (4.8)
	Eye haemorrhage	7 (0.4)	0	0	6 (85.7)	1 (14.3)	0
	Eye naevus	14 (0.8)	0	0	4 (28.6)	10 (71.4)	0
	Halo vision	2 (0.1)	0	0	2 (100.0)	0	0
	Macular degeneration	4 (0.2)	0	0	0	4 (100.0)	0
	Macular oedema	3 (0.2)	0	0	1 (33.3)	2 (66.7)	0
	Macular scar	1 (0.1)	0	0	1 (100.0)	0	0
	Maculopathy	1 (0.1)	0	0	0	1 (100.0)	0
	Optic atrophy	1 (0.1)	1 (100.0)	0	0	1 (100.0)	0
	Optic nerve disorder	2 (0.1)	0	0	1 (50.0)	1 (50.0)	0
	Photophobia	26 (1.5)	0	0	14 (53.9)	11 (42.3)	1 (3.9)
	Photopsia	152 (8.8)	0	0	105 (69.1)	45 (29.6)	2 (1.3)
	Retinal degeneration	7 (0.4)	0	0	1 (14.3)	6 (85.7)	0

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ROS1-Positive NSCLC and in All ALK+ NSCLC Patients in All Studies							
Risk Category	**Preferred Term**	**Total[a] (N = 1722) n (%)**	**Serious Events[b] n (%)**	**Fatal* n (%)**	**Recovered[c] n (%)**	**Not Recovered[c] n (%)**	**Unk n (%)**
	Retinal detachment	2 (0.1)	1 (50.0)	0	2 (100.0)	0	0
	Retinal disorder	2 (0.1)	0	0	0	2 (100.0)	0
	Retinal exudates	3 (0.2)	0	0	1 (33.3)	1 (33.3)	1 (33.3)
	Retinal haemorrhage	10 (0.6)	0	0	6 (60.0)	4 (40.0)	0
	Retinal pigment epitheliopathy	2 (0.1)	0	0	0	2 (100.0)	0
	Retinopathy	5 (0.3)	0	0	1 (20.0)	4 (80.0)	0
	Vision blurred	123 (7.1)	1 (0.8)	0	80 (65.0)	42 (34.2)	1 (0.8)
	Visual acuity reduced	17 (1.0)	0	0	8 (47.1)	8 (47.1)	1 (5.9)
	Visual field defect	17 (1.0)	0	0	10 (58.8)	7 (41.2)	0
	Visual impairment	809 (47.0)	0	0	510 (63.0)	292 (36.1)	7 (0.9)
	Visual perseveration	30 (1.7)	0	0	25 (83.3)	5 (16.7)	0
	Vitreous detachment	8 (0.5)	0	0	3 (37.5)	5 (62.5)	0
	Vitreous floaters	65 (3.8)	0	0	47 (72.3)	18 (27.7)	0
	Vitreous haemorrhage	1 (0.1)	1 (100.0)	0	1 (100.0)	0	0

ALK = anaplastic lymphoma kinase; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes Protocols: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.

a. Total patients with specific Preferred Term
b. Patients with Specific SAE for Preferred Term
c. For all patients (i.e not only those with SAE)

* Patients with AEGRADE = 5 for preferred Term.
Source: Table 14.3.1.13.1.2 Date of Table Generation: 24 September 2015.

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ALK-positive ALCL and ALK-positive IMT Paediatric Patients					
Risk Category	**Preferred Term**	**Total (N = 41) n (%) [a]**	**Fatal n (%) [b]**	**Recovered n (%) [c]**	**Not Recovered n (%) [c]**
Severe Vision Loss/Potential Sight Threatening Event	Dyschromatopsia	1 (2.4)	0	1 (100.0)	0
	Photophobia	3 (7.3)	0	3 (100.0)	0
	Photopsia	7 (17.1)	0	6 (85.7)	(14.3)
	Vision blurred	10 (24.4)	0	8 (80.0)	2 (20.0)

