15 September 2022
EMA/846028/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

XALKORI

International non-proprietary name: crizotinib

Procedure No. EMEA/H/C/002489/II/0072

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Table of contents

1. Background information on the procedure 5
1.1 Type II variation 5
1.2 Steps taken for the assessment of the product 6

2. Scientific discussion 7
2.1 Introduction 7
2.1.1 Problem statement 7
2.1.2 About the product 10
2.1.3 The development programme/compliance with CHMP guidance/scientific advice 11
2.1.4 General comments on compliance with GCP 11
2.2 Non-clinical aspects 11
2.2.1 Introduction 11
2.2.2 Ecotoxicity/environmental risk assessment 12
2.2.3 Discussion on non-clinical aspects 13
2.2.4 Conclusion on the non-clinical aspects 13
2.3 Clinical aspects 14
2.3.1 Introduction 14
2.3.2 Pharmacokinetics 14
2.3.3 Pharmacodynamics 36
2.3.4 Discussion on clinical pharmacology 36
2.3.5 Conclusions on clinical pharmacology 37
2.4 Clinical efficacy 37
2.4.1 Dose response study(ies) 37
2.4.2 Main study(ies) 38
2.4.3 Discussion on clinical efficacy 67
2.4.4 Conclusions on the clinical efficacy 72
2.5 Clinical safety 73

2.5.1 Discussion on clinical safety 128
2.5.2 Conclusions on clinical safety 132
2.5.3 PSUR cycle 132
2.5.4 Direct Healthcare Professional Communication 132
2.6 Risk management plan 133
2.7 Update of the Product information 136
2.7.1 User consultation 136

3. Benefit-Risk Balance 137
3.1 Therapeutic Context 137
3.1.1 Disease or condition 137
3.1.2 Available therapies and unmet medical need 137
3.1.3 Main clinical studies 137
3.2 Favourable effects 138
3.3 Uncertainties and limitations about favourable effects 139
3.4 Unfavourable effects 140
3.5 Uncertainties and limitations about unfavourable effects 141

3.6 Effects Table 141
3.7 Benefit-risk assessment and discussion 144
3.7.1 Importance of favourable and unfavourable effects 144
3.7.2 Balance of benefits and risks 146
3.7.3 Additional considerations on the benefit-risk balance 147
3.8 Conclusions 147
3. Recommendations 148
4. EPAR changes 149

List of abbreviations

List of abbreviations

AE: adverse event
ABMT: autologous bone marrow (or peripheral stem cell) transplantation
ADC: antibody drug conjugate
ALCL: anaplastic large cell lymphoma
ALK: anaplastic lymphoma kinase
BID: twice daily
BMT: bone marrow or stem-cell transplantation
BOR: best overall response
CI: confidence interval
CNS: central nervous system
CO: Clinical Overview
COG: Children's Oncology Group
CR: complete response
CRu: unconfirmed CR
CSR: clinical study report
CT: computed tomography
DFS: disease-free survival
DLBCL: diffuse large B-cell lymphoma
DLT: dose-limiting toxicity
DR: duration of response
EFS: event-free survival
EORTC: European Organisation for Research and Treatment of Cancer
FA: full analysis
HSCT: hematopoietic stem cell transplantation
IMT: inflammatory myofibroblastic tumour
IRS: Intergroup Rhabdomyosarcoma Study
IQR: interquartile range
IWG: International Working Group
MRI: magnetic resonance imaging
MTD: maximum tolerated dose
MTX: methotrexate
NCCN: National Comprehensive Cancer Network
NHL: Non-Hodgkin's lymphoma
NSCLC: non-small cell lung cancer
ORR: objective response rate
OS: overall survival
PD: progressive disease
PET: positron emission tomography
PFS: progression-free survival
PR: partial response
RD: relative dose
RE: Response Evaluable
RECIST: Response Evaluation Criteria in Solid Tumours
RP2D: Recommended Phase 2 dose
SA: Safety Analysis
SAP: Statistical Analysis Plan
SCT: stem cell transplantation
SD: standard deviation
TTR: time to tumour response

1. Background information on the procedure

1.1 Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 27 May 2021 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment of paediatric patients (age ≥ 6 to < 18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and with unresectable, recurrent, or refractory ALK-positive inflammatory myofibroblastic tumour (IMT) for XALKORI based on the results from Studies ADVL0912 and A8081013; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the ATC code for crizotinib. Moreover, the MAH took the opportunity to implement a minor change in the list of local representatives in the Package Leaflet.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0036/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0036/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH submitted a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2 Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	27 May 2021
Start of procedure	19 June 2021
CHMP Rapporteur's preliminary assessment report circulated on	20 August 2021
PRAC Rapporteur's preliminary assessment report circulated on	20 August 2021
Updated PRAC Rapporteur's assessment report circulated on	31 August 2021
PRAC RMP advice and assessment overview adopted by PRAC on	2 September 2021
Updated CHMP Rapporteur's assessment report circulated on	10 September 2021
Request for supplementary information adopted by the CHMP on	16 September 2021
MAH's responses submitted to the CHMP on	20 December 2021
CHMP/PRAC Rapporteur(s) preliminary joint assessment report on the MAH's responses circulated on	28 January 2022
PRAC RMP advice and assessment overview adopted by PRAC on	10 February 2022
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	18 February 2022
2nd Request for supplementary information adopted by the CHMP on	24 February 2022
MAH's responses submitted to the CHMP on	22 April 2022
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	24 May 2022
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	24 May 2022
Updated PRAC Rapporteur's assessment report on the MAH's responses circulated on	3 June 2022
PRAC RMP advice and assessment overview adopted by PRAC on	10 June 2022
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	16 June 2022
3rd Request for supplementary information adopted by the CHMP on	23 June 2022
MAH's responses submitted to the CHMP on	11 August 2022
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	31 August 2022
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	8 September 2022
CHMP opinion adopted on	15 September 2022
The CHMP adopted a report on similarity of XALKORI with Adcetris, Poteligeo and Ledaga on	15 September 2022

2. Scientific discussion

2.1 Introduction

2.1.1 Problem statement

Disease or condition

The therapeutic indication concerns the treatment of paediatric patients (age ≥6 to <18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and forrecurrent or refractory anaplastic lymphoma kinase (ALK) positive unresectable inflammatory myofibroblastic tumour (IMT).

Epidemiology

ALCL is a rare disease that occurs in adults and children, and an aggressive NHL subtype of T- cell origin that may appear in the lymph node, skin, bone, or soft tissue that is characterized by the consistent expression of CD30 antigen (Amin & Lai, 2007; Falini et al, 1995; Falini et al, 1999; Savage et al, 2008). ALCL accounts for about 10-15% of pediatric NHL (Ward et al, 2014; Drexler etal, 2000; Burkhardt et al, 2005; Prokoph et al, 2018; Amin et al, 2007) and about 2-3% of adult NHL (Drexler et al, 2000; Mussolin et al, 2010) globally. ALCL incidence rates range from 1.5-7.8% in both male and female children from 0-19 years of age (PDQ Pediatric Treatment Editorial Board). Approximately, 100 new cases of pediatric ALCL are diagnosed in the US each year (Sandlund et al, 1996 and Lowe et al, 2013). Furthermore, US SEER data (2017) showed an ALCL rate of 0.1 per 100,000 among individuals 0-19 years of age, 0.2 per 100,000 among individuals aged 20-64 years, and 0.5per 100,000 for those ≥ 65 years (Howlader et al, 2017). Using incidence estimates from 2008, the incidence of ALK-positive ALCL in Europe ranged from 0.1 to 0.2 per 100,000 among individuals under 14 years and was lower among those 15 to 39 years (0.04 to 0.10 per 100,000) (Ferlay et al, 2010). According to published data, the proportion of relapse in the pediatric ALCL population is in the range of 25-35% (Woessmann et al, 2011).

Biologic features

The 2016 WHO classification identifies 3 separate biological entities in ALCL, which include primary systemic ALK-positive ALCL, primary systemic ALK-negative ALCL, and primary cutaneous ALCL (Swerdlow et al, 2016). The majority (84-90%) of ALCL in children has been reported to be ALK-positive (Burkhardt et al, 2005; Le Deley et al, 2008; Mussolin et al, 2010); whereas, studies have shown only ~50% of adult ALCL contain the ALK fusion gene (Gascoyne et al, 1999; Mussolin et al, 2010). Approximately 70 to 80% of ALK-positive ALCL express the NPM-ALK fusion protein, which is derived from the t(2;5)(p23;q35) translocation, while the remaining 20-30% of translocations fuse ALK to other partners (eg, TFG, TPM3, TPM4) (Mossé et al, 2009).

Clinical presentation, diagnosis

The most common presenting features include lymphadenopathy and systemic symptoms, such as fever and weight loss; however, ALCL can also present with an unusual course of waxing and waning lymphadenopathy or other symptom constellations, which may confuse the initial diagnosis. ALCL

often presents with advanced stage disease and in extra-nodal locations, such as skin and bone. In 12% of patients, the presentation of ALCL will be complicated by features of concomitant hemophagocytic lymphohistiocytosis (HLH). Lung, bone marrow, and central nervous system (CNS) involvement has been found to be more common in patients presenting with HLH-associated ALCL, although the outcomes are similar to those without HLH.

The diagnosis of ALCL requires a biopsy of affected tissue, nodal or extra-nodal. Samples are required to be adequate for morphologic and molecular analysis, and therefore fine needle biopsies are discouraged as they often do not provide adequate tissue for evaluation. The staging evaluation includes physical examination, computed tomography (CT) scans or magnetic resonance imaging (MRI), and assessment of bone marrow (BM) and cerebrospinal fluid (CSF). In addition, [18F] fluorodeoxyglucose (FDG)-positron emission tomography (PET) scanning may be helpful if available. While FDG-PET modalities have been incorporated into the Lugano classification for NHL in adults, there are minimal data on its use in children with NHL.

ALK negative (-) ALCL has been shown to be a negative prognostic factor in adult ALCL. However, as the overwhelming majority of paediatric patients with ALCL are ALK positive (+), the prognostic significance of ALK-disease in childhood remains unclear. Histologic subtype has been shown to be associated with increased relapse risk in several studies.

Management

Current Therapies for Paediatric Patients with ALCL

ALCL is a chemosensitive malignancy both in paediatric and adult patients, and multiple combination therapies are used as first-line treatment in the US (NCCN 2018 Guidelines [a]), but no guidelines have yet been established in the EU. In North America, patients with ALCL traditionally received less intensive but prolonged chemotherapy without high-dose MTX (Laver et al, 2005). Most European paediatric groups and recent US-based regimens recommend treatment with short-pulse chemotherapy based on high-dose MTX, cyclophosphamide, vincristine, doxorubicin, vinblastine, and corticosteroids (Brugières et al, 1998; Le Deley et al, 2010; Lowe et al, 2009; Pillon et, al 2009; Reiter et al, 1994; Seidemann et al, 2001; Williams et al, 2002; ClinicalTrials.gov. Identifier NCT01979536). In studies evaluating front-line therapies in patients with ALCL, 5-year OS is reported to be 65-81% (Le Deley et al, 2008; Prokoph et al, 2018) and EFS or PFS at 5 years ranges from 59% to 75% (Massimino et al, 1995; Mori et al, 2003; Sandlund et al, 1994; Seidemann et al, 2001; Williams et al, 2002). As many as 35% of paediatric patients with ALCL are refractory to front-line therapy or develop recurrent disease (Brugières et al, 2009). Among the patients who develop recurrent disease, 5-year OS after first relapse decreases to 57-69% (Woessmann et al, 2011; Brugières et al, 2000). Furthermore, for paediatric patients whose disease relapses during first-line treatment, 5-year OS is only 25% (Woessmann et al, 2011).

There is no consensus on the treatment of relapsed or refractory paediatric ALCL. Unlike other lymphomas, ALCL is usually still chemosensitive at relapse, and most patients can achieve a second remission and undergo high-dose chemotherapy (Brugières et al, 2000). 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 HSCT after a second CR is frequently used for treatment of relapsed ALCL (Bordon et al, 2005; Brugières et al, 2000; Cesaro et al, 2005; Chen et al, 2008; Deconinck et al, 2000; Mori et al, 2006; Woessmann et al, 2006).

Patients with subsequent relapses can also obtain prolonged remission following the administration of single-agent vinblastine. Five-year EFS and OS rates were 30% and 65%, respectively, among 36 relapsed patients in a French Society of Paediatric Oncology study treated with single-agent vinblastine

(with or without steroids) (Brugières et al, 2009). However, a proportion of patients will relapse again and will require further treatment (Brugières et al, 2009).

After achieving a second remission, many patients undergo autologous or allogeneic HSCT, as a "consolidation" strategy after chemotherapy.

Although data are limited, allogeneic HSCT appears superior to autologous HSCT (Prokoph et al, 2018 and Fukano et al, 2015). Allogeneic HSCT is effective in patients with either chemoresistant disease or multiple relapses, with 5-year EFS of approximately 75% (Cesaro et al, 2005; Mori et al, 2006; Woessmann et al, 2006; Fukano et al, 2015). However, allogeneic HSCT is also associated with a high rate of toxicity and toxicity-related mortality (Chakraverty et al, 2011).

Unmet Need for Paediatric Patients with Relapsed or Refractory Systemic ALK-positive ALCL

Crizotinib is a first-in-class molecularly targeted therapy that acts as a small-molecule inhibitor of ALK, MET/HGFR, ROS1, and RON RTKs. Crizotinib represents a new treatment option for paediatric patients with ALK-positive relapsed or refractory ALCL, a molecularly defined subgroup that currently lacks any approved therapeutic agents. Given that most paediatric ALCL cases are ALK positive and that aberrant ALK activity, attributed to ALK gene rearrangement, is postulated to be the direct cause of pathogenesis for paediatric ALCL, ALK is an ideal target for treatment. Single-agent therapy with crizotinib, an ALK TKI, is a potentially important therapeutic option for patients with ALCL resistant or refractory to chemotherapy and patients who underwent several previous treatments followed by disease relapse. In these patient groups, crizotinib may act as a bridge to HSCT (eg, achieving CR in patients with chemoresistant disease) or may offer an alternative option to HSCT altogether. An alternative to HSCT could be a favourable option even for patients fit enough to undergo the procedure. Notably, crizotinib was added as a treatment option for second-line (or later) treatment of adult patients with ALK-positive ALCL, including patients intended or not intended to proceed to HSCT, in the most recent version of the NCCN treatment guidelines for ALCL (NCCN 2018 guidelines[a]).

Inflammatory Myofibroblastic Tumour (IMT)

IMT is a class of tumour that presents a characteristic histological picture comprising a spindle cell proliferation with a chronic inflammatory infiltrate of plasma cells, lymphocytes, and histiocytes (Souid et al, 1993). Originally described in the lung, these lesions have been reported in various extrapulmonary sites in the thorax, retroperitoneal or pelvic region (Tang et al, 1990).As a result of the uncertain etiology of IMT, the WHO refers to 6 synonyms (plasma cell granuloma; inflammatory myofibrohystiocytic proliferation; omental mesenteric myxoid hamartoma; inflammatory pseudotumour; inflammatory fibrosarcoma; and inflammatory myofibroblastic sarcoma) and highlights that pseudosarcomatous myofibroblastic proliferations can be difficult to distinguish from IMTs (Coffin et al, 2013).The identification of clonal genetic aberrations involving the ALK locus supports the etiology of a low grade mesenchymal neoplasm. Approximately 50%-70% of IMTs are positive for ALK expression (Dalton et al, 2016; Höhne et al, 2015; Chun et al, 2005; Lawrence et al, 2000; Mossé et al, 2009). The most common mechanism for aberrant ALK expression or activation involves structural rearrangements in the ALK gene leading to a chimeric fusion protein, which is predominately detected by immunohistochemistry(Cook et al, 2001) with fluorescence in situ hybridization or next-generation sequencing also being used (Casanova et al, 2020).

Current Therapies for Paediatric Patients with IMT

IMTs are commonly in the thorax, retroperitoneal or pelvic region, and are considered resistant to conventional chemotherapy and radiation (Schoffski et al, 2018). Surgical resection is the mainstay of treatment, but due to close proximity to vital structures, a complete surgical resection may not always be an option. If curative surgery is not possible, local recurrence can occur with tumour invasion into

adjacent structures. This invasion is most likely to have a fatal outcome for the patient, rather than the development of distant metastasis which is less common.

Unmet Need for Paediatric Patients with Relapsed or Refractory Systemic ALK-positive IMT

Treatment options are limited in cases of unresectable or advanced IMT (Schoffski et al, 2018). There are no approved therapies for patients with unresectable, recurrent, or refractory IMT. However, as a mesenchymal tumour admixed with an inflammatory component, IMTs may respond initially to systemic corticosteroid therapy or non-steroidal anti-inflammatory drugs (Mattei and Barnaby, 2008). Alterations in ALK may contribute to the aggressive behaviour of some tumours (Chiarle et al, 2008; Coffin et al, 1998; Hagenstad et al, 2003). There is no standard therapy for aggressive unresectable tumours. Varying responses have been obtained with several chemotherapeutics including vincristine, methotrexate, etoposide, cisplatin, cyclophosphamide, vinorelbine, doxorubicin, and dacarbazine, although some of these tumours represented IMT with malignant transformation (Dishop et al, 2003; Favini et al, 2010; Hagenstad et al, 2003). Crizotinib represents a new treatment option for paediatric patients with ALK-positive IMT, a molecularly defined subgroup that currently lacks any approved therapeutic agents. In addition, the NCCN currently recommends crizotinib for the treatment of IMT with ALK rearrangements (NCCN 2018 Guidelines [b]) based on literature reports (Schoffski et al, 2018).

2.1.2 About the product

Crizotinib is a first-in-class molecularly targeted therapy that acts as a small-molecule inhibitor of ALK, MET/HGFR, ROS1, and RON RTKs. Crizotinib received approval in the US for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is ALK- positive as detected by an FDA-approved test. Crizotinib also received approval in the EU for the treatment of adults with previously treated, and subsequently for previously untreated, ALK-positive advanced NSCLC. Additional approvals for the treatment of ALK-positive advanced NSCLC have been granted in more than 90 countries worldwide. A second crizotinib indication for the treatment of ROS1-positive advanced NSCLC was approved in the US and EU in March 2016 and August 2016, respectively, with additional approvals for this indication in more than 75 countries worldwide. On 14 January 2021, crizotinib received approval in the US for the treatment of paediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic ALCL that is ALK- positive and on 14 July 2022 crizotinib was approved in the US for the treatment of paediatric patients 1 year of age and older and young adults with unresectable, recurrent, or refractory (ALK)-positive IMT. Crizotinib was approved in Switzerland on 17 May 2022 for the treatment of paediatric patients (≥6 to <18 years) with relapsed or refractory systemic ALK-positive ALCL and for the treatment of paediatric patients (≥6 to <18 years) with unresectable, recurrent, or refractory ALK-positive IMT.

Molecular Biology and Early Clinical Activity

ALK was originally discovered in ALCL, where the chromosome translocation, t(2;5)(p23:q35), was observed (Morris et al, 1994; Shiota et al, 1994). This translocation generates the NPM-ALK oncogenic fusion protein, in which the kinase domain of ALK is fused to the N-terminal portion of the NPM protein and accounts for ~70%–80% of all ALK-positive ALCL (Mossé et al, 2009). A higher prevalence of NPM-ALK (~90% of all ALK fusions observed) has been reported in paediatric ALCL specimens (Damm-Welk et al, 2009; Perkins et al, 2005; Mussolin et al, 2010). The NPM-ALK fusion protein dimerizes and leads to ligand-independent, constitutive expression and activation of ALK and associated signalling pathways (STAT3, AKT/PI3K, RAS/ERK, etc), which control cell proliferation, survival, cell cycling, DNA methylation, activation of microRNA and expression of transcription factors (Mossé et al, 2009; Palmer et al, 2009; Eyre et al, 2014; Werner et al, 2017; Ducray et al, 2019). Other transforming ALK fusions, including TPM3-ALK, which appears to the be most common outside of NPM-ALK and the less prevalent TFG-, CLTC-, ATIC-, MHY9-, MSN-, AL017- ALK fusions, have also been reported in ALCL (Armstrong

et al, 2004; Pulford et al, 2004; Damm-Welk et al, 2009; Hallberg et al, 2013; Holla et al, 2017; Ducray et al, 2019).

In a panel of 602 cell lines derived from a variety of human cancers, 2 ALCL-derived cell lines (SU-DHL-1 and Karpas-299, both containing NPM-ALK) were reported (McDermott et al, 2008) to be particularly sensitive to ALK inhibitors, including crizotinib. Crizotinib demonstrated dose-dependent inhibition of phosphorylation of ALK as well as inhibition of activation of downstream ALK signaling targets ERK 1/2 (also known as MAPK 44/42), AKT, STAT3 and PLC-γ1 in these tumour cells, and induced apoptosis at clinically achievable doses (Pfizer Study Report PF-02341066-Pharm-001, Pfizer Study Report PF-02341066_Pharm_002, Hamedani et al, 2014, Wang et al, 2019).

In vivo data demonstrated antitumour efficacy of crizotinib, including marked cytoreductive antitumour activity, in tumour models implanted in athymic mice that expressed activated NPM-ALK, and complete regression of the tumour was observed in the Karpas-299 model at a dose of 100 mg/kg QD (Pfizer Study Report PF-02341066-Pharm-001; Pfizer Study Report PF-02341066_Pharm_002).

2.1.3 The development programme/compliance with CHMP guidance/scientific advice

The clinical development program for crizotinib as a treatment for paediatric patients with ALK-positive ALCL or ALK-positive IMT has been planned, conducted, and analysed in accordance with relevant regulatory requirements and guidance. Guidance for oncology drugs included the US FDA's "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" (US Food and Drug Administration, 2018), "Cancer Drugs and Biological Products – Clinical Data in Marketing Applications" (US Food and Drug Administration, 2001), and the EMA "Guidance on Evaluation of Anticancer Medicinal Product in Man" and relevant Appendix 1 (European Medicines Agency, 2019). Several meetings were held with FDA and EMA to discuss the clinical development program and regulatory submission plans for crizotinib for the treatment of paediatric patients with ALK-positive ALCL and paediatric patients with ALK-positive IMT.

2.1.4 General comments on compliance with GCP

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all GCP Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of study patients.

2.2 Non-clinical aspects

No new clinical data have been submitted in this application, with the exception of a revised environmental risk assessment (ERA) - which was considered acceptable by the CHMP.

2.2.1 Introduction

The MAH provided a revised environmental risk assessment (ERA) for the present extension of indication to the treatment

- of paediatric patients (age ⩾6 to <18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK) positive anaplastic large cell lymphoma (ALCL)
- of paediatric patients (age ⩾6 to <18 years) with, recurrent, or refractory anaplastic lymphoma kinase (ALK) unresectable positive inflammatory myofibroblastic tumour (IMT).