Number (%) of All-Causality Adverse Events by Seriousness/Outcomes by Risk Category and Preferred Term in ALK-positive ALCL and ALK-positive IMT Paediatric Patients					
Risk Category	**Preferred Term**	**Total (N = 41) n (%) [a]**	**Fatal n (%) [b]**	**Recovered n (%) [c]**	**Not Recovered n (%) [c]**
	Visual acuity reduced	1 (2.4)	0	1 (100.0)	0
	Visual impairment	8 (19.5)	0	6 (75.0)	2 (25.0)
	Vitreous floaters	6 (14.6)	0	4 (66.7)	2 (33.3)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08JAN2021)
N= total number of patients with ALCL or IMT in the safety analysis population.
[a] Total patients with specific preferred term.
[b] Patients with any event of CTCAE grade 5.
[c] For patients from ADVL0912, recovered patient has a non-missing resolution date for preferred term, and not recovered patient has a missing resolution date for preferred term. For patients from A8081013, adverse event outcome was collected on CRF.
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.
MedDRA v23.1 coding dictionary applied.
Source Table 14.3.1.2.7.2.9 Date of Generation: 04MAR2021

Severity and Nature of Risk

Number (%) of All-Causality Adverse Events Compatible With Possible Vision disorder in ROS1-Positive NSCLC and in All ALK-Positive NSCLC Patients in All Studies						
	Crizotinib (N=1722)					
Prefered Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any AEs[a]	1040 (60.4)	58 (3.4)	9 (0.5)	4 (0.2)	0	1111 (64.5)
Blindness	0	2 (0.1)	1 (0.1)	1 (0.1)	0	4 (0.2)
Blindness unilateral	1 (0.1)	1 (0.1)	0	0	0	2 (0.1)
Cystoid macular oedema	1 (0.1)	0	0	0	0	1 (0.1)
Diabetic retinopathy	1 (0.1)	0	0	0	0	1 (0.1)
Diplopia	30 (1.7)	5 (0.3)	0	0	0	35 (2.0)
Eye disorder	19 (1.1)	2 (0.1)	0	0	0	21 (1.2)
Eye haemorrhage	6 (0.3)	1 (0.1)	0	0	0	7 (0.4)
Eye naevus	14 (0.8)	0	0	0	0	14 (0.8)
Halo vision	2 (0.1)	0	0	0	0	2 (0.1)
Macular degeneration	2 (0.1)	2 (0.1)	0	0	0	4 (0.2)
Macular oedema	3 (0.2)	0	0	0	0	3 (0.2)
Macular scar	1 (0.1)	0	0	0	0	1 (0.1)
Maculopathy	1 (0.1)	0	0	0	0	1 (0.1)
Optic atrophy	0	0	0	1 (0.1)	0	1 (0.1)
Optic nerve disorder	1 (0.1)	0	0	1 (0.1)	0	2 (0.1)
Photophobia	26 (1.5)	0	0	0	0	26 (1.5)
Photopsia	148 (8.6)	4 (0.2)	0	0	0	152 (8.8)
Retinal degeneration	7 (0.4)	0	0	0	0	7 (0.4)
Retinal detachment	0	0	2 (0.1)	0	0	2 (0.1)
Retinal disorder	2 (0.1)	0	0	0	0	2 (0.1)

Number (%) of All-Causality Adverse Events Compatible With Possible Vision disorder in ROS1-Positive NSCLC and in All ALK-Positive NSCLC Patients in All Studies						
	Crizotinib (N=1722)					
Prefered Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Retinal exudates	3 (0.2)	0	0	0	0	3 (0.2)
Retinal haemorrhage	10 (0.6)	0	0	0	0	10 (0.6)
Retinal pigment epitheliopathy	2 (0.1)	0	0	0	0	2 (0.1)
Retinopathy	2 (0.1)	2 (0.1)	1 (0.1)	0	0	5 (0.3)
Vision blurred	105 (6.1)	16 (0.9)	2 (0.1)	0	0	123 (7.1)
Visual acuity reduced	15 (0.9)	2 (0.1)	0	0	0	17 (1.0)
Visual field defect	13 (0.8)	3 (0.2)	0	1 (0.1)	0	17 (1.0)
Visual impairment	786 (45.6)	19 (1.1)	4 (0.2)	0	0	809 (47.0)
Visual perseveration	29 (1.7)	1 (0.1)	0	0	0	30 (1.7)
Vitreous detachment	6 (0.3)	2 (0.1)	0	0	0	8 (0.5)
Vitreous floaters	64 (3.7)	1 (0.1)	0	0	0	65 (3.8)
Vitreous haemorrhage	0	0	1 (0.1)	0	0	1 (0.1)

AE = adverse event; ALK = anaplastic lymphoma kinase; CTCAE = Common Toxicty Criteria for Adverse Events; N = total number of subjects participated in study; n = number of subjects with the AE; NSCLC = non-small cell lung cancer.
Includes Protocols: A8081001 (RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib) and A8081001 (ROS1+, NSCLC) patients.
MedDRA (v17.1) coding dictionary applied.
a. Any AEs refers the number of subjects who had any treatment-emergent AEs indicative of the Preferred Term.
Source: Table 14.3.1.10.5.1.2 Date of Table Generation: 24 September 2015 (15:32)

Number (%) of All-Causality Adverse Events compatible with possible Severe Vision Loss/Potential Sight Threatening Event in ALK-positive ALCL and ALK-positive IMT Paediatric Patients						
Preferred Term	ALCL + IMT (N = 41)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs[a]	22 (53.7)	4 (9.8)	0	0	0	26 (63.4)
Dyschromatopsia	1 (2.4)	0	0	0	0	1 (2.4)
Photophobia	3 (7.3)	0	0	0	0	3 (7.3)
Photopsia	7 (17.1)	0	0	0	0	7 (17.1)
Vision Blurred	7 (17.1)	3 (7.3)	0	0	0	10 (24.4)
Visual acuity reduced	1 (2.4)	0	0	0	0	1 (2.4)
Visual impairment	7 (17.1)	1 (2.4)	0	0	0	8 (19.5)
Vitreous floaters	6 (14.6)	0	0	0	0	6 (14.6)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 08JAN2021)
a. Any AEs refers the number of subjects who had any treatment-emergent AEs indicative of the Preferred Term.
The table is summarized by maximum CTCAE grade.
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.
MedDRA v23.1 coding dictionary applied..
Table 14.3.1.2.7.3.9 Date of Generation: 04MAR2021

Post-marketing data in MAH Safety Database

Table 28. Post-Marketing AEs Severe Vision Loss/ Potential Sight Threatening Event by Outcome

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
Visual impairment	827 (47.5)	40 (4.8)	16 (1.9)	0	203 (24.5)	0	105 (12.7)	521 (62.8)
Vision blurred	261 (15)	32 (12.1)	15 (5.7)	0	56 (21.2)	0	46 (17.4)	162 (61.4)
Photopsia	243 (14)	15 (6.2)	3 (1.2)	0	70 (28.8)	2 (0.8)	31 (12.8)	140 (57.6)
Vitreous floaters	95 (5.5)	3 (3.2)	2 (2.1)	0	13 (13.7)	0	8 (8.4)	74 (77.9)
Diplopia	73 (4.2)	11 (15.1)	4 (5.5)	0	17 (23.3)	0	12 (16.4)	44 (60.3)
Photophobia	59 (3.4)	4 (6.8)	1 (1.7)	0	18 (30.5)	0	7 (11.9)	34 (57.6)

Reporting Period: Cumulative Through 15-July-2024

Total number of severe vision loss/potential sight threatening AEs 1740. AEs reported ≥2% are presented in the table.

* More than 1 event outcome reported in some cases

SVII.3.1.9.4. Risk Factors and Risk Groups

Risk groups or risk factors associated with increased risk of severe vision loss/ potential sight threatening event after administration of crizotinib is unknown. Cases of severe vision loss have been associated with brain metastases.

SVII.3.1.9.5. Preventability

It is expected that some degree of visual impairment which may be mild and transient, will occur in most patients treated with crizotinib. Thus, there are currently no known preventative measures.