2.2.2 Ecotoxicity/environmental risk assessment

Substance (INN/Invented Name):crizotinib					
CAS-number (if available): 877399-52-5					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	**OECD107, OPPTS 830.7550**	log P_{ow} : 0.169, 1.83, 3.88 at pH 4, 7, 9 respectively			Potential PBT: No
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}				B/not B
	BCF				B/not B
Persistence	DT50 or ready biodegradability	OECD 307: DT50soil1-4, 12°C= 209d – 401d OECD 308: No decreasing concentration until day 103 in sediment, reliable DT50sediment calculation not possible			vP
Toxicity	NOEC or CMR				T/not T
PBT-statement :	Crizotinib is very persistent into the environment.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC surfacewater, Fpen refined by prevalence published data	0.51	µg/L			> 0.01 threshold Y
Other concerns (e.g. chemical class)					**N**
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc\text{-}sludge}$ = 14,125 $K_{oc\text{-}soil}$ = 77,267 (mean of 2 soils and 2 sediments)			
Ready Biodegradability Test	OECD 301				Not submitted
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT50, water =0.95-1.2 d DT50, sediment =37.6 - no reliable calculation possible for the 2nd system DT50, whole system =37.1-109 days % shifting to sediment =44.72			vP, because no decreasing values in sediment in one system
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	0.0093 (growth rate)	mg/L	Pseudokirchneriella subcapitata
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.130	mg/L	Daphnia magna
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	0.070	mg/L	Pimephales promelas
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50	>1000	mg/L	
Phase IIb Studies					
Bioaccumulation Lepomis macrochirus	OECD 305	BCF	10	L/kg	%lipids:

Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	134.7 (geo mean, 20°C) 0.1-1.3%	days	DT50Loamy sand: 144 d (20°C) DT50Sandy loam: 188d (20°C) DT50Clay loam: 98d (20°C) DT50Sandy clay loam: 124d (20°C) vP in all soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	0.8-5.6%	mg/kg	Day 14
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	10	mg/kg	Day 21 Allium cepa Lolium perenne Brassica rapa Cucumis sativa Lactuca sativa Lycopersicon esculentum
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	10	mg/kg	Eisenia fetida
Collembola, Reproduction Test	ISO 11267	NOEC	1000	mg/kg	Folsomia candida
Sediment dwelling organism	OECD 218	NOEC	108	mg/kg	Chiromomus riparius

2.2.3 Discussion on non-clinical aspects

The calculated PEC in Phase I was greater than 0.01 µg/L which necessitated a Phase II assessment. The PEC/PNEC values for surface water, subsoil and microorganisms were less than 1. However, the Koc of the sludge was greater than 10,000, which required a more complete assessment of the terrestrial compartment. Since the log Kow was 3.88 at pH 9, an evaluation of the bioconcentration potential in fish was required. Phase II fish bioconcentration, chironomid, aerobic soil transformation, and terrestrial environmental toxicity studies (conducted on >3 different types) demonstrated no risk from crizotinib.

The revised environmental risk assessment (ERA) performed for the present extension of indication to the treatment was sufficient.

The proposed PI wording: "Any unused product or waste material should be disposed of in accordance with local requirements." Is therefore sufficient.

2.2.4 Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of crizotinib.

- Considering the above data, crizotinib should be used according to the precautions stated in the SmPC in order to minimize any potential risks to the environment.

2.3 Clinical aspects

2.3.1 Introduction

GCP

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1. Summary of clinical studies with crizotinib with ALK-positive ALCL or IMT (<18 years)

Protocol Number/ Sponsor	Protocol Title	Single or Multicenter/ Location	Study Dates and Status[a]	Study Treatment	Study Population (ALCL and IMT < 18 years)
Primary Study					
ADVL0912/COG	A 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	Multicenter (United States, Canada)	29 Sep 2009/ 19 Jan 2018, Completed	**Phase 1:** Escalating Dose groups: Crizotinib (Route: Oral; Dose Regimens: 100 mg/m² BID, 130 mg/m² BID, 165 mg/m² BID, 215 mg/m² BID, 280 mg/m² BID, 365 mg/m² BID). **Phase 2:** Crizotinib (Route: Oral; Dose Regimen: 280 mg/m² BID)	ALCL Population SA: 22 165 mg/m² BID: 6 280 mg/m² BID: 16 RE: 22 165 mg/m² BID: 6 280 mg/m² BID: 16 Treated: 22 165 mg/m² BID: 6 280 mg/m² BID: 16 IMT Population SA: 14 100 mg/m² BID: 1 165 mg/m² BID: 1 280 mg/m² BID: 12 RE: 14 100 mg/m² BID: 1 165 mg/m² BID: 1 280 mg/m² BID: 12 Treated: 14 100 mg/m² BID: 1 165 mg/m² BID: 1 280 mg/m² BID: 12
Supporting Study					
A8081013/ Pfizer	Phase 1b Open-Label Study of the Safety and Clinical Activity of Crizotinib (PF-02341066) in Tumors With Genetic Events Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus	Multicenter (China; Italy; Japan; Korea, Republic of; Russian Federation; Taiwan; United States)	22 Mar 2011/ongoing, data cutoff: 03 Sep 2019 for interim CSR	Crizotinib (Route: Oral; Dose Regimen: 250 mg BID)	ALCL Population SA: 3 RE: 3 Treated: 3 IMT Population SA: 2 RE: 2 Treated: 2

2.3.2 Pharmacokinetics

In the context of the new indication in paediatric patients over 6 years, the MAH provided new PK and Dose/Exposure analyses based on the data collected in Study ADVL0912 and the on-going Study A8081013.

These analyses consisted in:

- A conventional (NCA: Non-Compartmental Analysis) PK analysis of the data collected in paediatric patients from Studies ADVL0912 and A8081013
- A population-PK analysis based on data in paediatric patients from Studies ADVL0912 and A8081013.

- Results from the dose/exposure response analyses for antitumour activity in paediatric patients from Study ADVL0912.

- Results from the dose/exposure response analyses for selected safety endpoints in paediatric patients from Studies ADVL0912 and A8081013.

- **Non Compartmental Analysis of data from studies ADVL0912 and A8081013**

    - Study ADVL0912

Pharmacokinetics design:

For patients enrolled prior to Institutional Review Board(IRB)/Independent Ethics Committee (IEC) approval of Protocol Amendment 3C (26 May 2011), the following crizotinib pharmacokinetic (PK) sampling was conducted inPhase 1 (Part A) and Phase 2 (Part B and Part C):

- For C1D1, PK samples were collected at the following time points: predose (0 hour), 0.5, 1, 2, 4, 6, 8-10, and 22-26 hours after the morning dose for patients who weigh ≥10 kg, or predose (0 hour), 1, 2, 4, 6, 8-10, and 22-26 hours after the morning dose for patients who weigh <10 kg. The evening dose was not administered on Day 1. In addition, PK samples were collected prior to dose between Days 5-8, Days 12-15, Days 19-22, and Days 26-29 in Cycle 1.

For patients enrolled following IRB/IEC approval of Protocol Amendment 3C (26 May 2011), the following crizotinib PK sampling was conducted:

- On C1D1, samples were collected prior to the first dose of crizotinib. At steady state (between Cycle 1 Days 15 and 28), samples were collected at predose (12 hours after the last dose), 1, 2, 4, and 6-8 hours after the morning dose for all patients on Part A.

Additionally steady state samples at the same time points were also collected for patients in Part B or Part C who had obtained informed consent to participate in the PK evaluation.

Crizotinib plasma PK parameters (as appropriate for patients with serial PK sample collection) were estimated for each patient from plasma concentration-time data using a Pfizer validated noncompartmental analysis application system (eNCA version.2.2.4).

Samples below the lower limit of quantitation were set to 0 ng/mL for the PK analysis.

Actual sample collection times were used for the PK analysis where possible. However, nominal times were used for PK parameter estimations in situations where the dosing time was missing; this included C1D1 for all patients and at steady state for 3 patients (1 patient on C1D16 and 2 patients on C1D15, all at the 280 mg/m2 BID dose level). Additionally, nominal times were used for 2 PK samples for 1 patient on C1D22 at the 280 mg/m^2 BID dose level; the actual collection time was missing for the 4- and 6-hour postdose PK samples.

PK parameters evaluated in the study included:

- Single dose plasma PK parameters of maximum observed concentration (C_{max}), dose normalized maximum observed concentration ($C_{max,\ dn}$), time of maximum observed concentration (T_{max}), time of last observed concentration (T_{last}), area under the curve of last measurable quantity (AUC_{last}), and dose normalized area under the curve of last measurable quantity ($AUC_{last,\ dn}$) were determined for C1D1.
- Steady state plasma PK parameters C_{max}, $C_{max,\ dn}$, T_{max}, area under the plasma concentration-time profile from time zero to time tau, the dosing interval (tau=12 for BID dosing) (AUCtau), dose normalized area under the plasma concentration-time profile from time zero to time tau ($AUC_{tau,\ dn}$), apparent oral clearance (CL/F), lowest concentration prior to next administration of drug (C_{trough}), and dose normalized lowest concentration prior to next administration of drug ($C_{trough,\ dn}$) were determined during Cycle 1. For the determination of AUCtau, the predose (0 hour) concentration was also used as the 12 hour postdose concentration as they are expected to be similar at steady state.

Identity of Investigational Product(s)

Different formulations, strengths and dosage forms of crizotinib were used to support the different phases of clinical development.

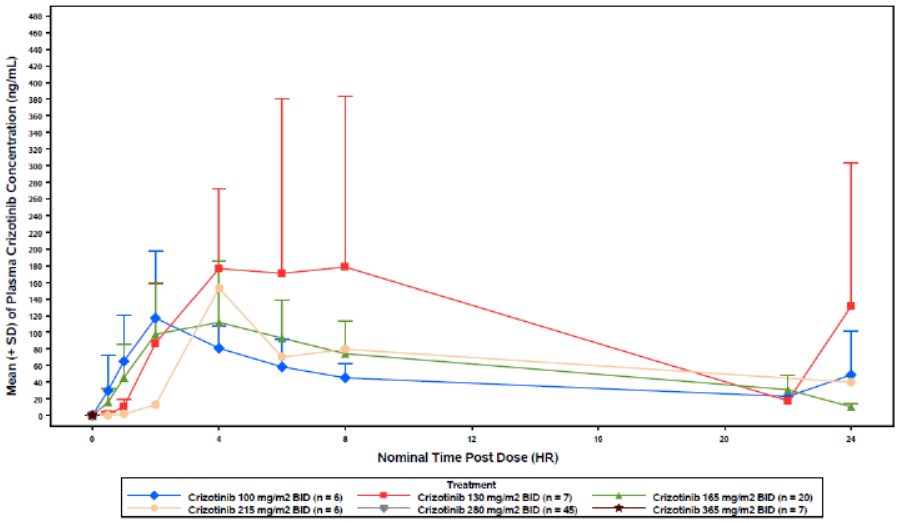
PK-Results:

Mean plasma crizotinib concentration-time profiles following the administration of single oral doses of 100 mg/m^2 BID, 130 mg/m^2 BID, 165 mg/m^2 BID, and 215 mg/m^2 BID are presented by dose levels for paediatric patients in Figure 1. There were no postdose PK samples collected for the 280 mg/m^2 BID and 365 mg/m^2 BID dose levels on C1D1:

Single dose crizotinib PK parameters by dose level are summarised for paediatric patients with any tumour type (ALCL, IMT) in Table 2.

Plots of individual and geometric mean crizotinib C_{max} values for patients in the total group (patients with ALCL, IMT, or Other Tumours) by dose level are presented in Figure 1 and Figure 2, respectively, for paediatric patients.

Figure 1 Cycle 1 Day 1 Mean (+SD) Plasma Crizotinib Concentration (ng/mL) versus Time Plot by Tumor Type and Dose Level (All Tumor Types, All Dose Levels, Age <18 years) – PK Concentration Analysis Set (Protocol ADVL0912)

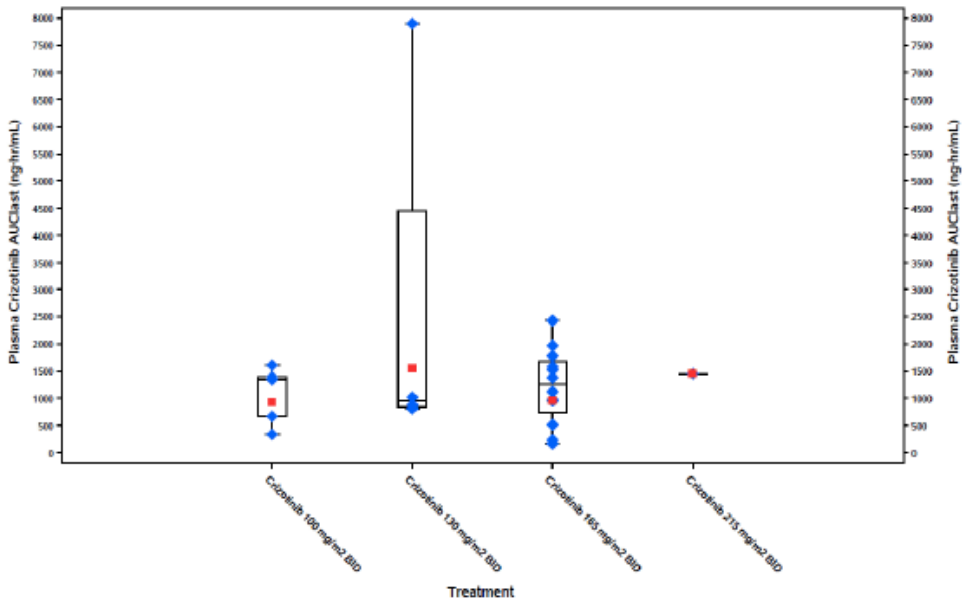


With the limited number of patients at most dose levels and limitations of the collection schedule (only up to 24 hours postdose), high interpatient variability was observed in PK parameters on C1D1. The plasma exposures of crizotinib across the dose levels largely overlapped.

Table 2 Summary of Plasma Crizotinib PK Parameters of Cycle 1 Day 1 by Tumor Type and Dose Level (All Tumor Types, All Dosage Levels, Age <18 years), Study ADVL0912 Tumor Type: Total

Parameter, unit[a]	Crizotinib 100 mg/m² BID (N=5)	Crizotinib 130 mg/m² BID (N=4)	Crizotinib 165 mg/m² BID (N=13)	Crizotinib 215 mg/m² BID (N=3)
N2	5	4	12	1
AUC_{last}, ng·hr/mL	921.7 (74)	1547 (151)	953.7 (103)	1450*
$AUC_{last, dn}$, ng·hr/mL/mg	9.386 (67)	9.746 (202)	5.671 (111)	4.04*
C_{max}, ng/mL	111.8 (55)	179.9 (88)	121.8 (62)	153*
$C_{max, dn}$, ng/mL/mg	1.139 (50)	1.133 (103)	0.7239 (68)	0.425*
T_{last}, hr	24.0 (8.00-24.0)	23.0 (8.00-24.0)	22.0 (6.00-24.0)	24*
T_{max}, hr	2.00 (1.00-4.00)	4.00 (2.00-6.00)	4.00 (2.00-8.00)	4*

Figure 2 Cycle 1 Day 1 Plasma Crizotinib Parameter (AUC) Plot by Dose Level (All Tumor Types, All Dose Levels Age <18 years) – PK Parameter Analysis Set (Protocol ADVL0912)



Mean plasma crizotinib concentration-time profiles at steady state at dose levels of 165 mg/m^2 BID, 215 mg/m^2 BID, 280 mg/m^2 BID and 365 mg/m^2 BID are presented by dose level for paediatric patients in Figure 3. Plasma crizotinib PK parameters at steady state are summarised by dose levels for paediatric patients with ALCL, IMT and any tumour type. The PK parameters compiling all the data (any tumour) are produced (Table 3).

Plots of individual and geometric mean crizotinib AUC_{tau} and C_{max} values for paediatric patients in the total group (patients with ALCL, IMT or Other Tumours) by dose are also provided. Although limited by the number of patients, results suggested that the crizotinib plasma exposure increased with increasing dose in an approximately dose proportional manner at steady state.

Figure 3 Steady State Mean (+SD) Plasma Crizotinib Concentration (ng/mL) Versus Time Plot by Tumor Type and Dose Level (All Tumor Types, All Dose Levels, Age <18 years) – PK Concentration Analysis Set (Protocol ADVL0912)

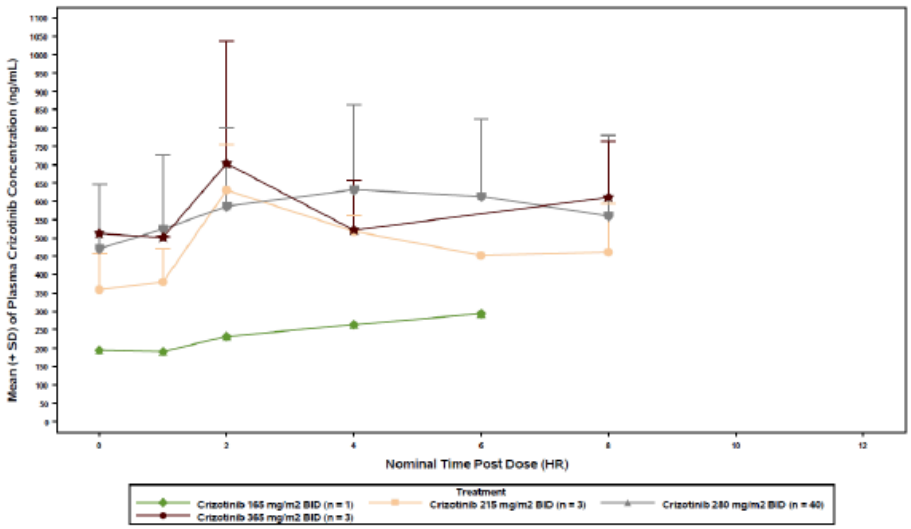


Table 3 Summary of Plasma Crizotinib PK Parameters of Steady State by Tumor Type and Dose Level (All Tumor Types, All Dose Levels, Age <18 years), Study ADVL0912 Tumor Type: Total

Parameter, unit[a]	Crizotinib 165 mg/m² BID (N=13)	Crizotinib 215 mg/m² BID (N=3)	Crizotinib 280 mg/m² BID (N=45)	Crizotinib 365 mg/m² BID (N=3)
N2, N3	1, 1	2, 2	39, 40	2, 2
AUC_{tau}, ng·hr/mL	2900*	6180, 5010*	6530 (34)	6090, 7400*
$AUC_{tau, dn}$, ng·hr/mL/mg	22.3*	34.3, 33.4*	22.34 (54)	15.2, 23.1*
CL/F, L/hr	44.8*	29.1, 29.9*	44.76 (53)	65.7, 43.2*
C_{max}, ng/mL	294*	719, 549*	620.8 (73)	562, 939*
$C_{max, dn}$, ng/mL/mg	2.26*	3.99, 3.66*	2.123 (90)	1.41, 2.93*
C_{trough}, ng/mL	195*	429, 289*	450.0 (40)	512, 657*
$C_{trough, dn}$, ng/mL/mg	1.5*	2.38, 1.93*	1.540 (53)	1.28, 2.05*
T_{max}, hr	5.98*	2, 4.08*	4.00 (0.000-6.38)	6, 1.25*

In order to explore the potential effect of age on plasma PK of crizotinib in paediatric patients, patients were divided into 4 groups according to their age at baseline (2-<6, 6-<12, 12-<18, and 18-≤21 years). The dose normalized crizotinib plasma exposure parameters $C_{max, dn}$ and $AUC_{last, dn}$ on C1D1 and $C_{max, dn}$ and $AUC_{tau, dn}$ at steady state are summarised in Table 4 and Table 5, respectively.

Plots of dose normalized parameters by age group are shown in Figure 4 and Figure 5 (C1D1) and Figure 6 and Figure 7 (steady state). In addition to the categories based on age defined above, an additional category with pooled data for all paediatric patients was also generated for relevant crizotinib PK parameters and included in the tables.

Based on visual examination of the data, on C1D1 (single dose), crizotinib dose normalized exposure measures ($AUC_{last, dn}$ and $C_{max, dn}$) appeared highest in the youngest paediatric patient group (2-<6 years) compared to the other age groups. However, there was high interpatient variability in crizotinib PK parameters across the age groups.

At steady state, a visual examination of the data indicated that mean crizotinib dose normalized exposure measures ($AUC_{tau, dn}$ and $C_{max, dn}$) appeared to decrease with the increase in age from 2-<6 years to 12-<18 years. The dose normalized exposures were similar between patients who were 12-<18 years and patients of 18-≤21 years, which were comparable with the dose normalized exposure from adult patients (Initial Crizotinib submission) largely overlapping. The individual values for patients of 18-≤21 years completely overlapped with those for paediatric patients. Of note, the steady-state dose-normalized exposures for patients who were 12-<18 years were comparable to that observed for adult patients with cancer (Initial Crizotinib data).

Table 4 Summary of Plasma Crizotinib Dose Normalized PK Parameters of Cycle 1 Day 1 by Age Group (All Tumor Types, All Dose Levels, All Ages), Study ADVL0912

Parameter, unit[a]	2-<6 (N=16)	6-<12 (N=36)	12-<18 (N=21)	<18 (N=73)	18-21 (N=14)
N2, N3	5, 5	9, 9	8, 8	22, 22	3, 4
$AUC_{last, dn}$, ng·hr/mL/mg	8.686 (51)	6.440 (108)	6.482 (169)	6.910 (111)	2.911 (132)
$C_{max, dn}$, ng/mL/mg	1.118 (28)	0.8035 (72)	0.7624 (97)	0.8497 (72)	0.3502 (66)

Source table: Table 14.4.5.1.5.1
N = Total number of participants in the treatment group in the PK parameter analysis set
N2 = Number of participants contributing to the summary statistics for $AUC_{last, dn}$
N3 = Number of participants contributing to the summary statistics for $C_{max, dn}$
a. Geometric mean (geometric %coefficient of variation) for all

Age subgroups: 2-<6 years, 6-<12 years, 12-<18 years, <18 years, 18-21 years

Table 5 Summary of Plasma Crizotinib Dose Normalized PK Parameters of Steady State by Age Group (All Tumor Types, All Dose Levels, All Ages), Study ADVL0912

Parameter, unit[a]	2-<6 (N=16)	6-<12 (N=36)	12-<18 (N=21)	<18 (N=73)	18-21 (N=14)
N2, N3	10, 10	23, 24	11, 11	44, 45	7, 8
$AUC_{tau, dn}$, ng·hr/mL/mg	35.46 (28)	23.21 (35)	14.15 (51)	22.58 (51)	14.25 (43)
$C_{max, dn}$, ng/mL/mg	3.791 (32)	2.146 (100)	1.358 (47)	2.178 (86)	1.470 (36)

Source table: Table 14.4.5.2.5.1
N = Total number of participants in the treatment group in the PK parameter analysis set
N2 = Number of participants contributing to the summary statistics for $AUC_{tau, dn}$
N3 = Number of participants contributing to the summary statistics for $C_{max, dn}$
a. Geometric mean (geometric %coefficient of variation) for all

Age subgroups: 2-<6 years, 6-<12 years, 12-<18 years, <18 years, 18-21 years

Figure 4 Cycle 1 Day 1 Plasma Crizotinib Dose Normalized Parameter ($AUC_{last, dn}$) Plot by Age Group (All Tumor Types, All Dose Levels, All Ages) - PK Parameter Analysis Set (Protocol ADVL0912)

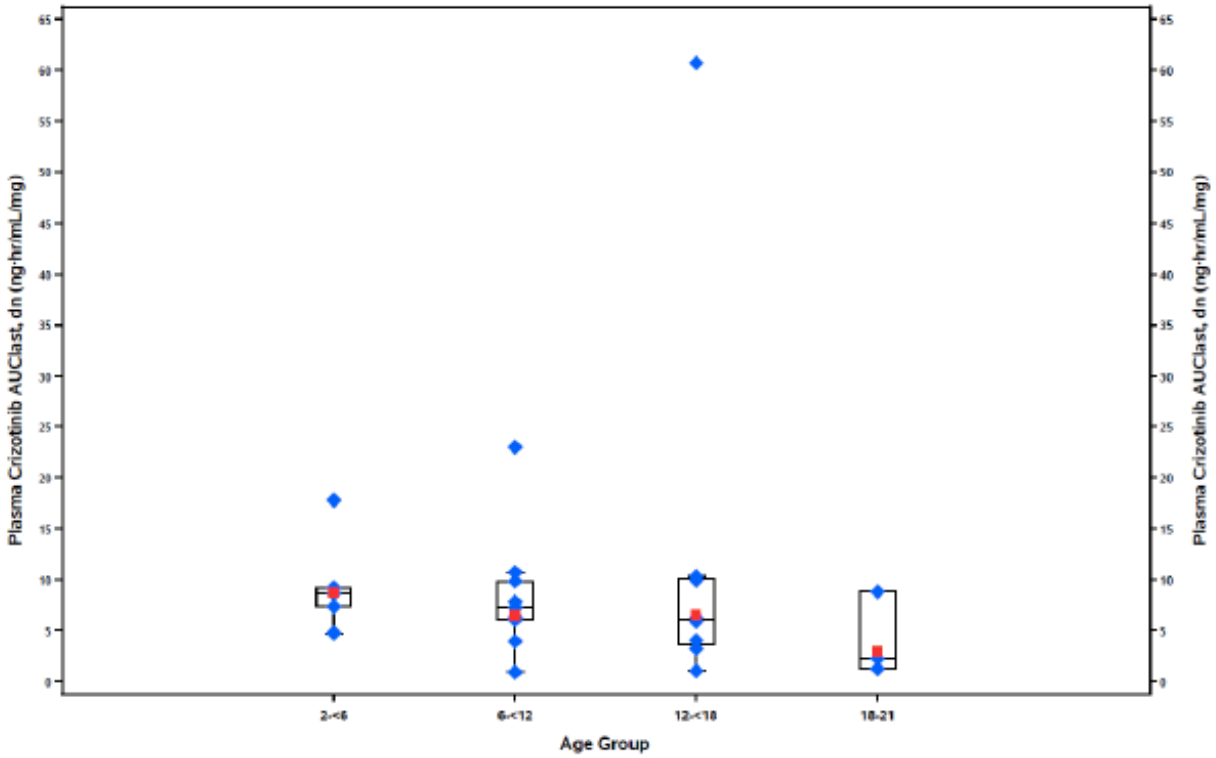


Figure 5 Cycle 1 Day 1 Plasma Crizotinib Dose Normalized Parameter ($C_{max, dn}$) Plot by Age Group (All Tumor Types, All Dose Levels, All Ages) - PK Parameter Analysis Set (Protocol ADVL0912)