SVII.3.1.9.6. Impact on the Risk-Benefit Balance of the Product

Depending upon the severity, visual impairment may be managed with crizotinib dose modification and/or dose reduction.

SVII.3.1.9.7. Public Health Impact

The majority of patients treated with crizotinib may experience mild and usually transient visual symptoms following exposure to crizotinib. Crizotinib-related visual symptoms have not been fully characterized, but they are usually described as shadows or “streaking” of visual images with changing light environments.

The potential public health impact is not clearly defined but appears to be limited due to the lack of severity and persistence of symptoms. Patients experiencing visual impairment

potentially impacting the ability to drive or use machines safely should use caution as long as the undesirable effects persist.

SVII.3.2. Presentation of the Missing Information

Missing information for crizotinib consists of patients undergoing long-term treatment.

SVII.3.2.1. Missing Information: Safety of crizotinib in Patients undergoing long-term treatment

Table 29. Missing Information - Patients undergoing long-term treatment

Evidence source and strength of evidence:	A formal crizotinib long-term treatment study has not been conducted.
Anticipated risk/consequence of the missing information:	Patients undergoing long-term treatment with crizotinib might be at greater risk for experiencing an important identified and potential risk.

Module SVIII. Summary of the Safety Concerns

Table 30. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Hepatotoxicity • Pneumonitis/ILD • QTc Prolongation • Bradycardia • Renal Cyst • Gastrointestinal perforation[a] • Cardiac failure[b]
Important potential risks	• Reproductive Toxicity (including pregnant and lactating women) • Severe Vision Loss/Potential Sight Threatening Event
Missing information	• Patients undergoing long-term treatment

ILD = Interstitisal Lung Disease.

a. Considered as an important identified risk in the EU and Switzerland.

b. Considered as an important identified risk in the EU, Japan, Switzerland and other ex-US countries.

PART.III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for safety concerns:**

None

- **Other forms of routine pharmacovigilance activities for safety concerns:**

None

III.2. Additional Pharmacovigilance Activities

Table 31. Additional Pharmacovigilance Activities

PASS short name summary	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
CRISP Study ITCC (Innovative Therapy for Children with Cancer) 053 (category: 3)	A phase 1B of crizotinib either in combination or as single agent in pediatric patients with ALK, ROS1 or MET positive malignancies.	To evaluate the risk factors manifestations, and outcomes of ocular toxicity associated with crizotinib in paediatric and young adult patients with ALK, ROS1 or MET positive malignancies.	Pooled analysis	Crizotinib patients, aged 12 months to ≤21 years	Final Analysis: 31 January 2031

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

Table 32. On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				

Table 32. On-going and planned additional pharmacovigilance activities

CRISP Study ITCC (Innovative Therapy for Children with Cancer) 053 (Category: 3)	A phase 1B of crizotinib either in combination or as single agent in pediatric patients with ALK, ROS1 or MET positive malignancies.	Ocular toxicities [a] associated with crizotinib in pediatric and young adult patients	Study Completion: 31 January 2030	Final Analysis: 31 January 2031

a. Ocular toxicity will be assessed as an important potential risk at the time of analysis for the CRISP ITCC study with data from the CRZ-NBALCL study, which was included an additional pharmacovigilance activity for the assessment of ocular toxicities with crizotinib in pediatric and young adult patients with a final analysis date of 30 September 2024.

PART.IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

Table 33. Planned and On-going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

Other Efficacy Study

Table 34. Other Efficacy Study

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Due Date
Ongoing[a]	• Study ADVL0912 (Completed): Phase 1/2 Study of PF-02341066, an Oral Small Molecule Inhibitor of Anaplastic Lymphoma Kinase (ALK) and c-MET, in Children with Relapsed/Refractory Solid Tumors and Anaplastic Large Cell Lymphoma. • CRZ-NBALCL Study (Protocol WI218627); A phase I/II study of crizotinib for recurrent or refractory ALK-positive ALCL and phase I study of this drug for recurrent or refractory neuroblastoma (Japan). • ITCC-053 Study (CRISP); A phase 1B study of crizotinib either in combination or as single agent in paediatric patients with ALK, ROS1 or MET positive malignancies; To submit antitumor activity and PK results of crizotinib in paediatric patients from the analysis of the pooled data of the 3 studies mentioned above. At least 25 paediatric or young adult	To evaluate the PK and efficacy of crizotinib at the lower dose of 165 mg/m^2 BID in paediatric patients.	31 August 2027

Table 34. Other Efficacy Study

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Due Date
	patients with ALCL are planned to be enrolled across 3 clinical studies.		

ALK = Anaplastic Lymphoma Kinase; ALCL = Anaplastic Large Cell Lymphoma; PK = Pharmacokinetic; BID = twice daily

a. One (1) study is complete, and the other 2 studies to complete the PMC are ongoing.

PART.V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

Table 35. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine Risk Minimisation Activities
Important identified risks	
Hepatotoxicity	Routine risk communication: SmPC sections 4.2, 4.4, 4.8 PL sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk Recommended dose for hepatotoxicity is included in SmPC section 4.2. Other routine risk minimisation measures beyond the Product Information: None
Pneumonitis/ILD	Routine risk communication: SmPC sections 4.2, 4.4, 4.8 PL sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk Recommended dose for Pneumonitis/ILD is included in SmPC section 4.2. Other routine risk minimisation measures beyond the Product Information: None
QTc prolongation	Routine risk communication: SmPC sections 4.2, 4.4, 4.8, 5.2 PL sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk Recommended dose for QTc prolongation is included in SmPC section 4.2. Other routine risk minimisation measures beyond the Product Information: None
Bradycardia	Routine risk communication: SmPC sections 4.2, 4.4, 4.5, 4.8 PL sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk Recommended dose for bradycardia is included in SmPC section 4.2. Other routine risk minimisation measures beyond the Product Information: None

Table 35. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine Risk Minimisation Activities
Renal cyst	Routine risk communication: SmPC section 4.8 PL section 4
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Gastrointestinal Perforation (EU and Switzerland)	Routine risk communication: SmPC sections 4.4, 4.8 PL sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Cardiac failure (EU, Japan, Switzerland and other ex-US Countries[a])	Routine risk communication: SmPC sections 4.4 PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Important Potential Risks	
Reproductive toxicity (including pregnant and lactating women)	Routine risk communication: SmPC section 4.6, 5.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Severe Vision Loss/Potential Sight Threatening Event	Routine risk communication: SmPC section 4.2, 4.4, 4.7, 4.8 PL sections 2,4 Routine risk minimisation activities recommending specific clinical measures to address the risk Recommended dose for vision disorder is included in SmPC section 4.2. Other routine risk minimisation measures beyond the Product Information: None

Table 35. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine Risk Minimisation Activities
Missing Information	
Patients undergoing long-term treatment	None

EU = European Union; ILD = Interstitial Lung Disease; PL = Patient Leaflet; QTc = QT Interval, Corrected for Heart Rate; SmPC = Summary of Product Characteristics; US = United States.

a. Cardiac failure added as ADR in local label upon request of national regulatory Agencies.

V.2. Additional Risk Minimisation Measures

Additional risk minimisation measures in the form of educational materials have been developed for the important identified and important potential risks. The informational brochure is intended to mitigate by informing the patient about the risks and the potential symptoms that may be experienced as a result of the risk.

Educational materials – Patient Brochure

Objectives: The objective of the proposed additional measure is to provide an appropriate tool designed to enhance the awareness and knowledge of patients about the following safety concerns; Hepatotoxicity, Pneumonitis/ILD, QTc prolongation, Bradycardia, Renal cyst, Gastrointestinal perforation, Cardiac failure, Reproductive toxicity (including pregnant and lactating women), and Severe vision loss/Potential sight threatening event; and to ensure the optimal use of crizotinib.

Rationale for the additional risk minimization activity:

- Additional awareness and knowledge of patients and caregivers about the risk will help to mitigate these risks.
- Target audience and plan for distribution:
- The target audience is patients and caregivers via their prescribing physicians. The communication plan varies by local legal and regulatory requirements.
- Plan to evaluate the effectiveness of the interventions and criteria for success:
- Routine pharmacovigilance activities to identify new safety signals and monitor reporting trends.