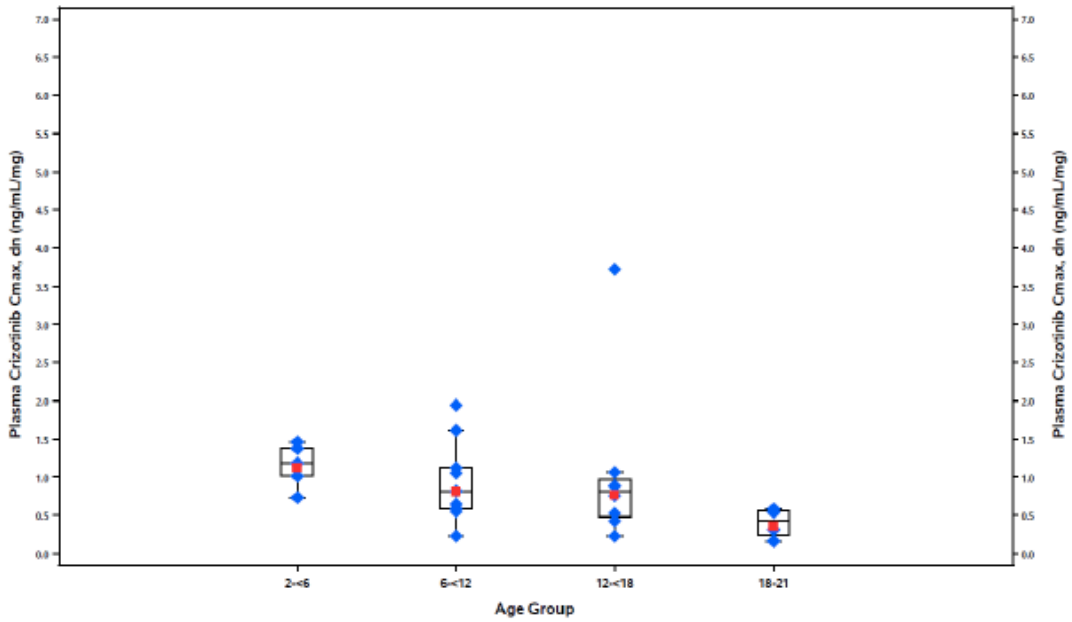


Figure 6 Steady State Plasma Crizotinib Dose Normalized Parameter ($AUC_{last, dn}$) Plot by Age Group (All Tumor Types, All Dose Levels, All Ages) – PK Parameter Analysis Set (Protocol ADVL0912)

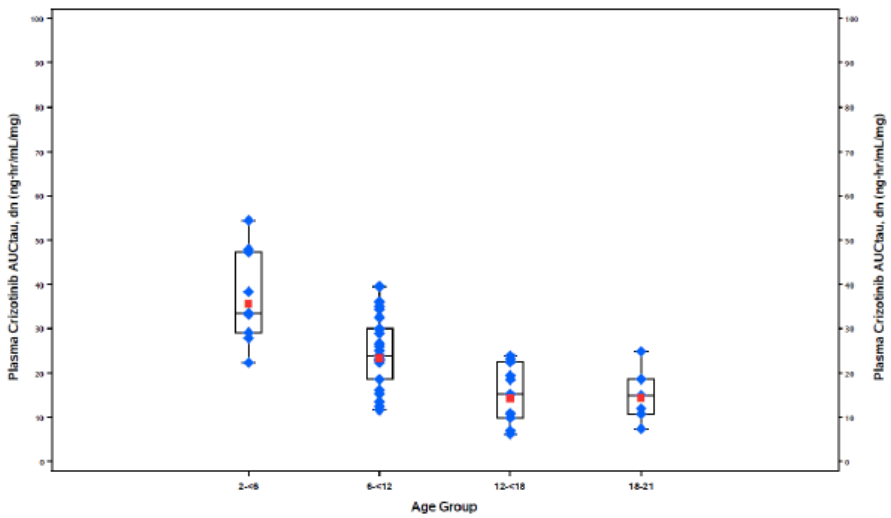
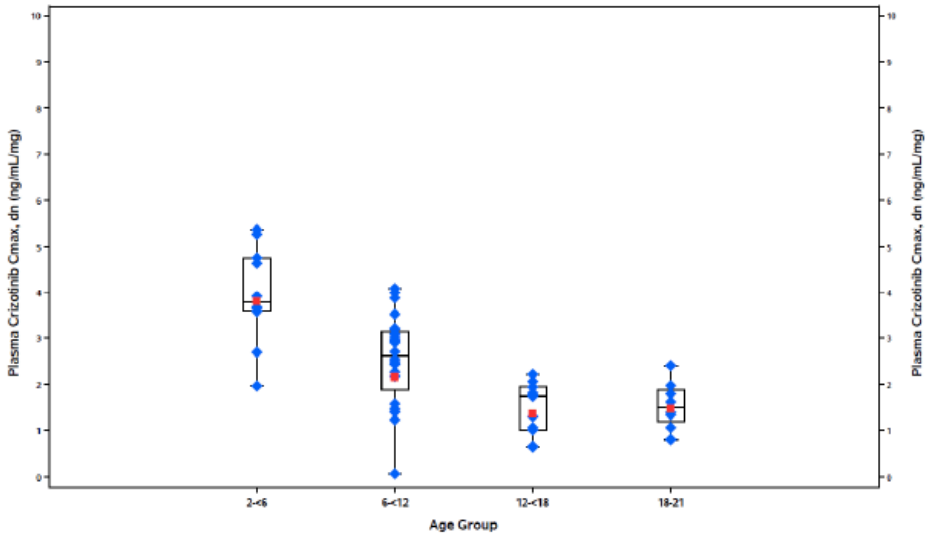


Figure 7 Steady State Plasma Crizotinib Dose Normalized Parameter ($C_{max, dn}$) Plot by Age Group (All Tumor Types, All Dose Levels, All Ages) – PK Parameter Analysis Set (Protocol ADVL0912)



- Study A8081013

  Study Design

  Study A8081013 is a Phase 1b, open label, multicentre, single arm exploratory study evaluating the antitumour activity, safety, and PK of crizotinib. Patients (≥15 years) with a histologic or cytologic proven diagnosis of ALCL or other advanced malignancy other than NSCLC, eg, IMT, for which no standard therapy was available and were positive for harboring a translocation, inversion, mutation or amplification event involving the ALK gene locus were enrolled.
  Patients could have continued treatment with crizotinib after disease progression if there was evidence of clinical benefit in the judgment of the Investigator.
  The study is still ongoing.

  Pharmacokinetic Results

  All patients in this study received a crizotinib starting oral dose of 250 mg BID. Of the 5 paediatric patients enrolled in this study, 3 were in the ALCL group 2 were in the IMT group (A8081013 CSR Table 16.2.5.4.1.2). The mean steady-state Ctrough values for these paediatric patients were comparable with the adult patients in this study (A8081013 CSR Tables 16.2.5.4.4.1 and 16.2.5.4.4.2).

- Population-PK analysis:

Additionally to the NCA analysis of the data from from Study ADVL0912 and Study A8081013 a Report labelled: "Population Pharmacokinetic Analysis of Crizotinib (Xalkori) in Paediatric Patients with Relapsed or Refractory Solid Tumours and Anaplastic Large Cell Lymphoma" is provided by the MAH

The objective of these investigations were:
• To explore the potential effect of age, body weight, body surface area (BSA), and tumour type (anaplastic large cell lymphoma (ALCL), inflammatory myofibroblastic tumour
(IMT), and Other Tumour) on crizotinib plasma pharmacokinetics (PK) in the paediatric population using observed steady-state trough concentration ($C_{trough,ss}$) and steady-state maximum observed concentration ($C_{max,ss}$),
• To develop a predictive population pharmacokinetic (popPK) model for crizotinib in the paediatric population if data permit, and

• To derive individual crizotinib plasma PK exposure metrics for all patients included in the popPK analysis to support exposure-response (ER) safety and efficacy analyses if a popPK model is built.

STUDY DATA OVERVIEW

The present analysis used paediatric patient data from Study ADVL0912 and Study A8081013. Only data from paediatric patients (age <18 years) who received at least one dose of crizotinib and have at least one on-treatment PK sample collection were included in the analysis.

All paediatric patients (age <18 years) in Study ADVL0912 and Study A8081013 who received at least one dose of crizotinib and had at least one post-dose drug plasma concentration available were included in the popPK analysis. A popPK dataset was created by the Global Biometrics and Data Management (GBDM) group following Pfizer standard operating procedures (SOPs). The analysed database consisted in: dosing, plasma crizotinib concentrations, and various demographic and treatment information for a total of 98 paediatric patients who received at least one dose of crizotinib and had at least one on-treatment PK sample; 93 patients were from Study ADVL0912 and 5 patients were from Study A8081013. In total, there are 595 PK records with measurable crizotinib concentration for paediatric patients.

The observed data for categorical demographic variables and the number of patients assigned to each dose level are summarised in Table 6.

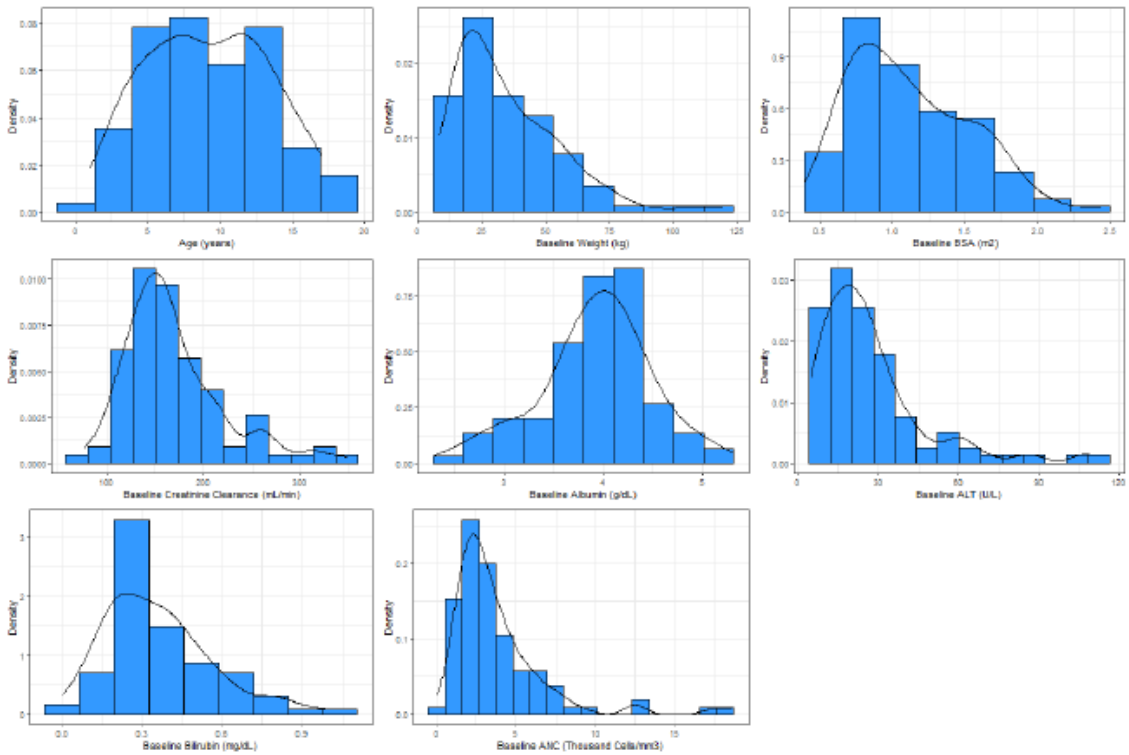
Table 6 Summary of Categorical Variables in Patients Included in the Population Pharmacokinetic Analysis

Variable	Category	N (%)
N (%)		98
Sex	Male	51 (52%)
	Female	47 (48%)
Tumor Type	Other	61 (62%)
	ALCL	24 (24%)
	IMT	13 (13%)
Race	White	66 (67%)
	Black	10 (10%)
	Asian	9 (9%)
	Other	13 (13%)
Dose Group (mg/m^2 BID)	100	6 (6%)
	130	6 (6%)
	215	8 (8%)
	250[a]	5 (5%)
	280	48 (49%)
	365	5 (5%)

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Dose Group category is based on planned starting dose groups.
a. The 250 dose group received 250 mg BID and was not adjusted by BSA.
ALCL=anaplastic large cell lymphoma; IMT=inflammatory myofibroblastic tumor; mg=milligram; m=meters; N=number of patients; Other=non-ALCL and non-IMT tumors.

The observed data for continuous variables are summarised in Table 2 and displayed in Figure 8 as histogram density plots.

Figure 8 Distribution of Potential Covariates to be Tested in the Population Pharmacokinetic Analysis



Repository artifact ID FI-4879765.
BSA=body surface area; kg=kilogram; mL=milliliter; min=minute; g=gram; L=liter; U=unit; dL=deciliter; mm=millimeter; m=meter; ALT=alanine aminotransferase; ANC=absolute neutrophil count.

METHODS

Covariate Analysis Using Observed Steady-State Concentrations

$C_{trough,ss}$ and $C_{max,ss}$ from Study ADVL0912 and Study A8081013 were analysed using linear models. Data processing and generation of tables and figures was conducted using R version 3.6.1. Linear mixed effects modeling was used to perform the covariate analysis on crizotinib plasma PK. $C_{trough,ss}$ and Cmax,ss were separately evaluated as measures of crizotinib plasma exposure. Each model used dose-normalized exposures, as patients received doses ranging from 100 to 365 mg/m^2. Each potential covariate effect was modeled independently of other potential covariates.

Population Pharmacokinetic Analysis

PopPK modeling was performed using the NONMEM version 7.4.3 software (ICON Development Solutions, Ellicott City, MD). Data processing and generation of figures and tables was performed in R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Stochastic approximation expectation-maximization / Monte Carlo importance sampling (SAEM/IMP) was used.

RESULTS:

Covariate Analysis Using Observed Steady-State Concentrations

Out of the 98 unique patients in Study ADVL0912 or Study A8081013 who provided post-dose PK samples, 85 patients provided 132 $C_{trough,ss}$ and 56 patients provided 56 $C_{max,ss}$.

Age, body weight, and BSA met the statistical criteria of $a<0.05$ for both the $C_{trough,ss}$ and $C_{max,ss}$ analyses, while ALCL tumour type met the statistical criteria of $a<0.05$ for the $C_{max,ss}$ analysis. For crizotinib $C_{trough,ss}$, an increase of 1 year of age, 1 kg of body weight, and 0.1 mg/m^2 of BSA resulted in a decrease of approximately 7.0%, 1.5%, and 7.5%, respectively.

For crizotinib $C_{max,ss}$, an increase of 1 year of age, 1 kg of body weight, and 0.1 mg/m^2 of BSA resulted in a decrease of approximately 7.9%, 1.8%, and 9.2%, respectively. Patients with ALCL tumours had on average approximately 41.3% lower crizotinib $C_{max,ss}$.

These evaluations of body size related covariates (age, body weight, and BSA) on crizotinib exposure and ALCL tumour type on crizotinib $C_{max,ss}$ are univariable analyses and do not adjust for other covariates. Crizotinib PK was evaluated using both 1-compartment and 2-compartment models. Allometric scaling of baseline body weight on apparent clearance (CL/F) and apparent central volume of distribution (Vc/F) were explored in various models, with CL/F and intercompartmental clearance (Q) scaled using an exponent of 0.75 and Vc/F and apparent peripheral volume of distribution (Vp/F) scaled using an exponent of 1.

Population Pharmacokinetic Analysis

Crizotinib PK in paediatric patients was well characterized by a 1-compartment model with first order absorption and a lag time. While crizotinib PK in adults was previously characterized by a 2-compartment popPK model, the PK sampling scheme and sparse PK data in paediatric patients did not allow for a predictive 2-compartment to be built. The estimated parameters of the base model are tabulated inTable 7 below.

Table 7 Base Model Parameter Estimates and Bootstrap

	Base Model			Bootstrap	
Parameter	Estimate	RSE (%)	Shrinkage (%)	Median	95% CI
$\theta_{CL\ (L/h)}$	44.65	5.492	-	43.94	(39.58 ; 50.07)
$\theta_{V_c\ (L)}$	36.99	19.18	-	35.67	(24.27 ; 52.81)
$\theta_{k_a\ (/h)}$	0.02398	10.82	-	0.0239	(0.01402 ; 0.03018)
	Base Model			**Bootstrap**	
Parameter	Estimate	RSE (%)	Shrinkage (%)	Median	95% CI
$\theta_{ALAG1\ (h)}$	0.445	17.6	-	0.4286	(0.294 ; 0.6165)
$\theta_{Res.\ Error}$	0.3774	7.645	-	0.3768	(0.3173 ; 0.4312)
IIV	Estimate	CV(%)	Shrinkage(%)	Median	95% CI
ω^2_{CL}	0.2928	54.11	5.093	0.2242	(0.0881 ; 0.5861)
$\omega^2_{V_c}$	0.549	74.1	60.87	0.5059	(0.1275 ; 1.452)
$\omega^2_{k_a}$	0.2687	51.83	48.91	0.2306	(0.08822 ; 1.464)
ω^2_{ALAG1}	0.5687	75.42	54.74	0.5411	(0.24 ; 1.045)
OFV	-163.3	-	-	-183	-

Repository artifact ID FI-5275809. Line 1 substituted.
The median and 95% CI are generated from a bootstrap run of 1000 resampled datasets.
RSE=relative standard error; CI=confidence interval; CL=apparent clearance; h=hour; L=liter; V_c=apparent central volume of distribution; k_a=first-order absorption rate constant; ALAG1=lag time prior to absorption; Res. Error=residual error; IIV=inter-individual variability; CV=coefficient of variation; OFV=objective function value.

The base model was then subjected to graphical examination (Etas versus covariate plots) and SCM to investigate whether there were covariates that influence crizotinib PK. The covariates tested in SCM are listed in Table 8.

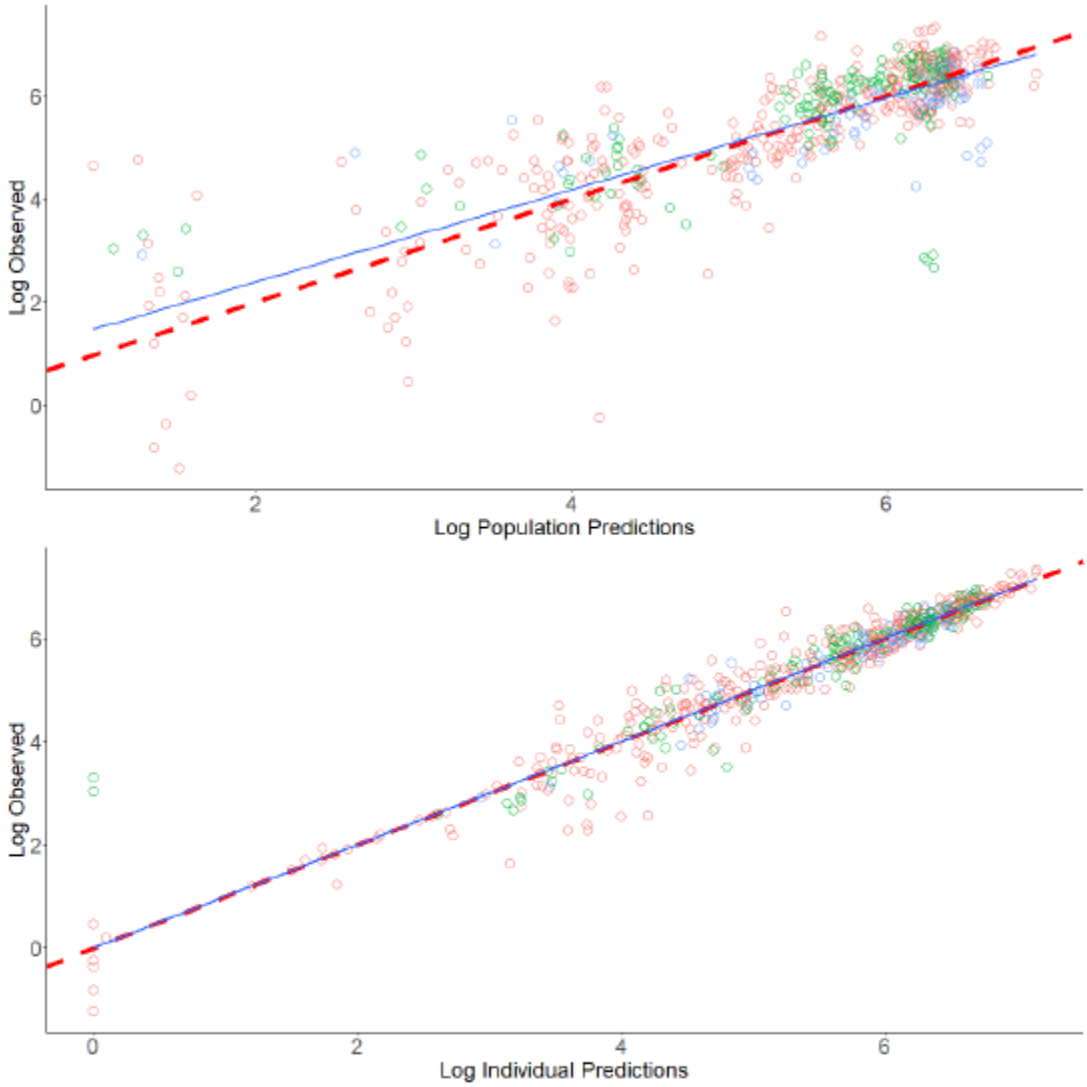
Table 8 Covariates Tested on the Population PK Base Model

PK Parameter	Covariates
CL/F	AGE, BSA, SEX, TUMT, RACE, BALB, BALT, BANC, BBIL, BCCL[a]
V_c/F	AGE, BSA, SEX, TUMT, RACE, BALB
k_a	AGE, BSA, SEX, TUMT, RACE

In backwards elimination, all of the covariates from the forward selection were removed using the statistical criteria of a < 0.001. As a result, the final model was the same model as the base model.

Assessment of Model Adequacy
Prediction-based diagnostic plots of the natural log transformed dependent variable (DV) versus EPRED and IPRED color-coded by tumour type are presented in Figure 9.