Direct Healthcare Professional Communication (DHPC)

Objectives: The objective of the proposed additional measure is to provide an appropriate communication designed to enhance the awareness and knowledge of healthcare professionals about the following safety concern ocular toxicity, including risk of severe visual loss, in paediatric patients with ALCL or IMT who receive crizotinib.

Rationale for the additional risk minimization activity:

- Additional healthcare professional awareness and knowledge about the risk will help to mitigate these risks.

Target audience and plan for distribution:

- The target audience is prescribing healthcare professionals. The communication plan varies by local legal and regulatory requirements.

Plan to evaluate the effectiveness of the interventions and criteria for success:

- Routine pharmacovigilance activities to identify new safety signals and monitor reporting trends.

V.3. Summary of Risk Minimisation Measures

Table 36. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Hepatotoxicity	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 PL sections 2, 4 Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Pneumonitis/ILD	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 PL sections 2, 4 Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
QTc prolongation	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8, 5.2 PL sections 2, 4 Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities:

Table 36. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		None
Bradycardia	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.5. 4.8 PL sections 2, 4 Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Renal cyst	Routine risk minimisation measures: SmPC section 4.8 PL sections 4 Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Gastrointestinal Perforation (EU and Switzerland)	Routine risk minimisation measures: SmPC sections 4.4,4.8 PL sections 2, 4 Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Cardiac failure (EU, Japan, Switzerland and other ex-US Countries[a])	Routine risk minimisation measures: SmPC section 4.4 PL section: 4 Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Important Potential Risks		
Reproductive toxicity (including pregnant and lactating women)	Routine risk minimisation measures: SmPC section 4.6, 5.3 PL section 2	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None

Table 36. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: Educational materials	Additional pharmacovigilance activities: None
Severe Vision Loss/Potential Sight Threatening Event	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.7, 4.8 PL sections 2, 4 Additional risk minimisation measures: Educational materials DHPC (specific to the paediatric population)	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: CRISP study ITCC 053 CRZ-NBALCL study
Missing Information		
Patients undergoing long-term treatment	None	None

EU = European Union; ILD = Interstitial Lung Disease; PL = Patient Leaflet; QTc = QT Interval, Corrected for Heart Rate; SmPC = Summary of Product Characteristics; US = United States.

a. Cardiac failure added as ADR in local label upon request of national regulatory Agencies.

PART.VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for XALKORI

This is a summary of the RMP for XALKORI. The RMP details important risks of XALKORI, how these risks can be minimised, and how more information will be obtained about XALKORI's risks.

XALKORI's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how XALKORI should be used.

This summary of the RMP for XALKORI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of XALKORI's RMP.

I. The Medicine and What It Is Used For

XALKORI is authorised for

- the first-line treatment of adults with ALK-positive advanced NSCLC, for the treatment of adults with previously treated ALK-positive advanced NSCLC and for the treatment of adults with ROS1-positive advanced NSCLC. It contains crizotinib as the active substance and it is given by oral route of administration.
- treatment of paediatric patients (age ≥1 to <18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL).
- treatment of paediatric patients (age ≥1 to <18 years) with recurrent or refractory anaplastic lymphoma kinase (ALK)-positive unresectable inflammatory myofibroblastic tumour (IMT).

Further information about the evaluation of XALKORI's benefits can be found in XALKORI's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to the EPAR summary landing page.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of XALKORI, together with measures to minimise such risks and the proposed studies for learning more about XALKORI's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of crizotinib, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant important risks, see below.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of XALKORI are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of XALKORI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 37. List of important risks and missing information

Important identified risks	• Hepatotoxicity • Pneumonitis/ILD • QTc Prolongation • Bradycardia • Renal Cyst • Gastrointestinal perforation[a] • Cardiac failure[b]
Important potential risks	• Reproductive Toxicity (including pregnant and lactating women) • Severe Vision Loss/Potential Sight Threatening Event
Missing information	• Patients undergoing long-term treatment

ILD = Interstitisal Lung Disease.

a. Considered as an important identified risk in the EU and Switzerland.

b. Considered as an important identified risk in the EU, Japan, Switzerland and other ex-US countries.