Figure 9 Log Observed Data Versus Log Population and Log Individual Predictions

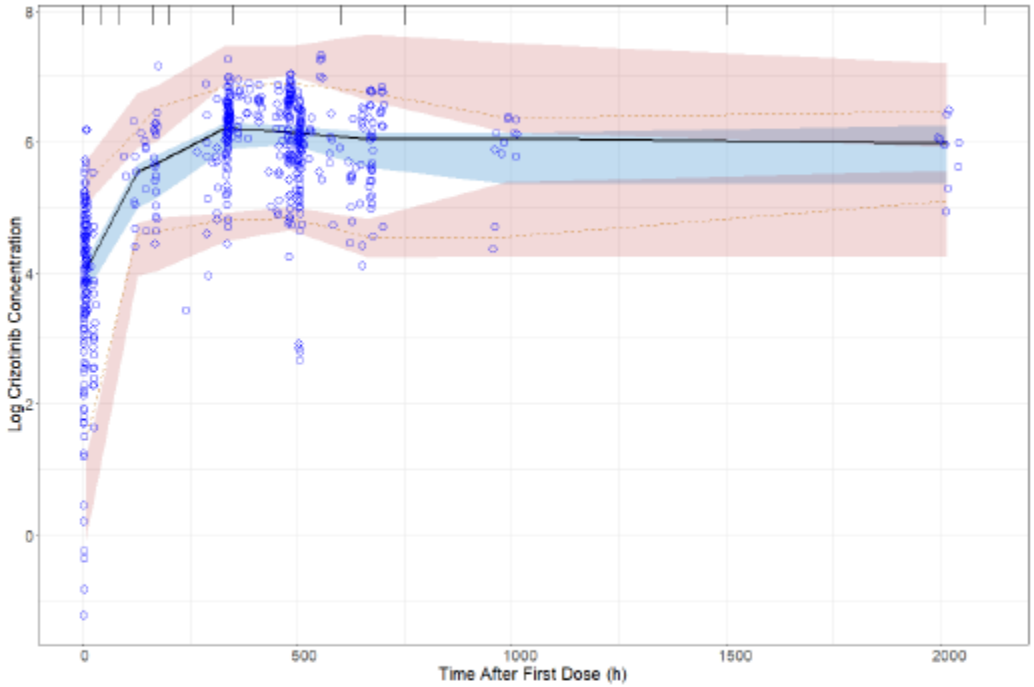


Repository artifact ID FI-5177274.
Red dashed line represents line of unity, blue line represents linear smooth. Green dots represent patients with ALCL tumors. Blue dots represent patients with IMT. Red dots represent patients with Other tumors.
Other=all tumor types that are not ALCL or IMT; ALCL=anaplastic large cell lymphoma; IMT=inflammatory myofibroblastic tumor.

Base Model Predictive Performance

A VPC was performed using PsN with the base model. The results are displayed in Figure 10. The model performed well in predicting the observed data, with 5th, 50th, and 95th percentiles of the observed data mostly lying within the 90% prediction intervals of the 5th, 50th, and 95th percentiles of the simulated data. A single-dose VPC, shown below, demonstrates the adequacy of the absorption model following first-order kinetics with a lag time.

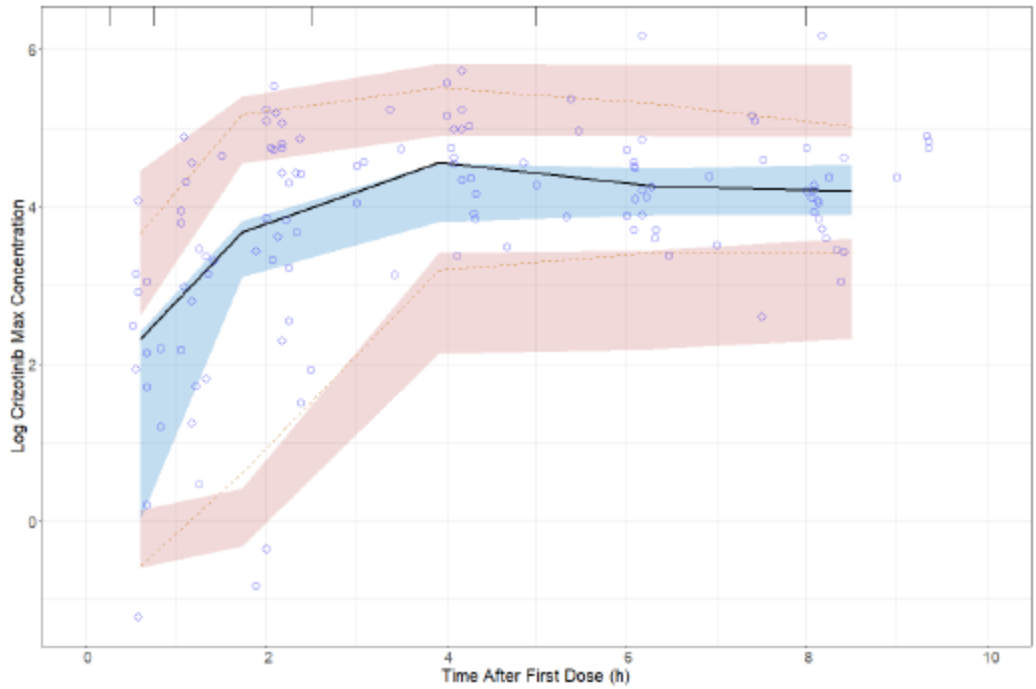
Figure 10 Base Model Visual Predictive Check



Repository artifact ID FI-5209358.

Figure shows time after first dose out to 2,000 hours. Shaded areas represent the 90% confidence intervals around the simulated 5th, 50th, and 95th percentiles (from 100 simulated trials) and lines represent the 5th, 50th, and 95th percentiles of the observed data. Individual observation data from the 98 patients included in this analysis are represented by the blue points.

Figure 11 Base Model Single Dose Visual Predictive Check



Repository artifact ID FI-5209361.

Figure shows time after first dose out to 10 hours. Shaded areas represent the 90% confidence intervals around the simulated 5th, 50th, and 95th percentiles (from 100 simulated trials) and lines represent the 5th, 50th, and 95th percentiles of the observed data. Individual observation data are represented by the blue points.

Evaluation of Crizotinib Pharmacokinetics Across Age Groups and Tumour Types:

The post-hoc PK parameter estimates of CL/F, Vc/F, ka, and Tlag from the final model are summarised in Table 9 by age group. The post-hoc parameters were used to estimate crizotinib plasma exposures following 280 mg/m^2 BID crizotinib dosing.

The simulated area under the concentration-time profile of dosing interval (AUCtau) following 280 mg/m^2 BID dosing and BSA-normalized apparent clearance (CL/F/BSA) are presented in the last rows of Table 9, and the AUCtau are represented graphically in Figure 12.

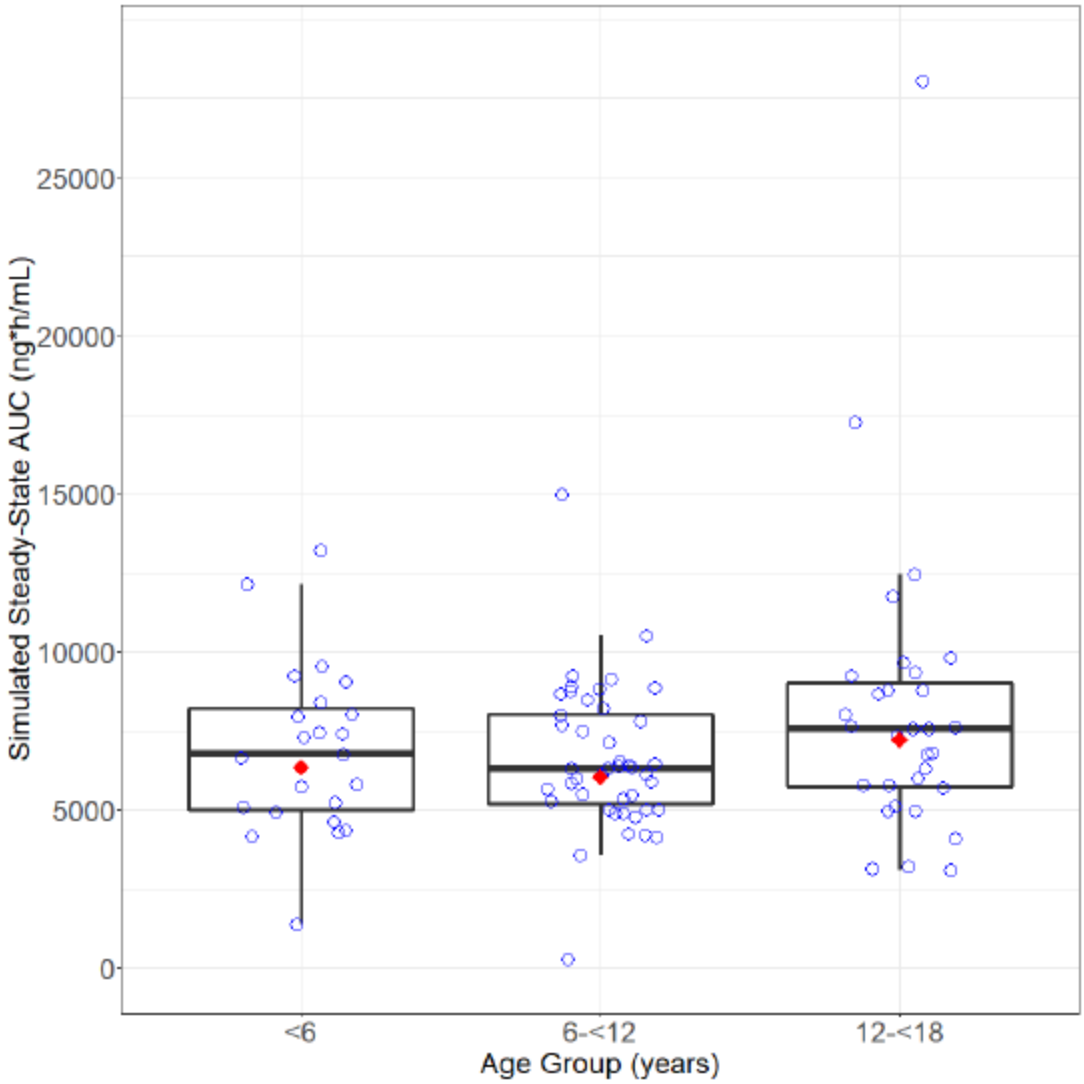
Table 9 Results of Crizotinib 280 mg/m^2 BID Dosing Simulation by Age Group

Variable	Age Group (years)	N	Geo Mean (95% CI)	Mean (SD)	Median (Min-Max)
CL/F (L/h)	<6	23	29.193 (24.641 ; 34.586)	32.082 (17.196)	27.983 (15.701-98.393)
	6-<12	44	47.236 (39.893 ; 55.931)	68.964 (152.32)	44.322 (18.699-1052.1)
	12-<18	31	60.223 (49.885 ; 72.703)	68.105 (33.963)	60.162 (9.7776-150.21)
V_c/F (L)	<6	23	18.2 (16.7 ; 20)	18.7 (4.07)	18.6 (10.6-28.3)
	6-<12	44	35.2 (30.6 ; 40.5)	39.5 (22.2)	32.9 (6.9-143)
	12-<18	31	69.8 (58.5 ; 83.2)	80.2 (53.1)	68.3 (27.3-304)
k_a (/h)	<6	23	0.0239 (0.0225 ; 0.0254)	0.0242 (0.00322)	0.0247 (0.0152-0.0291)
	6-<12	44	0.0248 (0.0229 ; 0.0269)	0.0258 (0.00819)	0.0249 (0.00813-0.0687)
	12-<18	31	0.0245 (0.0218 ; 0.0274)	0.0259 (0.0102)	0.0234 (0.0134-0.064)
Lag Time (h)	<6	23	0.434 (0.409 ; 0.46)	0.438 (0.0505)	0.443 (0.235-0.52)
	6-<12	44	0.466 (0.432 ; 0.502)	0.481 (0.134)	0.454 (0.184-0.964)
	12-<18	31	0.484 (0.428 ; 0.548)	0.529 (0.34)	0.447 (0.328-2.22)
AUC (ng*h/mL)	<6	23	6333 (5244.4 ; 7647.6)	6902.7 (2682.1)	6775.5 (1394.4-13207)
	6-<12	44	6024.4 (5116.7 ; 7093.3)	6601.5 (2298.1)	6309.9 (279.44-14974)
	12-<18	31	7210.6 (6113.6 ; 8504.5)	8100.9 (4732.4)	7551.1 (3094.2-28064)
CL/F/BSA (mL/min/m^2)	<6	23	736.88 (610.21 ; 889.84)	837.58 (591.49)	688.76 (353.35-3346.7)
	6-<12	44	774.62 (657.9 ; 912.05)	1112.5 (2413.4)	739.58 (311.65-16700)
	12-<18	31	647.19 (548.73 ; 763.33)	715.45 (327.64)	618.01 (166.29-1508.2)

Repository artifact ID FI-5496066. Line 1 substituted.

BID=twice daily; CL/F=apparent clearance; CL/F/BSA=BSA-normalized apparent clearance; V_c/F=apparent central volume of distribution; k_a=first-order absorption rate constant; AUC=area under the concentration-time profile of dosing interval; Group=Age group (in years); N=number of patients; Geo Mean=geometric mean; CI=confidence interval; SD=standard deviation; Min=minimum; Max=maximum; L=liter; h=hour; mg=milligram; m=meter; ng=nanogram; mL=milliliter.

Figure 12 Simulated Steady-State Crizotinib AUC Following 280 mg/m² BID Dosing by Age Group



Repository artifact ID FI-5496065.
Red diamonds represent geometric mean value for each age group. Age Group represents patient ages in years.
AUC=area under the concentration-time profile of dosing interval; BID=twice daily; mg=milligram; m=meter; ng=nanogram; h=hour; mL=milliliter.

The post-hoc PK parameter estimates of CL/F, Vc/F, ka, and Tlag from the final model are summarised in Table 10 by tumour type. The post-hoc parameters were used to estimate crizotinib plasma exposures following 280 mg/m² BID crizotinib dosing.
The simulated AUCtau following 280 mg/m² BID dosing and CL/F/BSA are presented in the last rows of Table 10, and the AUCtau are represented graphically in Figure 13.

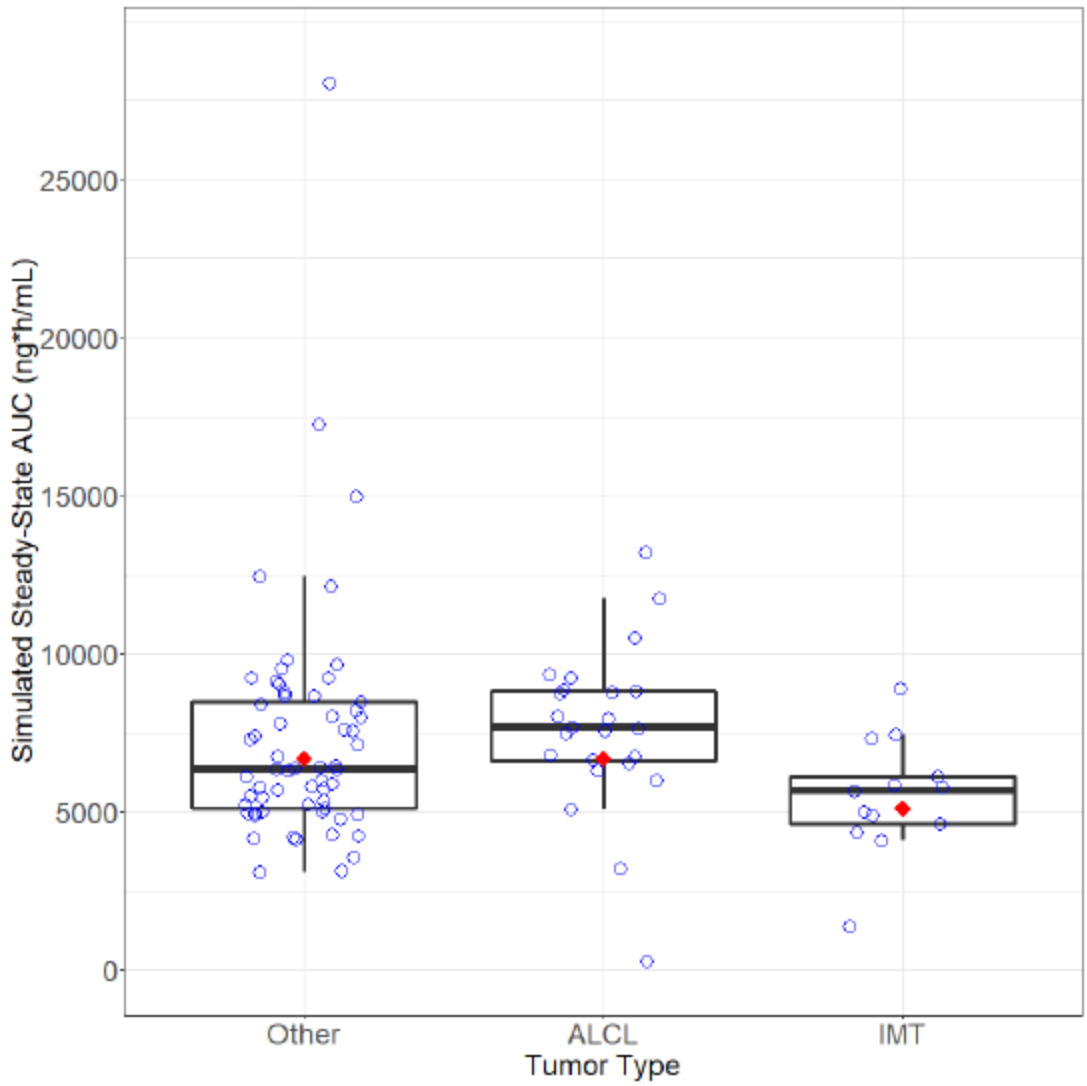
Table 10 Results of Crizotinib 280 mg/m^2 BID Dosing Simulation by Tumor Type

Variable	Tumor Type	N	Geo Mean (95% CI)	Mean (SD)	Median (Min-Max)
CL/F (L/h)	Other	61	41.585 (36.536 ; 47.333)	47.387 (26.427)	43.198 (9.7776-150.21)
	ALCL	24	53.68 (39.266 ; 73.384)	94.287 (205.86)	45.364 (17.597-1052.1)
	IMT	13	51.663 (41.193 ; 64.795)	56.155 (25.141)	48.026 (28.609-110.12)
V_c/F (L)	Other	61	34.6 (29.1 ; 41.2)	45.5 (45.6)	32.5 (6.9-304)
	ALCL	24	50.3 (40 ; 63.3)	59 (34.6)	45.9 (19.1-146)
	IMT	13	31.6 (24 ; 41.7)	35.6 (18.2)	27.8 (13.4-70.6)
k_a (/h)	Other	61	0.0244 (0.0228 ; 0.0262)	0.0253 (0.00735)	0.0252 (0.00813-0.064)
	ALCL	24	0.0234 (0.0218 ; 0.0251)	0.0238 (0.00477)	0.0233 (0.0147-0.0421)
	IMT	13	0.0269 (0.0222 ; 0.0326)	0.0289 (0.0138)	0.0246 (0.0194-0.0687)
Lag Time (h)	Other	61	0.47 (0.432 ; 0.512)	0.505 (0.268)	0.449 (0.184-2.22)
	ALCL	24	0.447 (0.435 ; 0.46)	0.448 (0.0324)	0.445 (0.384-0.522)
	IMT	13	0.464 (0.448 ; 0.481)	0.465 (0.0311)	0.465 (0.416-0.515)
AUC (ng*h/mL)	Other	61	6691.9 (6058.4 ; 7391.5)	7307 (3787.5)	6345.6 (3094.2-28064)
	ALCL	24	6675.8 (4979.8 ; 8949.4)	7632.9 (2602.5)	7668.8 (279.44-13207)
	IMT	13	5105.2 (3997.7 ; 6519.5)	5495.4 (1842.3)	5651 (1394.4-8887.2)
CL/F/BSA (mL/min/m^2)	Other	61	697.37 (631.36 ; 770.28)	747.99 (270.13)	735.42 (166.29-1508.2)
	ALCL	24	699.04 (521.45 ; 937.12)	1305.6 (3286)	608.53 (353.35-16700)
	IMT	13	914.1 (715.8 ; 1167.3)	1033.4 (718.01)	825.81 (525.1-3346.7)

Repository artifact ID FI-6210165. Line 1 substituted.

BID=twice daily; CL/F=apparent clearance; CL/F/BSA=BSA-normalized apparent clearance; V_c/F=apparent central volume of distribution; k_a=first-order absorption rate constant; AUC=area under the concentration-time profile of dosing interval; Group=Tumor type; ALCL=anaplastic large cell lymphoma; IMT=inflammatory myofibroblastic tumor; N=number of patients; Geo Mean=geometric mean; CI=confidence interval; SD=standard deviation; Min=minimum; Max=maximum; L=liter; h=hour; mg=milligram; m=meter; ng=nanogram; mL=milliliter.

Figure 13 Simulated Steady-State Crizotinib AUC Following 280 mg/m² BID Dosing by Tumor Type



Repository artifact ID FI-6210164.
Red diamonds represent geometric mean value for each age group.
ALCL=anaplastic large cell lymphoma; BID=twice daily; IMT=inflammatory myofibroblastic tumor; AUC=area under the concentration-time profile of dosing interval; mg=milligram; m=meter; ng=nanogram; h=hour; mL=milliliter.

Conclusions:

Based on the covariate analysis using observed crizotinib steady-state plasma concentrations and the popPK analysis:

- A 1-compartment first order plus lag time absorption model with body weight allometric scaling and proportional error adequately characterized crizotinib PK in paediatric patients.

- Body weight (included through allometric scaling of model parameters) was the only meaningful covariate on crizotinib plasma PK in paediatric patients. Higher body weight was associated with higher apparent clearance and higher apparent central volume of distribution.
- While age, body surface area, and tumour type were associated with changes in plasma crizotinib exposure, none of these covariates significantly affected crizotinib PK once body weight was accounted for in paediatric patients.

- Simulations of the recommended 280 mg/m^2 BID crizotinib dosing regimen resulted in consistent plasma exposures for paediatric patients. BSA-normalized apparent clearancewas consistent across age groups and tumour types.

- Exposure/Dose-Response Relationship:

  - Analysis of Dose-Efficacy Relationship (Study ADVL0912 only):

The analyses described below assessed the exposure and dose response relationships for efficacy endpoints, ie, ORR (including CR rate), DR and TTR, in paediatric patients receiving crizotinib treatment.
Baseline characteristics, and measures for exposure and efficacy for patients with ALCL and IMT were summarised by descriptive statistics and graphical methods. Exposure (or dose) response analyses for objective response and complete response were conducted using logistic regression. TTR was treated as a continuous variable and analysed with a linear model. Baseline covariates were individually assessed.
There were 22 ALCL and 12 IMT patients available for analysis of each efficacy endpoint. Due to the limited number of patients, the statistical analysis used an 80% confidence level for all estimates. With a lower confidence level and small sample size, these results should be interpreted with caution.
For ER (with any observed or predicted measures) analysis, no important relationships were identified and the predicted ER relationships were not well characterized.
The only important dose-response relationship observed was for average daily crizotinib dose (mg/m^2/day) and objective response which showed that the probability of response increased with increasing dose.
For ORR, the response rate was high (> 80%) regardless of the crizotinib plasma exposure or dose, and was similar for ALCL and IMT patients. Complete response rates were similar across exposure and dose but was different based on tumour type.

Analysis of Dose-Exposure Safety Relationship (Studies ADVL0912 and 8081013):

The analyses described below evaluated the ER and dose response for crizotinib for selected safety endpoints in paediatric patients with ALK-positive ALCL, ALK-positive IMT, or other tumour types (N=110).
The ER analysis for safety was based on treatment-related AEs observed in Studies ADVL0912 and A8081013. The analysis included treatment-related AEs that had Grade 3 or higher severity and occurred in more than 2% of patients or other selected treatment-related AEs of special interests. The safety endpoints described in this report were: Grade ≥3 treatment-related neutropenia Grade ≥3 treatment-related lymphopenia, Grade ≥3 treatment-related leukopenia, Grade ≥3 treatment-related anaemia, Grade ≥3 treatment-related elevated transaminases, Grade ≥3 treatment-related Diarrhoea, Grade ≥3 treatment-related Vomiting, any grade treatment-related vision disorder, any grade treatment-related bradycardia, dose reductions, dosing interruptions, permanent discontinuations associated with any AEs, and any Grade ≥3 AEs.

Crizotinib dosing metrics used in the analyses were planned starting dose level, average daily dose, and relative daily dose. Average steady-state trough concentration (Ctrough,ss) and steady-state maximum concentration (Cmax,ss) were the observed crizotinib exposure metrics evaluated in these analyses. Individual predicted crizotinib exposure metrics derived from the population PK model based on empirical Bayes estimates (EBE), including, steady-state area under the curve (AUCss), Cmax,ss, area under the curve following the first dose from time 0 to 12 hours (AUCsd), and maximum concentration following the first dose (Cmax,sd) were used for the predicted exposure-response analyses.
Covariates in the exposure response analysis with safety endpoints included treatment duration, age, race, sex, body weight, height, BMI and BSA.

For safety endpoints with a sufficient number of events (ie, event rate ≥10%), logistic regression for binary data was used to model the response. The base statistical model included exposure (or dose) and tumour type. A separate intercept for each tumour type category, ie ALCL, IMT, and Other tumour types, was included in the model (equivalent to stratifying by tumour type) with a linear slope term for exposure (or dose). A full covariate model using logistic regression with relevant covariates was developed. A stepwise backward elimination procedure (with α = 0.02) with the full model was used to determine potentially important covariates. Exposure (or dose) and tumour type were kept in the model throughout the stepwise process and in final model. For the final model, back-transformed estimates including the odds ratios for the exposure (or dose) and covariate parameters, 95% CIs and p-values were presented.

As a result of low event rates (<10%), the following safety endpoints were not modeled: Grade ≥3 treatment-related Diarrhoea, Grade ≥3 treatment-related Vomiting, and any grade treatment-related bradycardia. In all models, tumour type was included a *priori*. For Grade ≥3 treatment-related AEs of lymphopenia, leukopenia, elevated transaminases, and anaemia, the IMT tumour type could not be included in the model due to the lack of these AEs in this patient population.

In the ER analysis for Grade ≥3 treatment-related neutropenia, for every unit increase in log of observed crizotinib Ctrough,ss, the odds of experiencing Grade ≥3 treatment-related neutropenia increased by 2.57 times (95% CI: 1.05, 6.84). Similarly, for predicted crizotinib exposure, for every unit of increase in log of predicted AUCss, the odds of experiencing Grade ≥3 treatment-related neutropenia increased by 2.44 times (95% CI: 1.21, 5.49). Additionally, the patients with ALCL had higher odds of experiencing Grade ≥3 treatment-related neutropenia as compared to patients with IMT. No dose response relationships and no other significant covariates were identified for Grade ≥3 treatment-related neutropenia. A higher rate of treatment-related neutropenia is not unexpected in patients with ALCL given the underlying involvement of the bone marrow and the prior use of cytotoxic chemotherapies.

In the ER analysis, for every unit increase in log of observed crizotinib Ctrough,ss, the odds of experiencing Grade ≥3 treatment-related leukopenia increased by 3.14 times (95% CI: 0.74, 17.05). Similarly, for predicted crizotinib exposures, for every unit increase in log of predicted AUCsd, the odds of experiencing Grade ≥3 treatment-related LEUKOPENIA increased by 1.52 times (95% CI: 0.68, 4.05). The CI for the odds ratios were wide and encompassed 1 for crizotinib exposures. Patients with other tumours had lower odds of experiencing an event as compared to patients with ALCL. In the dose response analysis, there appeared to be a shallow, inverse relationship of relative dose and Grade ≥3 treatment-related LEUKOPENIA, but the CI encompassed 1 and is not considered meaningful [odds ratio 0.95 (95% CI: 0.90, 1.00)]. Additionally, log of treatment duration also exhibited an inverse relationship with Grade ≥3 treatment-related LEUKOPENIA [odds ratio 0.53 (95% CI: 0.28, 0.88)]. It appeared that patients who did not experience Grade ≥3 treatment-related LEUKOPENIA were able to receive study treatment longer and relative dose closer to 100%.

For every unit increase in log of crizotinib observed average Ctrough,ss, the odds of experiencing treatment-related VISION DISORDER increased by 3.75 times (odds ratio 3.75 [95% CI: 1.36, 11.94]). For every unit increase in log of crizotinib predicted AUCss, the odds of experiencing treatment-related VISION DISORDER increased by 6.36 times (odds ratio 6.36 [95% CI: 1.93, 24.69]). A small, positive dose response relationship was identified for treatment-related VISION DISORDER. For every unit increase in crizotinib average daily dose, the odds of experiencing treatment-related VISION DISORDER increased by 1.004 times (odds ratio 1.004 [95% CI: 1.002, 1.007]). In the final ER model with observed Ctrough,ss, patients with ALCL had 5.91 times higher odds (95% CI: 1.05, 41.51) of experiencing treatment-related VISION DISORDER, compared to patients with IMT. In the final ER model with predicted AUCss, log of crizotinib clearance (CL) and female sex were also identified as covariates. Female patients had 4.03 times higher odds (95% CI: 1.44, 12.58) of experiencing treatment-related VISION DISORDER as compared to male patients.

Crizotinib CL is correlated with age and various body size covariates, which may have confounded the results. Despite the ER relationships for treatment-related VISION DISORDER, in Studies

A8081013 and ADVL0912, all treatment-related VISION DISORDER were Grade 1 or 2 in severity, and there were no events of Grade 3 or higher.
An inverse relationship was identified with relative dose based on mg (%), where patients who received a crizotinib relative dose closer to 100% had lower odds of dosing interruptions (odds ratio 0.88 [95% CI: 0.81, 0.93). This is as expected, since patients who had more dosing interruptions received fewer doses of crizotinib relative to their planned dosing schedule, which resulted in lower relative doses. Log of treatment duration was included in all ER and dose response models and showed that patients with longer treatment duration had higher probability of dosing interruptions.
No ER or dose response relationships were identified for Grade ≥3 treatment-related lymphopenia, Grade ≥3 treatment-related leukopenia, Grade ≥3 treatment-related anaemia, Grade ≥3 treatment-related elevated transaminases, dose reductions, dosing interruptions, permanent discontinuations due to any AEs, or any Grade ≥3 AEs.
In all ER and dose response analyses in this report, the planned dose level of 280 mg/m^2 BID was explored further graphically by categorizing patients in this dose level as receiving starting daily doses of ≤500 mg/day or >500 mg/day. The predicted probabilities for all safety endpoints were similar between starting daily doses of ≤500 mg/day or >500 mg/day.

2.3.3 Pharmacodynamics

The analyses described below assessed the exposure and dose response relationships for efficacy endpoints, ie, ORR (including CR rate), DR and TTR, in paediatric patients receiving crizotinib treatment.

Baseline characteristics, and measures for exposure and efficacy for patients with ALCL and IMT were summarised by descriptive statistics and graphical methods. Exposure (or dose) response analyses for objective response and complete response were conducted using logistic regression. TTR was treated as a continuous variable and analysed with a linear model. Baseline covariates were individually assessed.

There were 22 ALCL and 12 IMT patients available for analysis of each efficacy endpoint. Due to the limited number of patients, the statistical analysis used an 80% confidence level for all estimates. With a lower confidence level and small sample size, these results should be interpreted with caution.

For ER (with any observed or predicted measures) analysis, no important relationships were identified and the predicted ER relationships were not well characterized.

The only important dose-response relationship observed was for average daily crizotinib dose (mg/m^2/day) and objective response which showed that the probability of response increased with increasing dose.

For ORR, the response rate was high (> 80%) regardless of the crizotinib plasma exposure or dose, and was similar for ALCL and IMT patients. Complete response rates were similar across exposure and dose but was different based on tumour type.

2.3.4 Discussion on clinical pharmacology

The analyses submitted by the MAH assessed the exposure and dose response relationships for efficacy exploratory endpoints in paediatric patients receiving crizotinib. In Study ADVL0912, 22 ALCL and 12 IMT patients were available for the assessment.

Average daily dose based on mg/m^2/day showed a positive dose-response relationship with ORRs. An additional dose-response analysis with objective and complete response in a subset of patients receiving a planned starting dose of 280 mg/m² BID was done. The first administered total daily dose was grouped as ≤500 mg *v.s.* >500 mg and analysed with logistic regression. The MAH claims that no objective response analysis was done due to limitations in the data. For complete response, patients receiving a first administered total daily dose ≤500 mg had a higher probability of response.

For ORR, the response rate was high (>80%) regardless of the level of exposure or dose and were similar for ALCL and IMT patients. For ALCL at the median dose, the ORR is 91%. The ORR for IMT patients is estimated to be similar to that observed in ALCL patients at the median average daily dose. Complete response rates were similar across exposure and dose but were different based on tumour type.

Average daily dose showed a positive dose-response relationship with objective response. However, the predicted probability curve showed that for patients with a higher doses, there was a lower predicted probability of experiencing a complete response. It is to be noted that the dose-response relationship with crizotinib is expected to be not very well estimated because of wide confidence bands. Indeed, the statistical analysis used an 80% confidence level for all assessments due to the limited number of enrolled patients. With a lower confidence level, and the small sample size, these results are difficult to interpret.

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. At this regimen, observed crizotinib predose concentration (C_{trough}) at steady state is similar regardless of body weight quartiles. The observed mean C_{trough} at steady state in paediatric patients at 280 mg/m^2 twice daily is 482 ng/mL, while observed mean C_{trough} at steady state in adult cancer patients at 250 mg twice daily across different clinical studies ranged from 263 to 316 ng/mL (see SmPC).

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 recommended starting dose of crizotinib in patients with moderate hepatic impairment (any AST and total bilirubin >1.5 × ULN and ≤3 × ULN) is the first dose reduction based on BSA as shown in Table 4 of the SmPC. The recommended starting dose of crizotinib in patients with severe hepatic impairment (any AST and total bilirubin >3 × ULN) is the second dose reduction based on BSA (see SmPC section 4.2). No starting dose adjustment of crizotinib is recommended for patients with mild (60 ≤ creatinine [CL_{cr}] <90 mL/min) or moderate (30 ≤CL_{cr} <60 mL/min) renal impairment calculated using the Schwartz equation. The recommended starting dose of crizotinib in patients with severe renal impairment (CL_{cr} <30 mL/min) not requiring dialysis is the second dose reduction based on BSA as shown in Table 4 of the SmPC. The dose may be increased to the first dose reduction based on BSA (see SmPC section 4.2) and on individual safety and tolerability after at least 4 weeks of treatment.

2.3.5 Conclusions on clinical pharmacology

Clinical pharmacology analyses submitted are considered adequate. Relevant information has been included in the SmPC sections 4.2 and 5.2.

The following measures (category 3 studies, see RMP) are considered necessary to address issues related to clinical pharmacology:

- The MAH will further assess the PK of crizotinib at the lower dose of 165 mg/m^2 BID in paediatric patients enrolled at 280mg/m² BID and efficacy analysis performed in this setting.

2.4 Clinical efficacy

2.4.1 Dose response study(ies)

See Clinical Pharmacology section

Analysis of Clinical Information Relevant to Dosing recommendations

In Study ADVL0912, the MTD and RP2D were estimated to be 280 mg/m² BID and objective responses in ALK-positive ALCL and ALK positive IMT were observed in paediatric patients at doses of 165 mg/m² BID and 280 mg/m² BID. To further evaluate the efficacy of the 280 mg/m² BID MTD dose relative to the approved adult starting dose of 250 mg BID, additional analyses were conducted comparing paediatric patients who received a starting dose ≤ 250 mg BID versus those who received a starting dose > 250 mg BID.

There were 16 patients in the ALCL group who received crizotinib at a starting dose of 280 mg/m² BID. Of these 16 patients, 3 received crizotinib at a starting dose of ≤ 250 mg BID and 13 received crizotinib at a starting dose of >250 mg BID. In terms of efficacy, the ORRs were similar between the 2 subgroups, 100% (3/3; 95% CI: 43.9, 100) for the ≤ 250 mg BID subgroup and 84.6% (11/13; 95% CI: 57.8, 95.7) for the >250 mg BID subgroup. Although the median DR was longer for the ≤ 250 mg BID subgroup than the >250 mg (14.1 months vs 1.2 months), no responders (0/3) in the ≤ 250 mg BID subgroup proceeded to HSCT; whereas, 8/11 responders in the > 250 mg BID proceeded to HSCT. For patients with ALK-positive IMT at 280mg/m^2 BID, ORRs and DRs were comparable between starting doses ≤250 mg BID (N=7) and starting doses > 250mg BID (N=5) (100% vs 80.0%, respectively, and 12.7 months vs 11.4 months, respectively).

2.4.2 Main study(ies)

Study ADVL0912

The primary study supporting the clinical antitumour activity in this application is the COG-sponsored Study ADVL0912. A full description of this study is provided in the Study ADVL0912 Protocol, and a summary is provided below.

Methods

This was a Phase 1/2, open-label, multicentre study of the evaluation of crizotinib in paediatric patients with relapsed or refractory solid tumours (including IMT) or with relapsed or refractory systemic ALK-positive ALCL (hereafter referred to as "patients with ALK-positive ALCL"). Phase 1 was a rolling-6, dose-finding study of crizotinib to estimate the maximum dose that was safe and tolerable. During Phase 2, an expansion at the MTD added 2 new parts of the study (Parts B and C) which was made to obtain preliminary antitumour activity data in patients with relapsed or refractory ALK-positive NB or ALCL. In addition, patients with any ALK-activated or MET-activated tumour continued to be enrolled in Part A2.

Paediatric patients (aged >12 months and ≤21 years) with a histologic verification of malignancy at original diagnosis or relapse were enrolled as follows:

· Phase 1 (determination of MTD):

· Part A1: Patients with relapsed or refractory solid tumours (including IMT) or ALCL (excluding patients with primary or metastatic CNS tumours as of Protocol Amendment 3C [26 May 2011] or patients with primary cutaneous ALCL).

· Part A2: Patients with confirmed ALK fusion proteins, ALK mutations, ALK amplification (defined as greater than 4-fold increase in the ALK signal number as compared to reference signal number on chromosome 2q arm) or MET mutation or amplification. Patients with unresectable, recurrent, or refractory ALK-positive IMT (hereafter referred to as "patients with ALK-positive IMT") could have also been enrolled during Part A2.

· Part A3: Patients with relapsed or refractory NB, with or without bone marrow involvement, who are not eligible for Part A1 or A2 or could not have enrolled in Part A1 because of stratum suspension or lack of available slots.

· Phase 2 (antitumour activity data):

· Part A2: Patients with diagnoses other than NB or ALCL with confirmed ALK fusion proteins, ALK mutations, ALK amplification (defined as greater than 4-fold increase in the ALK signal number as compared to reference signal number on chromosome 2q arm) or MET mutation or amplification. Patients with ALK-positive IMT could have also been enrolled during Part A2.

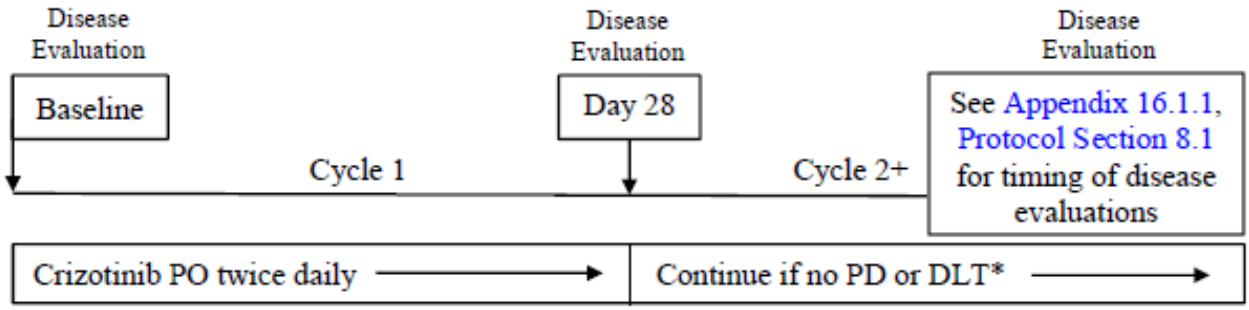
· Part B: Patients with relapsed or refractory ALK-positive NB.

· Part C: Patients with ALK-positive ALCL (excluding patients with primary cutaneous ALCL). A Simon's optimal two stage design will be used.

In Phase 1, patients received a starting dose of crizotinib of 100 mg/m2 administered orally in a continuous, BID dosing regimen. The dose was further escalated until the MTD was established. Patients in the initial Phase 2 expansion were treated at the recommended dose from the Phase 1 component of this study, which was 280 mg/m²BID.

The study design is presented in Figure 14. Refer to Appendix 16.1.1, Protocol Section 2.5 for further details regarding the study design.

Figure 14 Study design



* Twice daily treatment with crizotinib was to be discontinued if there was evidence of PD or drug-related DLT that required removal from therapy. Patients with stable disease or better who were having clinical benefit from crizotinib could continue to receive protocol therapy provided that the patient met the criteria for starting subsequent cycles (Appendix 16.1.1, Protocol Section 5.2) and did not meet any of the criteria for removal from protocol therapy or off study criteria (Appendix 16.1.1, Protocol Section 10.0).
Source: Appendix 16.1.1, Protocol.

Inclusion criteria

1. Age: Patients must have been >12 months and ≤21 years of age at the time of study enrolment.

2. BSA (Phase 2): Patients who received the FCs must have had a BSA ≥0.63 m2 at the time of study enrolment.

3. Diagnosis:
Patients must have had histologic verification of malignancy at original diagnosis or relapse.

4. Disease Status:
• Phase 1 (Part A): Patients must have had either measurable and/or evaluable disease.
• Phase 2 (Part B): Patients with NB must have had proven ALK-positive disease with either measurable and/or evaluable disease as indicated below:
  - Measurable tumour on MRI, CT scan or X-ray obtained within 2 weeks prior to study enrolment.
  - Evaluable tumour by MIBG scan and/or bone marrow involvement with tumour cells seen on routine morphology.
• Phase 2 (Part C): Patients must have had proven ALK-positive disease with either measurable or evaluable disease.

6. Prior therapy:
Patients must have fully recovered from the acute toxic effects of all prior anticancer therapy.

7. Organ function requirements:
• Adequate bone marrow function
• Adequate renal function defined as:

- Creatinine clearance or radioisotope GFR ≥70 mL/min/1.73 m2 or

- A serum creatinine level within the normal range based on age/gender as follows

Table 11 Serum creatinine levels based on age/gender

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to <2 years	0.6	0.6
2 to <6 years	0.8	0.8
6 to <10 years	1	1
10 to <13 years	1.2	1.2
13 to <16 years	1.5	1.4
≥16 years	1.7	1.4
Note: The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR (Schwartz and Gauthier, 1985) utilizing child length and stature data published by the CDC.		

•Adequate liver function

•Adequate cardiac function

Exclusion Criteria

- Pregnancy or breast-feeding:

Pregnant or breast-feeding women were not allowed to enter the study, as there was no available information regarding human fetal or teratogenic toxicities. Pregnancy tests were obtained in girls who were post-menarchal.

Males or females of reproductive potential could not participate unless they had agreed to use an effective contraceptive method.

- Concomitant medications:

1. Corticosteroids: Patients who received corticosteroids and who had not been on a stable or decreasing dose of corticosteroid for the prior 7 days were not eligible.

2. Investigational drugs: Patients who were currently receiving another investigational drug were not eligible.

3. Anticancer agents: Patients who were currently receiving other anticancer agents, with the exception of hydroxyurea for patients with ALCL, were not eligible.

4. CYP3A4 substrates with narrow therapeutic indices: As crizotinib is an inhibitor of CYP3A4, patients who chronically received medications known to be metabolized by CYP3A4 and with narrow therapeutic indices including pimozide, aripiprazole, triazolam, ergotamine, and halofantrine were not eligible. The topical use of these medications (if applicable) was allowed.

5. CYP3A4 inhibitors: Patients who chronically received drugs that were known potent CYP3A4 inhibitors within 7 days prior to study enrolment, including but not limited to ketoconazole, itraconazole, miconazole, clarithromycin, erythromycin, ritonavir, indinavir, nelfinavir, saquinavir, amprenavir, delavirdine, nefazodone, diltiazem, verapamil, and grapefruit juice were not eligible. The topical use of these medications (if applicable), eg, 2% ketoconazole cream, was allowed.

6. CYP3A4 inducers: Patients who chronically received drugs that were known potent CYP3A4 inducers within 12 days prior to study enrolment, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, tipranavir, ritonavir, and St. John's wort were not eligible. The topical use of these medications (if applicable) was allowed.

3. Patients with known interstitial fibrosis or ILD were not eligible.

4. Patients with a known history of myocardial infarction or cerebrovascular accident were not eligible.

5. Patients with CNS tumours or known CNS metastases were not eligible. Patients with a history of CNS metastases that had been surgically resected were eligible only if the baseline evaluation showed no evidence of current CNS metastases. Patients with any evidence of CNS metastases on baseline evaluation were not eligible, regardless of whether the lesions had been previously treated and/or appeared stable.

6. Infection:

Patients who had an uncontrolled infection were not eligible.

7. Patients who in the opinion of the investigator might not be able to comply with the safety monitoring requirements of the study were not eligible

Objectives and endpoints

Primary and secondary endpoints:

Table 12 Study objectives and endpoints

Type	Objective	Endpoint
Primary		
Safety	• To estimate the MTD and recommend a Phase 2 dose of crizotinib administered orally BID to pediatric patients with relapsed/refractory solid tumors and ALCL.	• Occurrence of DLTs.
	• To define and describe the toxicities of crizotinib administered on this schedule.	• Occurrence of DLTs.
PK	• To characterize the PK of crizotinib in pediatric patients with refractory cancer.	• After single dose: T_{max}, C_{max}, and AUC_{last} if data permit. • At steady-state: T_{max}, C_{max}, C_{trough}, AUC_{tau}, and CL/F if data permit.
Secondary		
Efficacy	• To preliminarily define the antitumor activity of crizotinib within the confines of a Phase 1 study.	• ORR, DR, and TTR.
	• To obtain initial Phase 2 data on the antitumor activity of crizotinib in pediatric patients with relapsed/refractory ALK-positive NB and ALCL.	• ORR, DR, and TTR.
Biomarker	• To preliminarily examine the relationship between ALK status (eg, the presence of a mutation, duplication, amplification, and/or translocation) in pediatric patients with NB or ALCL and response to crizotinib.	• ALK status in pediatric patients with IMT or ALCL.
	• To preliminarily examine the relationship between MRD status and clinical response to crizotinib in pediatric patients with ALCL.	• Measurement of normalized copy numbers of NPM-ALK by qRT-PCR.

Type	Objective	Endpoint
Taste Feedback	• To use a questionnaire to gather preliminary information on the palatability of the OS formulation of crizotinib.	• Weekly taste responses for pediatric patients using Crizotinib OS using Taste Feedback Questionnaire.
Safety	• To evaluate the overall safety profile of crizotinib.	• AEs (as graded by NCI CTCAE v4.03); laboratory test abnormalities and vital signs of potential clinical importance which were to be reported as AEs.
	• To evaluate for potential alterations in bone growth in pediatric patients.	• Radiology assessment which included pediatric patient's tibial growth plate status, evidence of growth plate thickening or other changes based on tibial radiograph, and knee MRI and X-ray follow-up.

Response Criteria for Patients with ALCL

1/ Complete Response:

Disappearance of all evidence of disease from all sites for at least 4 weeks. This will be determined by PE and imaging. Bone marrow aspirate/biopsy must be normal and any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. PET scans must be negative if initially positive.