II.B Summary of Important Risks

Table 38. Summary of Important Risks

Important Identified Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine:	All non-clinical and all company-sponsored clinical studies; and post-marketing reports.
Risk factors and risk groups:	There are currently no known risk groups or risk factors for the development of hepatotoxity in patients receiving crizotinib. Refer to SVII 3.1.1.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 Additional risk minimisation measures: Educational Materials
Important Identified Risk: Pneumonitis/Interstitial Lung Disease	
Evidence for linking the risk to the medicine:	All non-clinical and all company-sponsored clinical studies; and post-marketing reports.

Table 38. Summary of Important Risks

Risk factors and risk groups:	There are currently no known risk groups or risk factors for the development of pneumonitis/ILD in patients receiving crizotinib. Factors that could potentially be associated with an increased risk of developing pneumonitis/interstitial lung disease under ongoing treatment with crizotinib include a history of pre-existing pulmonary disease, prior or concomitant treatment with medications with known pulmonary toxicity: antibiotics (nitrofurantoin, amphotericin B, minocycline); chemotherapy (bleomycin, methotrexate, cyclophosphamide); antiarrhythmics (amiodarone), radiation therapy, immune suppression resulting in pneumonia (bacterial, viral, fungal, or protozoal), a predisoposition to allergic pulmonary disease, autoimmune diseases (SLE, rheumatoid arthritis, etc.), occupational exposure (smoke, dust, silicone, asbestos), and other factors. Further, the underlying malignancy, particularly lymphangiosis carcinomatosa may also increase the risk of pneumonitis and additionally confound the diagnosis. Refer to SVII 3.1.2.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 Additional risk minimisation measures: Educational Materials
Important Identified Risk: QTc Prolongation	
Evidence for linking the risk to the medicine:	All non-clinical and all company-sponsored clinical studies; and post-marketing reports
Risk factors and risk groups:	No specific risk factors have been identified which may predispose patients to develop symptomatic QTc prolongation as a result of treatment with crizotinib. Based on known general risk factors for QTc prolongation, patient factors that may potentially be associated with an increased risk of developing QTc prolongation under treatment with crizotinib may include pre-existing conditions such as a Long QT Syndrome, a history of cardiac dysrhythmia, electrolyte disturbances, cardiac ischemia, and the concomitant use of medications with the potential to prolong QTc. Refer to SVII 3.1.3.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8, 5.2 Additional risk minimisation measures: Educational Materials
Important Identified Risk: Bradycardia	
Evidence for linking the risk to the medicine:	All non-clinical and all company-sponsored clinical studies; and post-marketing reports.
Risk factors and risk groups:	No specific risk groups or risk factors have been identified that might predispose patients to the development of bradycardia. However, pre-existing bradycardia, sinus node dysfunction, atrioventricular conduction disturbances, as well as concomitant medications affecting heart rate, such as beta blockers and non-dihydropyridine calcium channel blockers may increase the risk of developing bradycardia. Refer to SVII.3.1.4.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.5, 4.8 Additional risk minimisation measures:

Table 38. Summary of Important Risks

	Educational Materials
Important Identified Risk: Renal Cyst	
Evidence for linking the risk to the medicine:	All non-clinical and all company-sponsored clinical studies; and post-marketing reports.
Risk factors and risk groups:	It is possible that patients with pre-existing renal cysts are at increased risk of developing new (or enlarged) renal cysts under crizotinib. Refer to SVII 3.1.5.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.8 Additional risk minimisation measures: Educational Materials
Important Identified Risk: Gastrointestinal Perforation	
Evidence for linking the risk to the medicine:	All non-clinical and all company-sponsored clinical studies; and post-marketing reports.
Risk factors and risk groups:	Patients with conditions such as history of diverticulitis, metastases to theb gastrointestinal tract, or concomitant use of medications with a recognized risk of gastrointestinal perforation are predisposed to developing gastrointestinal perforation. Refer to SVII 3.1.6.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.4, 4.8 Additional risk minimisation measures: Educational Materials
Important Identified Risk: Cardiac failure	
Evidence for linking the risk to the medicine:	All non-clinical and all company-sponsored clinical studies; and post-marketing reports.
Risk factors and risk groups:	No clear risk factors have been identified. It is theoretically possible that patients with a history of cardiac disease, cardiac risk factors, or prior therapy with cardiotoxic drugs have a higher risk developing ventricular dysfunction while receiving crizotinib. Refer to SVII 3.1.7.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.4 Additional risk minimisation measures: Educational Materials
Important Potential Risk: Reproductive Toxicity (including pregnant and lactating women)	
Evidence for linking the risk to the medicine:	All non-clinical and all company-sponsored clinical studies; and post-marketing reports.

Table 38. Summary of Important Risks

Risk factors and risk groups:	Risk factors and risk groups include women of childbearing potential, pregnant women, and lactating women. Refer to SVII 3.1.8.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.6, 5.3 Additional risk minimisation measures: Educational Materials
Important Potential Risk: Severe Vision Loss/Potential Sight Threatening Event	
Evidence for linking the risk to the medicine:	All non-clinical and all company-sponsored clinical studies; and post-marketing reports.
Risk factors and risk groups:	Risk groups or risk factors associated with increased risk of severe vision loss/potential sight threatening event after administration of crizotinib is unknown. Cases of severe vision loss have been associated with brain metastases. Refer to SVII 3.1.9.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.7, 4.8 Additional risk minimisation measures: Educational Materials DHPC (specific to the paediatric population)

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

The following studies are conditions of the marketing authorisation:

None

II.C.2 Other Studies in Post-Authorisation Development Plan

Study name: CRISP Study ITCC 053: A phase 1B of crizotinib either in combination or as single agent in pediatric patients with ALK, ROS1 or MET positive malignancies.

Purpose of the study: To evaluate the risk factors manifestations, and outcomes of ocular toxicities associated with crizotinib in paediatric and young adult patients

PART.VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

None

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Draft - key messages of the additional risk minimisation measures

Educational material

Prior to the launch of XALKORI in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational material, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational material programme is aimed to communicate the risks with crizotinib and associated recommendations.

The MAH shall ensure that in each Member State where XALKORI is marketed, all healthcare professionals who are expected to use and/or prescribe XALKORI are provided with an educational pack.:

1. Summary of Product Characteristics and Package Leaflet.
2. Patient brochure including a Patient Card (text as agreed by the CHMP).

The Patient Information brochure should contain the following key elements:

- Brief introduction to crizotinib and the purpose of the risk minimisation tools.
- Information on how to take crizotinib, including what to do if a dose is missed
- Description of serious side effects associated with crizotinib, including how to manage these and to notify the doctor immediately if the patient develops:
    - Breathing problems associated with pneumonitis/ILD
    - Light-headedness, fainting, chest discomfort or irregular heartbeat associated with bradycardia, QT prolongation and cardiac failure
    - Abnormalities in liver blood tests associated with hepatotoxicity
    - Visual changes, including guidance to assess visual symptoms in the paediatric population
    - Stomach disorders associated with gastrointestinal perforation
- The importance of notifying the doctor, nurse or pharmacist if the patient uses any other medications
- Information that crizotinib should not be used during pregnancy and the need to use secure contraception (beyond oral contraceptives) during treatment

The Patient Card should contain the following key elements discussed in the Patient Information Brochure. The role/use of the detachable patient card is to show to healthcare professionals outside of the patient's healthcare team.

- Details of the key elements discussed in the Patient Information Brochure

Direct Healthcare Professional Communication (DHPC)

The objective of the proposed additional measure is to provide an appropriate communication designed to enhance the awareness and knowledge of healthcare professionals about the safety concern ocular toxicity including risk of severe visual loss, in paediatric patients with ALK-positive ALCL or ALK-positive IMT who receive crizotinib.