2/ Complete Response Unconfirmed:

A residual lymph node mass > 1.5 cm in greatest transverse diameter that has regressed by >75% in sum of the products of the greatest perpendicular diameters (SPD), or any residual lesions in organs that have decreased by >75% and with a negative PET scan and SUV <3. Patients with only residual positive bone lesions on PET scans will be considered in CRu. Patients with bone involvement may have positive lesions o n P ET s cans f or sometime; therefore, these patients will be considered in CRu if the other residual lesions have disappeared, or of the residual lymph node mass or masses >1.5 cm in greatest transverse diameter have regressed by >75% in sum of the products of the greatest perpendicular diameters (SPD).

3/ Partial Response:

≥50% decrease in the SPD of the lesions. No new lesions

4/ No Response (Stable Disease):

Failure to qualify for a PR. No new lesions.

5/ Progressive disease:

≥25% increase in the size of any lesions or appearance of new lesions.

Response Criteria for Patients with Solid Tumours and Measurable Disease

This study will use a minor modification of the (RECIST) Response Evaluation Criteria in Solid Tumours from the NCI for assessment of radiographic response.

1/ Measurable Disease:

The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 10 mm. The investigator will identify up to 10 measurable lesions to be followed for response. Previously irradiated lesions that have not demonstrated clear progression post radiation do not qualify as being measurable or evaluable. Serial measurements of lesions are to be done with

appropriate imaging modalities. The same method of assessment is to be used to characterize each identified and reported lesion at baseline and during follow-up.

2/ Quantification of Disease Burden

The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the disease measurement.

3/ End-of-Cycle Response

a) Complete Response (CR)

Disappearance of all target and non-target lesions. If immunocytology is available, no disease must be detected by that methodology.

b) Partial Response (PR)

At least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study enrollment.

c) Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for P D, taking as reference the smallest disease measurement since the treatment started.

d) Progressive Disease (PD)

At least a 20% increase in the disease measurement, taking as reference the smallest disease measurement recorded since the start of treatment, or the appearance of one or more new lesions, or evidence of laboratory or clinical progression.

Response Criteria for Patients with Solid Tumours and Evaluable Disease

1/ Evaluable Disease

The presence of at least one lesion that cannot be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumour markers or other reliable measures.

2 /Complete Response (CR)

Disappearance of all evaluable disease.

3/ Partial response

Partial responses cannot be determined in patients with evaluable disease.

4/ Stable Disease (SD)

That which does not qualify as Complete Response (CR), Partial Response (PR), or Progressive Disease.

5/ Progressive Disease (PD)

The appearance of one or more new lesions or evidence of laboratory, clinical, or radiographic progression.

Overall Best Response Assessment

Each patient will be classified according to their "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statutes.

Table 13 Objective statuses with corresponding best response

1st Status	2nd Status	3rd Status	Best Response
Progression			Progressive disease
Stable, PR, CR	Progression		Progressive disease
Unknown	Progression		Progressive disease
Stable	Stable	Progression	Stable
Stable, Unknown	PR, CR	Progression	Stable
Stable, Unknown	Unknown	Progression	Unknown
PR	PR	Progression	PR
PR	CR	Progression	PR
PR, CR	Unknown	Progression	Unknown
CR	CR	Progression	CR
Unknown	Stable	Progression	Stable

Treatments

Patients received crizotinib BID on a continuous schedule in cycles of 28 days duration. Crizotinib was given orally (as capsules or OS) and may have been administered on an outpatient basis. A dosing nomogram was used to minimize inter patient variability. Patients were instructed to take their medication at approximately the same time each day and to not take more than the prescribed dose at any time. The doses may have been taken with or without food or beverage. If a dose was missed or forgotten, it could have been taken up to (but not greater than) 6 hours later to help prevent missed doses. Drug doses were adjusted based on the BSA determined based on height and weight obtained within 1 week prior to the beginning of each cycle.

Table 14 Dosing recommendations for crizotinib (PF-02341066) 280 mg/m^2 /dose BID (dose level 5 and recommended phase 2 dose)

PF-02341066 Dose Assignment: 280 mg/m^2/dose BID
(DOSE LEVEL 5 and RECOMMENDED PHASE 2 DOSE)

	PF-02341066 (mg/day)	PF-02341066 (mg PO BID)	
BSA (m^2)	Total Daily Dose	mg q am	mg q hs
0.63-0.80	400	200	200
0.81-0.98	500	250	250
0.99-1.16	600	300	300
1.17-1.33	700	350	350
1.34-1.51	800	400	400
1.52-1.69	900	450	450
1.70-1.87	1000	500	500
1.88-≥ 2.0	1100	550	550

For 1st **dose reduction** due to toxicity

	PF-02341066 (mg/day)	PF-02341066 (mg PO BID)	
BSA (m^2)	Total Daily Dose	mg q am	mg q hs
0.63-0.80	300	150	150
0.81-0.98	350	200	150
0.99-1.16	400	200	200
1.17-1.33	500	250	250
1.34-1.51	600	300	300
1.52-1.69	650	350	300
1.70-1.87	700	350	350
1.88-≥ 2.0	800	400	400

For 2nd **dose reduction** due to toxicity

	PF-02341066 (mg/day)	PF-02341066 (mg PO BID)	
BSA (m^2)	Total Daily Dose	mg q am	mg q hs
0.63-0.80*	*	*	*
0.81-0.98*	*	*	*
0.99-1.16	300	150	150
1.17-1.33	350	200	150
1.34-1.51	400	200	200
1.52-1.69	450	250	200
1.70-1.87	500	250	250
1.88-≥ 2.0	600	300	300

*These patients will receive oral solution if 2nd dose reduction is required

Statistical Methods

The analysis populations, SA and antitumour activity objectives, endpoints, evaluations, and statistical analyses for paediatric patients with ALK-positive ALCL or ALK-positive IMT in Study ADVL0912 are summarised in this section.

Table 15 Study ADVL0912 analysis population

Analysis Population	Definition
FA	Includes all enrolled patients. This population was used in evaluating patient disposition.
SA	Includes all enrolled patients who received at least 1 dose of crizotinib. This is the primary population for evaluating treatment administration, safety, demographics, and baseline disease characteristics.
RE	Includes all patients in the SA who had measurable or evaluable disease at baseline by Investigator assessment or had baseline disease assessment per central review. This is the primary population for evaluating all response-related antitumor activity endpoints.

Table 16 Antitumour activity objectives, endpoints, evaluation and statistical analysis

Objectives	Endpoints	Definition/Evaluation	Analysis Population	Statistical Analyses
Secondary • To preliminarily define the antitumor activity of PF-02341066 within the confines of a Phase 1 study • To obtain initial Phase 2 data on the antitumor activity of PF-02341066 in children with relapsed/refractory neuroblastoma and ALCL.	*Secondary* Objective Response	Tumor response criteria for different tumor types are described in Study ADVL0912 Protocol Section 12.0. • Patients with non-CNS solid tumors including IMT had disease assessed following RECIST Version 1.0 for response assessment. The protocol was designed using IWG response criteria for ALCL and revised Cheson criteria[a] for response assessment. • Patients with ALCL also had disease evaluated retrospectively using the Lugano Classification[b] during central review. For ALCL, CR was disappearance of all evidence of disease from all sites for at least 4 weeks as determined by physical exam and imaging; CRu was defined as more than 75% shrinkage in the sums of the perpendicular diameters of the lesions and no residual FDG PET activity; PR was a decrease of 50% or more in the sums of the perpendicular diameters of the lesions with no new lesions. Objective responses (CR, CRu, PR) and prolonged stable disease on protocol therapy for ≥ 6 cycles were assessed by independent central radiology review for confirmation of responses and used for summary of this data. Best overall response was determined from the sequence of the objective status. Two objective status determinations of disease status, by CT or MRI, obtained on 2 consecutive determinations, separated by at least a 3-week time period, were required to determine the patient's best overall response. A responder was defined as a patient who achieved a best objective response of CR, CRu (for ALCL only), or PR on the study. All other patients were considered non-responders.	RE	The frequency (number and percentage) of patients with BOR of CR, CRu (ALCL only), PR, stable disease, PD, and NE was provided with a summary of ORR and corresponding 2-sided 95% CI using Wilson method.[c] • Patients responding to therapy (PR, CR/CRu [ALCL only]) or had long term stable disease on protocol therapy (≥ 6 cycles) were centrally reviewed. • ORR was defined as the percentage of patients with CR or CRu (ALCL only) or PR. ORR analysis was performed based on confirmed independent central review assessments. • Investigator assessment of tumor response data was listed only.
	Secondary DR	Defined as time from first documentation of objective tumor response (CR, CRu [ALCL only] or PR) subsequently confirmed by independent central radiology review, to the first documentation of objective tumor progression or death on study due to any cause, whichever occurred first. Patients with an ongoing objective response who went to transplant (considered anticancer therapy) were censored at the time of their last tumor assessment prior to transplant.	RE	• Summarized for the subgroup of patients with confirmed objective tumor response using the Kaplan-Meier method. Median event time (if appropriate) and 2-sided 95% CI for the median using Brookmeyer-Crowley method[d] were provided. • Summarized descriptively and a "swimmer plot" was generated for the subgroup of patients with objective tumor response. If there were too few events to meaningfully interpret the Kaplan-Meier analysis results, only descriptive summaries were planned to be provided. • Summarized by transplant status and dose level by age group as a supportive analysis.
	Secondary TTR	Defined as time from first dose (C1D1) to first documentation of objective tumor response (CR, CRu [ALCL only] or PR) subsequently confirmed by independent central radiology review.	RE	Summarized using descriptive statistics for subgroup of patients with confirmed objective tumor response per independent central radiology review.

Results

Participant flow

Demographics and Baseline Characteristics

Table 17 Demographic characteristics by dose level

	Crizotinib 165 mg/m^2 BID (N=6)	Crizotinib 280 mg/m^2 BID (N=16)	Total (N=22)
Age, years			
Mean (SD)	6.8 (4.12)	10.8 (3.15)	9.7 (3.78)
Median	5.0	11.0	11.0
Range (min, max)	(3, 13)	(6, 16)	(3, 16)
Age Category, n (%)			
<2	0	0	0
2-<6	4 (66.7)	0	4 (18.2)
6-<12	1 (16.7)	10 (62.5)	11 (50.0)
12-<18	1 (16.7)	6 (37.5)	7 (31.8)
Gender, n (%)			
Male	5 (83.3)	12 (75.0)	17 (77.3)
Female	1 (16.7)	4 (25.0)	5 (22.7)
Race, n (%)			
White	4 (66.7)	7 (43.8)	11 (50.0)
Black or African American	0	5 (31.3)	5 (22.7)
Asian	1 (16.7)	1 (6.3)	2 (9.1)
Unknown	1 (16.7)	3 (18.8)	4 (18.2)
Ethnicity, n (%)			
Hispanic or Latino	1 (16.7)	2 (12.5)	3 (13.6)
Not Hispanic or Latino	5 (83.3)	13 (81.3)	18 (81.8)
Unknown	0	1 (6.3)	1 (4.5)

Table 18 Disposition Events summary by tumour type

Number (%) of Subjects	ALCL (N=26) n (%)	IMT (N=14) n (%)	Other Tumors (N=82) n (%)	Total (N=122) n (%)
Disposition Phase: Treatment				
Subjects Not Entered:	0	0	1 (1.2)	1 (0.8)
Subjects Entered:	26 (100)	14 (100)	81 (98.8)	121 (99.2)
Discontinued [1]	24 (92.3)	11 (78.6)	80 (97.6)	115 (94.3)
Adverse Event	2 (7.7)	4 (28.6)	6 (7.3)	12 (9.8)
Lost to Follow-Up	1 (3.8)	0	0	1 (0.8)
Non-Compliance With Study Drug	1 (3.8)	2 (14.3)	0	3 (2.5)
Physician Decision	8 (30.8)	4 (28.6)	1 (1.2)	13 (10.7)
Progressive Disease	3 (11.5)	0	65 (79.3)	68 (55.7)
No Longer Meets Eligibility Criteria	1 (3.8)	0	0	1 (0.8)
Refusal of Further Protocol Therapy by Patient/Parent/Guardian [2]	7 (26.9)	1 (7.1)	8 (9.8)	16 (13.1)
Withdrawal of Consent	1 (3.8)	0	0	1 (0.8)
Completed [3]	2 (7.7)	3 (21.4)	1 (1.2)	6 (4.9)

Table 19 Prior therapies by tumour type

Number (%) of Subjects	ALCL (N=22) n (%)	IMT (N=14) n (%)	Other Tumors (N=69) n (%)	Total (N=105) n (%)
Prior Therapy Type: [1]				
Bone Marrow Transplant	2 (9.1)	0	24 (34.8)	26 (24.8)
Chemotherapy Multi-Agent Systemic	22 (100)	3 (21.4)	61 (88.4)	86 (81.9)
Chemotherapy Non-Cytotoxic	0	0	7 (10.1)	7 (6.7)
Chemotherapy Not Otherwise Specified (NOS)	1 (4.5)	1 (7.1)	2 (2.9)	4 (3.8)
Chemotherapy Single Agent Systemic	2 (9.1)	0	24 (34.8)	26 (24.8)
Extensive Radiation	0	0	8 (11.6)	8 (7.6)
Immunotherapy	1 (4.5)	0	19 (27.5)	20 (19.0)
Limited Radiation	1 (4.5)	0	35 (50.7)	36 (34.3)
Oncolytic Virotherapy	0	0	1 (1.4)	1 (1.0)
Prior Therapy NOS	4 (18.2)	4 (28.6)	20 (29.0)	28 (26.7)
Radiotherapy Not Otherwise Specified	0	0	15 (21.7)	15 (14.3)
Surgery	2 (9.1)	8 (57.1)	49 (71.0)	59 (56.2)

Objective Response

ALCL Group

The ORR for the 22 paediatric patients was 86.4% (95%CI: 66.7, 95.3) across both dose levels.

1. For the 6 patients enrolled at the 165 mg/m^2 BID dose level, the ORR was 83.3% (95%CI: 43.6, 97.0).

2. For the 16 patients enrolled at the 280 mg/m^2 BID dose level, the ORR was 87.5% (95%CI: 64.0, 96.5).

3. CRs were observed in 77.3% (17/22) of paediatric patients across both dose levels.

1. At the 165 mg/m^2 BID dose level, CRs were observed in 83.3% (5/6) of patients.
2. At the 280 mg/m^2 BID dose level, CRs were observed in 75.0% (12/16) of patients.

IMT Group

The ORR for the 14 paediatric patients was 85.7% (95%CI: 60.1, 96.0) across all dose levels.
1. 1 patient was enrolled at the 100 mg/m^2 BID dose level and did not have an objective response.
2. 1 patient was enrolled at the 165 mg/m^2 BID dose level and had an objective response (PR).
3. For the 12 patients enrolled at the 280 mg/m^2 BID dose level, the ORR was 91.7% (95%CI: 64.6, 98.5).

CRs were observed in 35.7% (5/14) of paediatric patients in the IMT group across dose levels.
4. Neither patient at the 100 mg/m^2 BID nor 165 mg/m^{2}BID dose level had a CR.
5. At the 280 mg/m^2 BID dose level, CRs were observed in 41.7% (5/12) of patients.

Other Tumours Group

19 patients were evaluated for best overall response. Objective responses were observed in 5 paediatric patients, all of whom had NB. PRs were observed in 2 paediatric patients at the 280mg/m^2 BID dose level. CRs were observed in 3 paediatric patients across all dose levels as follows:

1. At the 165 mg/m^2 BID dose level, 1 patient had a CR;
2. At the 280 mg/m^2 BID dose level, 1 patient had a CR;
3. At the 365 mg/m^2 BID dose level, 1 patient had a CR.

Table 20 Summary of BOR by dose level, ALCL – Response Evaluable analysis set

	Crizotinib 165 mg/m^2 BID (N=6)				Crizotinib 280 mg/m^2 BID (N=16)				Total (N=22)			
	2-<6 (N1=4)	6-<12 (N1=1)	12-<18 (N1=1)	<18 (N1=6)	2-<6 (N1=0)	6-<12 (N1=10)	12-<18 (N1=6)	<18 (N1=16)	2-<6 (N1=4)	6-<12 (N1=11)	12-<18 (N1=7)	<18 (N1=22)
Best Overall Response, n (%) [1]												
Complete response	4 (100)	1 (100)	0	5 (83.3)	0	7 (70.0)	5 (83.3)	12 (75.0)	4 (100)	8 (72.7)	5 (71.4)	17 (77.3)
Partial response	0	0	0	0	0	2 (20.0)	0	2 (12.5)	0	2 (18.2)	0	2 (9.1)
Stable disease	0	0	1 (100)	1 (16.7)	0	1 (10.0)	1 (16.7)	2 (12.5)	0	1 (9.1)	2 (28.6)	3 (13.6)
Progressive disease	0	0	0	0	0	0	0	0	0	0	0	0
Not evaluable	0	0	0	0	0	0	0	0	0	0	0	0
Objective Response (CR, CRu [for ALCL only] and PR), n (%) [2]	4 (100)	1 (100)	0	5 (83.3)	0	9 (90.0)	5 (83.3)	14 (87.5)	4 (100)	10 (90.9)	5 (71.4)	19 (86.4)
95% CI [3]	51.0, 100.0	20.7, 100.0	0.0, 79.3	43.6, 97.0	NE, NE	59.6, 98.2	43.6, 97.0	64.0, 96.5	51.0, 100.0	62.3, 98.4	35.9, 91.8	66.7, 95.3

Table 21 Summary of BOR by dose level, IMT– Response Evaluable analysis set

	Crizotinib 100 mg/m² BID (N=1)				Crizotinib 165 mg/m² BID (N=1)				Crizotinib 280 mg/m² BID (N=12)				Total (N=14)			
	2-<6 (N1=0)	6-<12 (N1=1)	12-<18 (N1=0)	<18 (N1=1)	2-<6 (N1=0)	6-<12 (N1=1)	12-<18 (N1=0)	<18 (N1=1)	2-<6 (N1=4)	6-<12 (N1=6)	12-<18 (N1=2)	<18 (N1=12)	2-<6 (N1=4)	6-<12 (N1=8)	12-<18 (N1=2)	<18 (N1=14)
Best Overall Response, n (%) [1]																
Complete response	0	0	0	0	0	0	0	0	2 (50.0)	2 (33.3)	1 (50.0)	5 (41.7)	2 (50.0)	2 (25.0)	1 (50.0)	5 (35.7)
Partial response	0	0	0	0	0	1 (100)	0	1 (100)	2 (50.0)	3 (50.0)	1 (50.0)	6 (50.0)	2 (50.0)	4 (50.0)	1 (50.0)	7 (50.0)
Stable disease	0	1 (100)	0	1 (100)	0	0	0	0	0	1 (16.7)	0	1 (8.3)	0	2 (25.0)	0	2 (14.3)
Progressive disease	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Not evaluable	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Objective Response (CR and PR), n (%) [2]	0	0	0	0	0	1 (100)	0	1 (100)	4 (100)	5 (83.3)	2 (100)	11 (91.7)	4 (100)	6 (75.0)	2 (100)	12 (85.7)
95% CI [3]	NE, NE	0.0, 79.3	NE, NE	0.0, 79.3	NE, NE	20.7, 100.0	NE, NE	20.7, 100.0	51.0, 100.0	43.6, 97.0	34.2, 100.0	64.6, 98.5	51.0, 100.0	40.9, 92.9	34.2, 100.0	60.1, 96.0

Age Group Analysis

ALCL Group

ORRs by age group were as follows:

1. Age 2-<6 years: 100% (95%CI: 51.0, 100.0) (4 patients; youngest patient was 3 years old);
2. Age 6-<12 years: 90.9% (95%CI: 62.3, 98.4) (11 patients);
3. Age 12-<18 years: 71.4% (95%CI: 35.9, 91.8) (7 patients);
4. Age 18-≤21 years: 100% (95%CI: 51.0, 100.0) (4 patients).

CRs by age group were as follows:

5. Age 2-<6 years: 4/4 patients (100%) (Youngest patient was 3 years old);
6. Age 6-<12 years: 8/11 patients (72.7%);
7. Age 12-<18 years: 5/7 patients (71.4%);
8. Age 18-≤21 years: 4/4 patients (100%).

IMT Group

ORRs by age group were as follows:

•Age 2-<6 years: 100% (95%CI: 51.0, 100.0) (4 patients);
•Age 6-<12 years: 75.0% (95%CI: 40.9, 92.9) (8 patients);
•Age 12-<18 years: 100% (95%CI: 34.2, 100.0) (2 patients);
•Age 18-≤21 years: no patients in this age group.

CRs by age group were as follows:

9. Age 2-<6 years: 2/4 patients (50.0%);
10. Age 6-<12 years: 2/8 patients (25.0%);
11. Age 12-<18 years: 1/2 patients (50.0%);
12. Age 18-≤21 years: no patients in this age group.

The tables below summarise OR by Dose level and Age group, for ALCL and MTI:

Table 22 Summary of BOR by dose level– Response Evaluable analysis set

		ALCL		IMT	
Dose Level	**Age groups (years)**	**N**	**Objective Response, n (%) [1]**	**N**	**Objective Response, n (%) [1]**
Crizotinib 100 mg/m² BID	All ages < 18 years	0	0	1	0
	< 2	0	0	0	0
	2 -< 6	0	0	0	0
	6 -< 12	0	0	1	0
	12 -< 18	0	0	0	0
Crizotinib 165 mg/m² BID	All ages < 18 years	6	5 (83.3)	1	1 (100.0)
	< 2	0	0	0	0
	2 -< 6	4	4 (100.0)	0	0
	6 -< 12	1	1 (100.0)	1	1 (100.0)
	12 -< 18	1	0	0	0
Crizotinib 280 mg/m² BID	All ages < 18 years	16	14 (87.5)	12	11 (91.7)
	< 2	0	0	0	0
	2 -< 6	0	0	4	4 (100.0)
	6 -< 12	10	9 (90.0)	6	5 (83.3)
	12 -< 18	6	5 (83.3)	2	2 (100.0)

Table 23 Summary of BOR by dose level, age group (18-21) – Response Evaluable analysis set

		ALCL		IMT	
Dose Level	**Age groups (years)**	**N**	**Objective Response, n (%) [1]**	**N**	**Objective Response, n (%) [1]**
Crizotinib 100 mg/m² BID	All ages ≤ 21 years	0	0	1	0
	18-21	0	0	0	0
Crizotinib 165 mg/m² BID	All ages ≤ 21 years	6	5 (83.3)	1	1 (100.0)
	18-21	0	0	0	0
Crizotinib 280 mg/m² BID	All ages ≤ 21 years	20	18 (90.0)	12	11 (91.7)
	18-21	4	4 (100.0)	0	0

Duration of Response (DR)

ALCL Group:

Median DR for patients with objective tumour response (23 patients) was 3.9 months (range: 0.0 to 18.6 months).

Table 24 DR by dose level ALCL– Subjects with OR in Response Evaluable analysis set

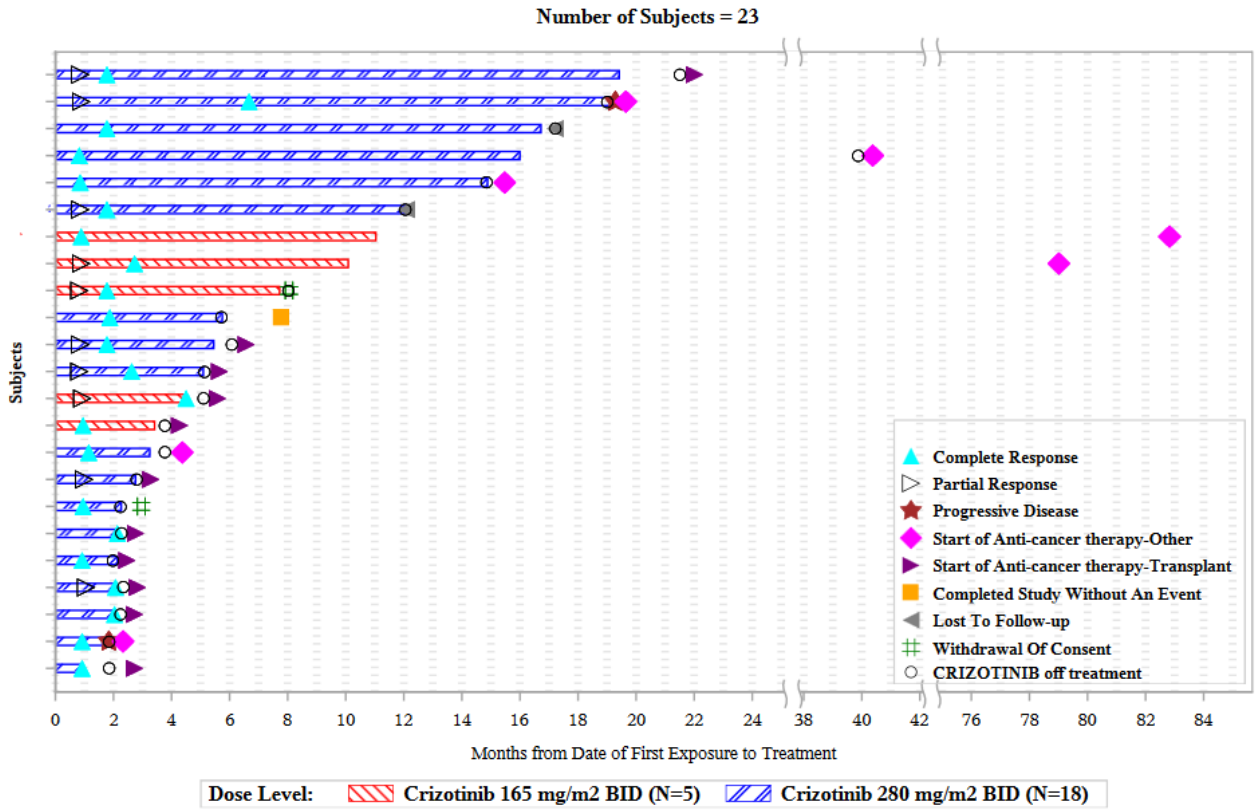
	Crizotinib 165 mg/m² BID (N=5)		Crizotinib 280 mg/m² BID (N=18)		Total (N=23)	
	18-21 (N1=0)	**≤ 21 (N1=5)**	**18-21 (N1=4)**	**≤ 21 (N1=18)**	**18-21 (N1=4)**	**≤ 21 (N1=23)**
Subjects with event, n (%)[1]	0	0	1 (25.0)	2 (11.1)	1 (25.0)	2 (8.7)
Type of event, n (%)						
Progressive disease	0	0	1 (25.0)	2 (11.1)	1 (25.0)	2 (8.7)
Death	0	0	0	0	0	0
Subjects censored, n (%)[1]	0	5 (100)	3 (75.0)	16 (88.9)	3 (75.0)	21 (91.3)
Reason for censoring, n (%)						
Start of new anti-cancer therapy	0	4 (80.0)	2 (50.0)	12 (66.7)	2 (50.0)	16 (69.6)
Event after ≥ 2 missing or inadequate post-baseline assessments	0	0	0	0	0	0
Withdrawal of consent	0	1 (20.0)	1 (25.0)	1 (5.6)	1 (25.0)	2 (8.7)
Lost to follow-up	0	0	0	2 (11.1)	0	2 (8.7)
Completed without an event	0	0	0	1 (5.6)	0	1 (4.3)
Duration of response (months)						
Mean (SD)	NE (NE)	6.49 (3.376)	13.40 (8.183)	6.33 (6.909)	13.40 (8.183)	6.37 (6.242)
Q1	NE	3.6	8.3	1.1	8.3	1.2
Median	NE	6.9	16.8	3.0	16.8	3.9
Q3	NE	9.2	18.5	14.1	18.5	11.2
Range (min, max)	(NE, NE)	(2.5, 10.2)	(1.3, 18.6)	(0.0, 18.6)	(1.3, 18.6)	(0.0, 18.6)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]						
Median	NE (NE, NE)	NE (NE, NE)	NE (18.4, NE)	18.4 (18.4, NE)	NE (18.4, NE)	18.4 (18.4, NE)

• For the 5 patients with objective tumour response at the 165 mg/m2 BID dose level, the median DR was 6.9 months (range:2.5 to 10.2 months).

• For the 18 patients with objective tumour response at the 280 mg/m2 BID dose level, the median DR was 3.0 months (range:0.0 to 18.6 months).

However, DR was underestimated because 11 patients with objective tumour response underwent HSCT (2 at the 165 mg/m^2 BID dose level and 9 at the 280 mg/m^2 BID dose level).

Figure 15 Swimmer plot to tumour response and DR ALCL (Age ≤ 21 years)-Subjects with OR in Response Evaluable analysis set



IMT Group:

All patients were paediatric patients and will be discussed below.

Additional summaries of DR for all patients are presented by:

Kaplan-Meier Plot of Duration of Response (Age ≤ 21 years)-Subjects with Objective Tumour Response in Response Evaluable Analysis Set Figure below.

Figure 16 Kaplan-Meier Plot of Duration of Response (Age ≤ 21 years)-Subjects with Objective Tumour Response in Response Evaluable Analysis Set

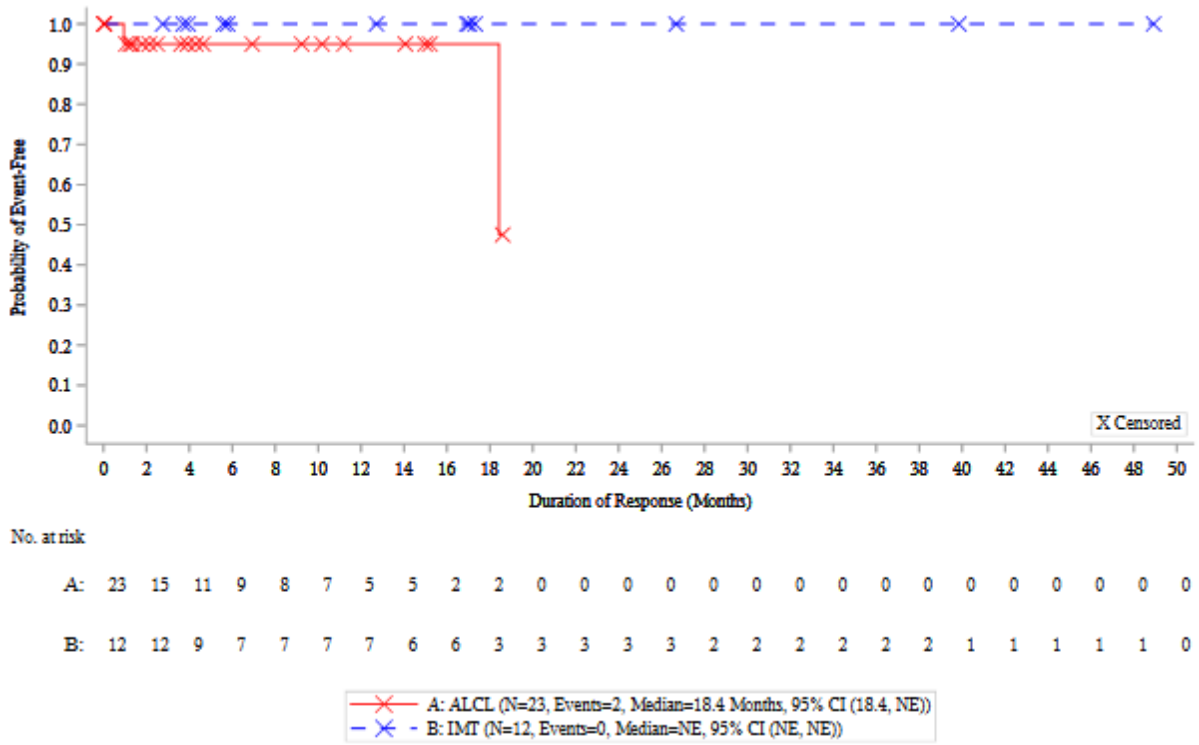


Table 25 Duration of Response by dose IMT (Age ≤ 21 years)-Subjects with Objective Tumour Response in Response Evaluable Analysis Set

	Crizotinib 165 mg/m² BID (N=1)	Crizotinib 280 mg/m² BID (N=11)	Total (N=12)
Subjects with event, n (%)[1]	0	0	0
Type of event, n (%)			
Progressive disease	0	0	0
Death	0	0	0
Subjects censored, n (%)[1]	1 (100)	11 (100)	12 (100)
Reason for censoring, n (%)			
Start of new anti-cancer therapy	1 (100)	2 (18.2)	3 (25.0)
Event after ≥ 2 missing or inadequate post-baseline assessments	0	0	0
Withdrawal of consent	0	0	0
Lost to follow-up	0	1 (9.1)	1 (8.3)
Completed without an event	0	8 (72.7)	8 (66.7)
Duration of response (months)			
Mean (SD)	48.92 (NE)	13.85 (11.537)	16.77 (14.950)
Q1	48.9	3.9	4.8
Median	48.9	12.7	14.8
Q3	48.9	17.3	22.0
Range (min, max)	(48.9, 48.9)	(2.8, 39.9)	(2.8, 48.9)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]			
Median	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Age Group Analysis of DR

ALCL Group

Median DRs by age group for patients with objective tumour response were as follows:

•Age 2-<6 years: 6.4 months (range: 2.5 to 10.2 months) (4 patients; youngest patient was3 years old).

13. With HSCT: 3.1 months (range: 2.5 to 3.6 months) (2 patients)

14. Without HSCT: 9.7 months (range: 9.2 to 10.2 months) (2 patients)

•Age 6-<12 years: 2.0 months (range: 0.0 to 15.0 months) (10 patients).

15. With HSCT: 1.1 months (range: 0.0 to 4.6 months) (6 patients)

16. Without HSCT: 10.5 months (range: 2.1 to 15.0 months) (4 patients)

•Age 12-<18 years: 3.9 months (range: 0.0 to 11.2 months) (5 patients).

17. With HSCT: 2.2 months (range: 0.0 to 4.3 months) (2 patients)

18. Without HSCT: 3.9 months (range: 1.0 to 11.2 months) (3 patients)

•Age 18-≤21 years: 16.8 months (range: 1.3 to 18.6 months) (4 patients)

IMT Group

Median DRs by age group for patients with objective tumour response were as follows:

•Age 2-<6 years: 22.0 months (range: 3.9 to 39.9 months) (4 patients);

•Age 6-<12 years: 9.1 months (range: 2.8 to 48.9 months) (6 patients);

•Age 12-<18 years: 11.4 months (range: 5.8 to 16.9 months) (2 patients);

•Age 18-≤21 years: no patients in this age group.

Time to Tumour Response

ALCL Group

For the 19 patients with objective tumour responses, the responses were rapid, with a median TTR of 0.9 months (range: 0.8 to 2.1 months) across both dose levels corresponding to the approximate time of the first on-treatment tumour scan.

• For the 5 patients with objective tumour response at the 165 mg/m² BID dose level, the median TTR was 0.9 months (range: 0.8 to 1.0 months).

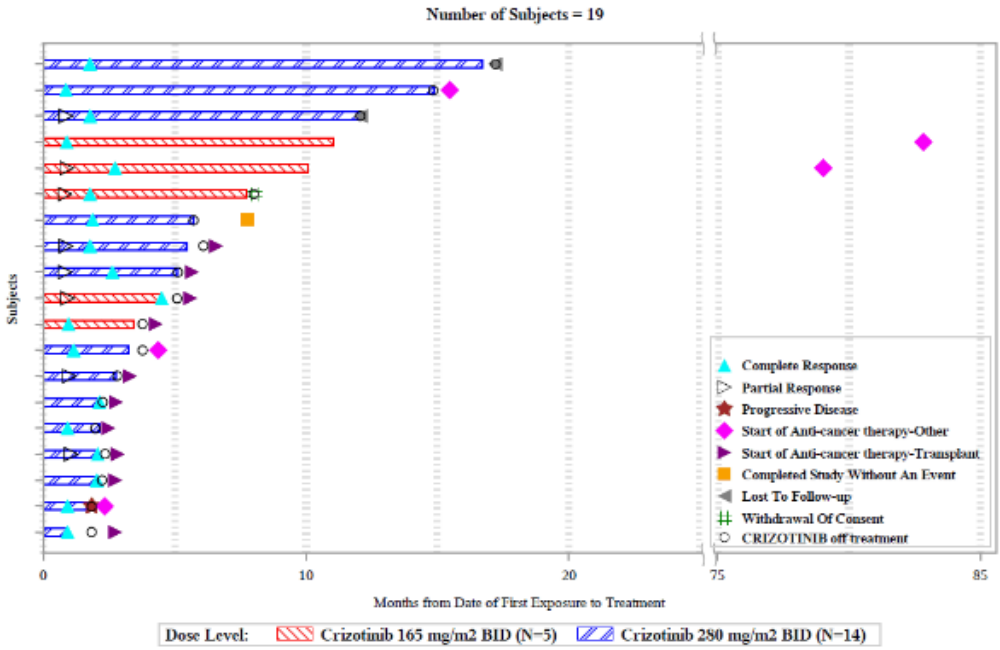
•For the 14 patients with objective tumour response at the 280 mg/m^2 BID dose level, the median TTR was 1.0 month (range: 0.8 to 2.1 months).

TTR is plotted for paediatric patients in the ALCL group with objective tumour response in Figure 2 which indicates most patients had first tumour response within the first month of treatment.

Table 26 TTR by dose level ALCL (Age <18 years)-Subjects with Objective Tumour Response in Response Evaluable Analysis Set

	Crizotinib 165 mg/m² BID (N=5)				Crizotinib 280 mg/m² BID (N=14)				Total (N=19)			
	2 -< 6 (N1=4)	6 -< 12 (N1=1)	12 -< 18 (N1=0)	< 18 (N1=5)	2 -< 6 (N1=0)	6 -< 12 (N1=9)	12 -< 18 (N1=5)	< 18 (N1=14)	2 -< 6 (N1=4)	6 -< 12 (N1=10)	12 -< 18 (N1=5)	< 18 (N1=19)
Time to Tumor Response (TTR) (Months)												
Mean (SD)	0.91 (0.031)	0.82 (NE)	NE (NE)	0.89 (0.049)	NE (NE)	1.17 (0.432)	1.32 (0.632)	1.22 (0.493)	0.91 (0.031)	1.14 (0.422)	1.32 (0.632)	1.14 (0.445)
Q1	0.9	0.8	NE	0.9	NE	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Median	0.9	0.8	NE	0.9	NE	1.0	0.9	1.0	0.9	1.0	0.9	0.9
Q3	0.9	0.8	NE	0.9	NE	1.1	1.9	1.8	0.9	1.1	1.9	1.1
Range (min, max)	(0.9, 1.0)	(0.8, 0.8)	(NE, NE)	(0.8, 1.0)	(NE, NE)	(0.9, 2.0)	(0.8, 2.1)	(0.8, 2.1)	(0.9, 1.0)	(0.8, 2.0)	(0.8, 2.1)	(0.8, 2.1)

Figure 17 Swimmer plot to TTR and DR ALCL (Age <18 years)-Subjects with OR in Response Evaluable analysis set



IMT Group

For the 12 patients with objective tumour responses, the responses were rapid, with a median TTR of 1.0 month (range: 0.8 to 4.6 months) across all dose levels corresponding to the approximate time of the first on-treatment tumour scan.

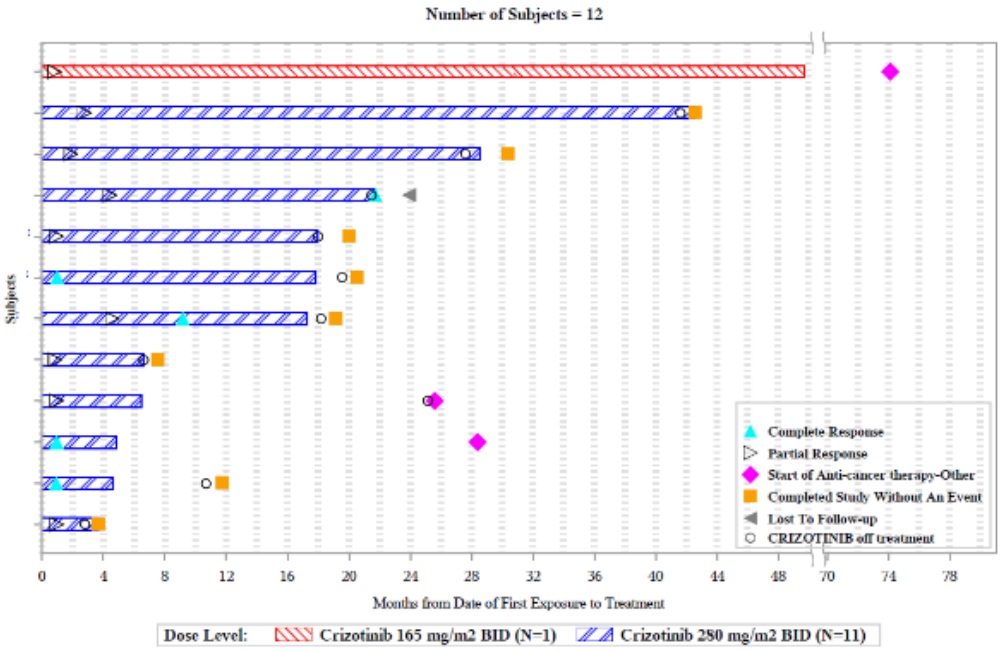
•The 1 patient at the 100 mg/m² BID dose level did not have an objective tumour response.

•The 1 patient at the 165 mg/m² BID dose level had an objective tumour response with a median TTR of 0.8 months.

•For the 11 patients with objective tumour response at the 280 mg/m² BID dose level, the median TTR was 1.0 month (range: 0.9 to 4.6 months).

TTR is plotted for paediatric patients in the IMT group with objective tumour response in *Figure 18* which indicates most patients had first tumour response within the first month of treatment.

Figure 18 Swimmer plot of TTR and DR by dose level IMT (Age <18 years)-Subjects with Objective Tumour Response in Response Evaluable Analysis Set



Age Group Analysis

ALCL Group

Median TTRs by age group for patients with objective tumour response were as follows (Table21):

•Age 2-<6 years: 0.9 months (range: 0.9 to 1.0 months) (4 patients; youngest patient was 3 years old);

•Age 6-<12 years: 1.0 month (range: 0.8 to 2.0 months) (10 patients);

•Age 12-<18 years: 0.9 months (range: 0.8 to 2.1 months) (5 patients);

•Age 18-≤21 years: 0.9 months (range: 0.8 to 1.0 months) (4 patients).

IMT Group

Median TTRs by age group for patients with objective tumour response were as follows:

•Age 2-<6 years: 2.3 months (range: 1.0 to 4.4 months) (4 patients);

•Age 6-<12 years: 1.0 month (range: 0.8 to 4.6 months) (6 patients);

•Age 12-<18 years: 0.9 months (range: 0.9 to 1.0 months) (2 patients);

•Age 18-≤21 years: no patients in this age group.

Table 27 Efficacy and safety data _ ALCL patients at 280 mg/m² BID

	Endpoint	Starting dose ≤ 250 mg BID	Starting dose > 250 mg BID
N		3	13
Efficacy			
	ORR % (n/N) (95% CI)	100% (3/3) (43.9, 100)	84.6% (11/13) (57.8, 95.7)
	Median DR (months)	14.1	1.2
Safety		n (%)	n (%)
	Permanent Discontinuations Associated with AEs	0	1 (7.7)
	All-Causality Grade 3 or 4 AEs	3 (100)	13 (100)
	All-Causality Grade 5 AEs	0	0
	Treatment-Related Grade 3 or 4 AEs	3 (100)	10 (76.9)
	All-Causality SAEs	1 (33.3)	3 (23.1)
	Treatment-Related SAEs	0	2 (15.4)
	Dose Reductions	0	3 (23.1)

Table 28 Efficacy and safety data _ IMT patients at 280 mg/m² BID

	Endpoint	Starting dose ≤ 250 mg BID	Starting dose > 250 mg BID
N		7	5
Efficacy			
	ORR % (n/N) (95% CI)	100% (7/7) (64.6, 100)	80.0% (4/5) (37.6, 96.4)
	Median DR (months)	12.7	11.4
Safety		n (%)	n (%)
	Permanent Discontinuations Associated with AEs	1 (14.3)	3 (60.0)
	All-Causality Grade 3 or 4 AEs	6 (85.7)	4 (80.0)
	All-Causality Grade 5 AEs	0	0
	Treatment-Related Grade 3 or 4 AEs	5 (71.4)	3 (60.0)
	All-Causality SAEs	1 (14.3)	0
	Treatment-Related SAEs	1 (14.3)	0
	Dose Reductions	2 (28.6)	2 (40.0)

Supportive study(ies)

Study A8081013

The supportive study providing clinical antitumour activity in this submission is the Pfizer-sponsored Study A8081013. A full description of this study is provided in the Study A8081013 Protocol, and a summary is provided below.

Methods

Study A8081013 is a Phase 1b, open-label, multicentre, single-arm exploratory study evaluating the antitumour activity, safety, and PK of crizotinib. Patients (≥ 15 years) with a histologic or cytological proven diagnosis of ALCL or other advanced malignancy other than NSCLC, e.g. IMT, for which no standard therapy was available and who were positive for harbouring a translocation, inversion, mutation or amplification event involving the ALK gene locus were enrolled. Inclusion and exclusion criteria are further described in Study A8081013 Protocol Section 4.1 and Section 4.2.

Patients could have continued treatment with crizotinib after disease progression if there was evidence of clinical benefit in the judgment of the Investigator. This study is ongoing (data cut-off date: 03 September 2019).

Study population

Main eligibility criteria:

1- Age ≥ 15 years

2- Histologically or cytologically proven diagnosis of ALCL or other advanced malignancy other than NSCLC for whom no standard therapy is available

3- Positive for translocation or inversion event involving the ALK gene locus

4- Positive for ALK amplification events

5- Positive for ALK activating point mutations

6- Solid tumours must be measurable per RECIST version 1.1, and lymphomas must be measurable per NCI International Response Criteria for Non-Hodgkin's Lymphoma

7- ECOG performance status 0-3

Main ineligibility criteria:

1- Mutations of amplifications involving the c-Met gene but not the ALK gene

2- Concurrent treatment on another therapeutic clinical trial

3- Prior therapy specifically directed against ALK

Sample size:

The sample size for this study was determined empirically based on expected small numbers of patients in the population of interest. It was anticipated that a total of approximately 40 patients were to be enrolled in this study.

Objectives and endpoints

Efficacy:

The **primary** efficacy endpoint was ORR based on RECIST version 1.1 for solid tumours and the NCI International Response Criteria for Non-Hodgkin Lymphoma for patients with ALCL or other NHL (Cheson et al. 2007).

Secondary endpoints were:

- PFS, OS, DR

- Estimated probability of survival at 6-months and 1 year.

- Plasma concentrations of crizotinib,

- Proportion of patients with each of the ALK genetic events (translocation, mutation, amplification).

- Phosphorylation status of ALK in the tumour samples from surgery or biopsy pre- and post-treatment, when available.

Safety:

The **primary** safety endpoint was type, incidence, severity, seriousness and relationship to study medications of adverse events (AE) and any laboratory abnormalities.

Treatments

In the study, patients received crizotinib at a starting dose of 250 mg BID orally continuously.

Dosing interruption and/or intrapatient dose reduction by 1 and if needed, 2 dose level(s) was allowed depending on the type and severity of toxicity encountered (Dose Level -1 was 200 mg BID; Dose Level -2 was 250 mg QD).

Efficacy Analyses

The analysis populations (Table 29); and antitumour activity objectives, endpoints, evaluations, and statistical analyses (Table 30) for paediatric patients with ALK-positive ALCL or ALK-positive IMT in Study A8081013 are summarised in this section.

Table 29 Study A8081013 Analysis populations

Analysis Population	Definition
SA	Includes all enrolled patients who received at least 1 dose of crizotinib. This is the primary population for evaluating demographics, safety, summaries of time-to-event antitumor activity data, and treatment evaluations.
RE	Includes all patients in the SA who had an adequate baseline tumor assessment (as defined in Study A8081013 SAP Section 5.3) by either RECIST 1.1 (Eisenhauer et al, 2009) or Cheson criteria (Cheson et al, 2007). This is the primary population for evaluating all response-related antitumor activity evaluations.

Table 30 Antitumour activity objectives, endpoints, evaluation and statistical analysis

Objectives	Endpoints	Definition/Evaluation	Analysis Population
Primary • Assess safety of oral single-agent crizotinib administered to patients with advanced ALK-positive ALCL or other advanced malignancy other than NSCLC known to have an ALK genetic event[a] and screen for efficacy in these patients.	*Primary* ORR	• Defined as percentage of patients with confirmed CR or PR according to RECIST Version 1.1 as determined by investigators. • ORR based on Cheson criteria was defined similarly however, confirmation of response was not required. If a patient had tumor response assessed only by RECIST or Cheson, then ORR was based on the single result. If tumor response was assessed by RECIST and Cheson, then ORR was reported based on tumor response by Cheson criteria unless the Cheson had indeterminate result, in which case the RECIST result was reported. Patients were considered non responders until proven otherwise. Patients were counted as non-responders in the assessment of ORR if they: • Did not have CR or PR while on treatment, or • Did not have a post-baseline tumor evaluation, or • Received antitumor treatment other than study medication prior to reaching a CR or PR, or • Died, progressed, or dropped out for any reason prior to reaching a CR or PR. To be assigned a status of PR or CR using RECIST 1.1, changes in tumor measurements in patients with responding tumors had to be confirmed by repeat tumor assessment performed at least 4 weeks after criteria for response were first met. Confirmation of response was not required for status of PR or CR using Cheson criteria. If a patient had not achieved an objective response but remained stable for at least 6 weeks after first dose, then best overall response for such a patient was stable disease.	RE
Secondary • To correlate ALK genetic events to efficacy outcome measures including PFS and OS	*Secondary* DR	• Defined as time from first documentation of objective tumor response (CR or PR) to first documentation of objective tumor progression or to death on treatment due to any cause, whichever occurred first. DR (in weeks) was calculated as (first date of PD or death − first date of CR or PR +1)/7.0. • If patient had tumor response assessed only by RECIST or Cheson, the first objective tumor response date was based on single result of either RECIST 1.1 or Cheson criteria (note: RECIST 1.1 results had to be subsequently confirmed, but Cheson criteria did not require response confirmation). If tumor response was reported by both RECIST 1.1 and Cheson criteria, earliest date of tumor response by either was used. • If tumor progression data included more than 1 date, first date was used. First date of PD was defined the same as for PFS. Censoring for DR was identical to the censoring rules presented for PFS when patients had at least 1 on-treatment disease assessment.	RE
	Secondary PFS	• Defined as time from date of first dose of study medication to date of first documentation of objective tumor progression or death on treatment due to any cause, whichever occurred first. If tumor progression data included more than 1 date, the first date was used. PFS (in weeks) was calculated as (date of first event − date of first dose +1)/7.0. • Tumor assessments were performed within ± 7 days of scheduled visits. Unscheduled scans were performed to confirm response (≥ 4 weeks after initial assessment of response) and when disease progression was suspected. If PD was documented between scheduled visits, actual date of progression was used as an un-censored value in PFS analysis. If PD was reported by both RECIST 1.1 and Cheson criteria, then earliest date of PD by either was used in PFS calculation. Otherwise date of PD by either RECIST 1.1 (if all tumor assessments were by RECIST 1.1) or Cheson criteria (if all tumor assessments were by Cheson criteria) was used. • Patients with inadequate baseline assessments had their event time censored on date of first dose of study medication. Patients lacking evaluation of tumor response after first dose or for whom the first	SA

Objectives	Endpoints	Definition/Evaluation	Analysis Population	
		on-treatment tumor evaluation occurred more than 14 weeks after first dose also had their event time censored on date of first dose unless death occurred ≤ Week 14 (in which case the death was an event). • If patients had at least 1 on-treatment disease assessment, PFS data were censored on the date of the last evaluable on-treatment tumor assessment by either RECIST 1.1 or Cheson criteria documenting absence of progressive disease for patients: • Alive, on treatment and progression free at the time of the analysis; • Who discontinued treatment without documented disease progression and did not progress or die on treatment; • Who had documentation of disease progression or death > 14 weeks after last on-treatment tumor assessments; • Who received antitumor treatment other than the study medication while on treatment and prior to documented disease progression or death on treatment. In this case, last evaluable assessment prior to start of antitumor treatment was used. One exception was for patients with documented PD or death within 14 days of anticancer therapy, and PD or death was considered an event.		
	Secondary OS	• Defined as time from date of first dose of study medication to date of death due to any cause. OS (in months) was calculated as (date of death − date of first dose +1)/30.42. • For patients alive at time of the analysis, for those lost to follow-up, and those who withdrew consent for additional follow-up, OS was censored on last date patients were known to be alive. Patients lacking data beyond the first dose had their OS censored at date of first dose.	SA	Pediatr (<18 ye separat and IM

a. Safety results are provided in the Study A8081013 CSR Section 12 and SCS (Module 2.7.4).

The study population for all analyses will include patients enrolled in the study who receive at least one dose of crizotinib. Data summaries/listings will be presented overall as well as separately for ALCL patients and patients with other malignancies (by tumour type, as applicable). Data for patients who are enrolled in the study but are later found to not have an ALK genetic event will be presented separately.

Due to the exploratory nature of this study, no confirmatory inferential analyses are planned, and no imputation for missing data will be done. Descriptive statistics (such as means, medians, standard deviations and ranges for continuous data and percentages for categorical data) will be used to summarise patient characteristics, treatment administration, efficacy, safety, molecular medicine and pharmacokinetic parameters. Data will also be displayed graphically, where appropriate.

Primary Efficacy Analysis:

The best response (CR, PR, SD or PD) per RECIST version 1.1, or the NCI International Response Criteria for Non-Hodgkin's Lymphoma (2007) where applicable, will be summarised. The objective response rate (ORR) will also be summarised along with the corresponding exact 2-sided 95% confidence interval calculated using a method based on the F distribution.

Secondary Efficacy Analysis:

Secondary, time to event endpoints (eg, PFS, OS), will be summarised descriptively using Kaplan-Meier methods and displayed graphically, where appropriate.

Efficacy results

Study participants

Study A8081013 is ongoing and was conducted at 16 sites in 7 countries: USA (5), Japan (3), Republic of Korea (2), China (3), Italy (1), Taiwan (1) and Russian Federation (1).

The study start date was 22 March 2011 (First Patient First Visit).

The data cutoff date was 03 September 2019.

The study report date is 28 February 2020.

Overall Population

As of the data cutoff date (03 September 2019), a total of 44 patients (17 in the ALCL group, 9 in the IMT group and 18 in the Other Tumours group) were assigned to receive study treatment. Among these, there were 3 paediatric patients in the ALCL group and 2 in the IMT group.

Ten (58.8%) patients in the ALCL group, 5 (55.6%) patients in the IMT group and 1 (5.6%) patients in Other Tumours group, were still on treatment.

Paediatric Population

Four paediatric patients were still on treatment (2 in the ALCL group and 2 in the IMT group). One paediatric patient in the ALCL group permanently discontinued from treatment due to global deterioration of health status.

Baseline data

Table 31 Baseline Demographic Characteristics, Paediatric Subjects

	ALCL (N=3)	IMT (N=2)	ALCL+IMT (N=5)
Age, years			
Mean (SD)	15.3 (0.58)	16.5 (0.71)	15.8 (0.84)
Median	15.0	16.5	16.0
Range	(15.0, 16.0)	(16.0, 17.0)	(15.0, 17.0)
Age Category, n (%)			
<18	3 (100.0%)	2 (100.0%)	5 (100.0%)
Sex, n (%)			
Male	2 (66.7%)	1 (50.0%)	3 (60.0%)
Female	1 (33.3%)	1 (50.0%)	2 (40.0%)
Race, n (%)			
White	1 (33.3%)	0	1 (20.0%)
Black	0	0	0
Asian	2 (66.7%)	2 (100.0%)	4 (80.0%)
Other	0	0	0
Racial Designation for Asian, n (%)			
Japanese	1 (33.3%)	0	1 (20.0%)
Korean	0	0	0
Chinese	1 (33.3%)	2 (100.0%)	3 (60.0%)
Other	0	0	0

Efficacy results

Antitumour activity data are provided in the Table below.

Table 32 Antitumour Activity Results for Paediatric Patients with ALK-Positive ALCL or ALK-Positive IMT (Data Cutoff Date: 03.09.19)

	ALCL	IMT
Primary Endpoint		
Objective Response	Among the 3 patients, 2 patients had objective responses; 1 patient had a CR and 1 patient had a PR. Both patients were still on treatment as of the data cutoff date. The third patient had a best overall response of stable disease with a duration of 2.8 months (Study A8081013 CSR Table 16.2.6.5.2).	Among the 2 patients, 1 patient had a PR. The second patient had a best overall response of stable disease with a duration of 51.0 months (Study A8081013 CSR Table 16.2.6.5.2). Both patients were still on treatment as of the data cutoff date.
Secondary Endpoints		
Duration of Response	Among the 2 patients with objective responses, the 1 patient who had a CR had a DR of 31.2 months, and the 1 patient with PR had a DR of 27.6 months. Both patients were still on treatment as of the data cutoff date (Study A8081013 Table 16.2.6.5.2).	The one patient who had a PR had a DR of 69.0 months. This patient was still on treatment as of the data cutoff date (Study A8081013 Table 16.2.6.5.2).
Progression-Free Survival	Among the 3 patients, 1 patient had PFS of 32.0 months, 1 patient had PFS of 28.8 months, and 1 patient with stable disease had PFS of 2.8 months. The two responding patients were still on treatment as of the data cutoff date, and the third patient had permanently discontinued crizotinib treatment due to global deterioration of health status (Study A8081013 Table 16.2.6.5.2).	Among the 2 patients, 1 patient had PFS of 70.4 months and 1 patient had PFS of 51.0 months. Both patients were still on treatment as of the data cutoff date (Study A8081013 Table 16.2.6.5.2).
Overall Survival	Among the 3 patients, 1 patient had an OS of 77.7 months (still on treatment as of the data cutoff date), 1 patient had an OS of 77.1 months (still on treatment at the time of data cutoff), and 1 patient had an OS of 45.6 months (patient permanently discontinued crizotinib on Day 88 and was censored at the time of completing the protocol-specified follow-up time as per Protocol Amendment 5) (Study A8081013 Table 16.2.6.5.2).	Among the 2 patients, 1 patient had an OS of 75.7 months and 1 patient had an OS of 76.3 months. Both patients were still on treatment as of the data cutoff date (Study A8081013 Table 16.2.6.5.2).

Pharmacokinetic Results

Due to the limited number of paediatric patients, no PK conclusions could be made.

Biomarker Results

All paediatric ALCL and IMT patients were positive for ALK-translocation by local testing using IHC and FISH, respectively.

Historical control

ALCL

There is no standard of care for the 25-35% of patients who develop recurrent disease (Brugières et al, 2009). Relapsed ALCL is traditionally chemosensitive, with a 30-83% rate of achieving a second remission (Woessmann et al, 2011). However, multiple relapses are not uncommon, with 40% of patients able to achieve a second CR reported to have subsequent relapse(s) (Brugières et al, 2000). Current treatment options for paediatric patients in the relapsed or refractory setting include aggressive intravenous salvage therapies such as vinblastine, high-dose therapies (including total body irradiation, etoposide, cyclophosphamide, busulfan, carmustine, melphalan, and/or cytarabine) followed by autologous HSCT or allogeneic stem HSCT, but not all patients are expected to benefit from these current options. HSCT is limited to those fit enough to undergo the procedure and who have an eligible donor. Furthermore, studies evaluating HSCT for relapsed or refractory ALCL showed some patient groups are less likely to benefit from the procedures (eg, patients with refractory disease or those unable to achieve a second, or later, CR in advance of HSCT) (Woessmann et al, 2006; Gross et al, 2010). Furthermore, all current therapies are associated with significant toxicity (Brugières et al, 2009; Woessmann et al, 2006; Woessmann et al, 2011; Harriset al, 2011). In paediatric populations, 100-day transplant-related mortality rates between 14% and 17% have been reported, and the transplant complication of venoocclusive liver disease has been reported to occur in up to 40% of paediatric patients (Gross et al, 2010; Miano et al, 2008). Secondary malignancies have been documented in paediatric ALCL following multiagent chemotherapy, with an expected increasing potential risk in the setting of multiple relapses and use of radiotherapy (Cairo and Perkins, 2012). While vinblastine offers the potential for efficacious single-agent therapy for recurrent disease, long-term remission is expected to be most likely with long treatment durations (2 years or more) (Brugières et al, 2009). Toxicities associated with vinblastine therapy include permanent effects such as hearing loss and dyspnea requiring chronic therapy (vinblastine sulfate USPI).

Brentuximab vedotin, an ADC directed against CD30 protein, is approved for the treatment of adults with systemic ALCL after failure of at least 1 prior multi-agent chemotherapy regimen and is currently under investigation in paediatric patients (ClinicalTrials.gov. Identifier NCT01492088). In this study, 17 paediatric patients with relapsed or refractory ALCL received brentuximab vedotin IV once every 21 days for up to 16 cycles. For the 17 paediatric patients, the ORR was 53% and the median EFS was 4.8 months (Locatelli et al, 2018).

Collectively, the ORR, CR rate, and the durability of responses reported for Study ADVL0912 (N=22 paediatric patients) demonstrate improvement in antitumour effect over current available therapies for paediatric patients with relapsed or refractory ALCL. At a starting dose of 280mg/m2BID, an ORR of 87.5% and CR rate of 75.0%, by independent central radiological review, were reported. While there are no approved therapies or established standard-of-care treatment of relapsed or refractory paediatric ALCL, ORRs of approximately 30-83%and 53-83% are reported for currently used multiagent chemotherapy and monotherapy regimens, respectively (Brugières et al, 2009; Woessmann et al, 2011; Locatelli et al, 2018).

In Study ADVL0912, median DR was 3.6 months (range: 0.0 -15.0 months) for the 19 responders across both dose levels. However, 52.6% of the patients proceeded to transplant after the occurrence of an objective response, resulting in a shorter median DR (1.5 months), as DR was censored at the time of last tumour assessment prior to transplant. A longer median DR (9.2 months) was observed for patients with ALK- positive ALCL who did not receive a transplant. Still taking this into account, crizotinib treatment was associated with durable tumour responses.

As shown in Study ADVL0912 by the 10 patients with objective response who went on to receive HSCT, crizotinib may act as a bridge to HSCT or may offer an alternative option to HSCT altogether. An alternative to HSCT could be a favourable option even for patients fit enough to undergo the procedure. In paediatric patients, a clear benefit for HSCT has not been consistently shown across the limited available studies (Brugières et al, 2000).

Furthermore, unlike all other current therapies, crizotinib offers the advantage of oral administration, eliminating the risks of infusion-related reactions/injection site effects and providing increased convenience/quality of life for patients and their families. Based on a literature review of studies reporting route of treatment administration preferences among patients with cancer, there was a general patient preference for oral versus IV administration; the ability to receive treatment at home was a main factor for this preference (Eek et al, 2016). The convenience of oral therapy administration is also preferred by paediatric caregivers. Multiple studies have demonstrated that treatment at home can be beneficial to patients with cancer (Stevens et al, 2006; Crisp et al, 2014; Delgado et al, 2009; Mandhaniya et al, 2011). Benefits for paediatric patients can include increased time for play, study, improved school attendance, and more participation in normal activities (Stevens et al, 2006).

IMT

Given the rarity of IMT tumours in the paediatric population, and the fact that that the mainstay of primary therapy has been complete surgical resection, there are few prospective studies and limited published data on outcomes after systemic therapy beyond case reports.

The largest series of paediatric patients with IMT reported to date is from the European Paediatric Soft Tissue Sarcoma Study Group who recently published data on 60 paediatric patients with IMT treated between 2005-2016 (Casanova et al, 2020). Forty (66.7%) of the 60 patients were ALK positive (detected by IHC in 14 cases, by FISH only in 1, and by both in 25), and 20 were ALK negative. In 28/60 cases, systemic therapy was administered (19 cases as part of first-line treatment, and 9 cases as second-line treatment). Overall response (CR + PR) to front- or second-line therapy was 63% (12/19 patients) and 66% (6/9 patients), respectively. In patients receiving systemic first- or second-line therapies, 8/10 cases responded to vinblastine-methotrexate chemotherapy and 5/5 cases responded to ALK-inhibitors (these cases of IMT were ALK positive). The median duration of response was not reported in this publication. For all 60 patients, the 5-year EFS and OS were 82.9% and 98.1%, respectively (median follow-up of 59 months). In a univariate analysis for EFS, none of the variables analysed correlated with outcomes, including gender, age at diagnosis (< 10 vs ≥10 years), site of disease (head-neck, vs. abdomen, vs. chest), ALK status, tumour invasiveness, size of the primary tumour (≤ 5 cm vs >5 cm), loco- regional lymph node involvement, or IRS staging group.

Table 33 Systemic treatment given as first or second line Therapy and response (Casanova et al, 2020)

	Treatment	Number of Cases	Response	Duration of Treatment (months)
First-line therapy	High-dose steroids	6	1 CR, 3 PR ≥ 2/3, 2 SD	2-15
	Vinblastine and methotrexate	5	3 PR ≥ 2/3, 1 PR < 2/3, 1 PD	4-14
	ALK inhibitors[a]	3	2 CR, 1 PR ≥ 2/3	6-24[b]
	Ifosfamide-based chemotherapy	2	2 SD	3-6
	Vinorelbine and low-dose cyclophosphamide	2	1 CR, 1 PD	4-12
	Vincristine and actinomycin-D	1	1 SD	2
	Total	19 (18 group III, 1 group IV)		
Second-line therapy	High-dose steroids	1	1 SD	3
	Vinblastine and methotrexate	5	4 PR ≥ 2/3, 1 PD	2-28
	ALK inhibitors[a]	2	2 PR ≥ 2/3	19-21
	Ifosfamide-based chemotherapy	1	1 PD	3
	Total	9		

The outcomes reported in this series are comparable to what has been published by the German cooperative Weichteilsarkom Studiengruppe (Kube et al, 2018), consisting of 38 paediatric patients treated between 2000 and 2014, with reported 5-year EFS and OS rates of 74% and 91%, respectively.

In this series, 18 patients initially received systemic therapy, most frequently consisting of alkylator-based regimens (n=11). Objective responses were observed after primary systemic therapy in 5/18 patients: n=2 with vincristine/dactinomycin/ifosfamide/doxorubicin; n=1 with ifosfamide/vincristine/dactinomycin; n=1 with methotrexate/vinblastine/dexamethasone/ ibuprofen; and, n=1 with cefaclor. Because of the treatment period summarised in this publication took place mainly before the approval of ALK inhibitors, only 1 patient received treatment with crizotinib (starting dose not provided). This patient initially received previous systemic therapy regimens consisting of methotrexate/vinblastine/dexamethasone and vincristine/dactinomycin/cyclophosphamide /ibuprofen/ methylprednisolone, and then achieved a response with crizotinib. In this series, 3 patients had recurrent IMT; all 3 received regimens consisting of vincristine/dactinomycin/cyclophosphamide that led to tumour shrinkage, although only 1 of these patients achieved a CR and 2 were alive with disease 2.1 and 3.4 years following treatment.

In another series of 20 adult and paediatric patients (age range: 5-77 years) with IMT (ALK-positive= 12, under assessment = 8). Thirteen patients (65%) received systemic treatment with an anthracycline-based regimen, and 7 (35%) received methotrexate and vinorelbine/vinblastine (Baldiet al, 2019). In 12 evaluable patients, responses were as follows: 1 CR (8%), 6 PR (50%), 2 stable disease (17%), 3 PD (25%), for an ORR = 58%.

While the findings summarised above support a benefit for chemotherapy in unresectable, recurrent, or refractory IMT, the authors also point to a benefit for crizotinib and other targeted therapies as the tumour responses observed with ALK inhibitors, specifically crizotinib, are comparable or superior to what has been observed with chemotherapy and other systemic treatments.

Collectively, the ORR, CR rate, and the durability of responses reported in Study ADVL0912 (N=14 paediatric patients) demonstrate improvement in antitumour activity over available systemic therapies for paediatric patients with unresectable, recurrent, or refractory IMT. ORR for paediatric patients with ALK- positive IMT was 85.7% (95% CI: 60.1, 96.0) across all dose levels, with an ORR of 91.7% (95% CI: 64.6, 98.5) at 280mg/m2BID (N=12). CRs were observed in 35.7% (5/14) across dose levels, with CR observed in 41.7% (5/12) of patients treated at 280mg/m2BID. For the 12 objective responses, the responses were rapid, with a median TTR of 1.0 month corresponding to the approximate time of the first on-treatment tumour scan.

Additionally, objective responses were durable, with a median DR of 14.8 months (range: 2.8 to 48.9 months) for the 12 responders. Of note, the published results from Study ADVL0912, along with the data from the EORTC CREATE study, prompted the US NCCN to recommend the use of crizotinib as the standard of care for locally advanced or metastatic ALK-positive IMT in their 2018 clinical practice guidelines (NCCN 2018 Guidelines[b]).

2.4.3 Discussion on clinical efficacy

Crizotinib is a first-in-class inhibitor of ALK, MET/HGFR, ROS1, and RON RTKs which received approval for the treatment of patients with NSCLC in EU and recently in the US for the treatment of paediatric patients 1 year of age and older and young adults with relapsed or refractory systemic ALK-positive-ALCL and in unresectable, recurrent, or refractory ALK-positive IMT.

The MAH is seeking an extension of the original indication for crizotinib to include treatment of paediatric patients (age ≥ 6 to < 18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and with unresectable, recurrent, or refractory ALK-positive inflammatory myofibroblastic tumour (IMT).

Design and conduct of clinical studies

Efficacy data are mainly based on these 2 non-comparative studies. Study ADVL0912 was a phase I/II trial with a dose-escalation part and a dose expansion part. Efficacy population of study ADVL0912

includes 22 paediatric patients with ALK-positive ALCL and 14 paediatric patients with ALK-positive IMT. Study A8081013 is a supportive ongoing phase Ib trial in which 3 paediatric patients with ALK-positive ALCL and 2 paediatric patients with ALK-positive IMT were included.

It is acknowledged that a randomisation trial in this paediatric population would be difficult and that it would be difficult to enrol enough subjects in these rare populations to fully power a randomised trial. However, it should be noted that only descriptive data are provided which could not convincingly demonstrate improvement of the efficacy of crizotinib over existing treatments. In view of the unmet medical need in targeted paediatric setting, the combined phase 1/2 study design is anyway considered appropriate to establish a recommended dose to test by the phase 1 part and to detect the evidence of antitumour activity of single agent crizotinib in the phase 2 part of this open label single-arm study. The data obtained from historical comparator studies for other available treatments could serve to assist with the interpretation and further support the relevance of efficacy data from the submitted single-arm studies, rather than demonstrate the superior efficacy of crizotinib over a comparator group in paediatric population.

Pivotal Study ADVL0912 was a phase I/II trial with a dose-escalation part and a dose expansion part. Primary endpoints were established to estimate the MTD and the RP2D administered orally twice daily to children with relapsed/refractory solid tumours and ALCL and to define the toxicities and pharmacokinetics of crizotinib.

Efficacy was assessed as part of secondary endpoints, which included objective response (CR, CRu or PR), duration of response (DR) and time to tumour response (TTR). Disease response was assessed using RECIST criteria for solid tumours, the International Working Group (IWG1) response criteria for ALCL and the revised Cheson criteria for response assessment. Efficacy assessments and antitumour activity were only considered as secondary endpoints in this study. It is to be noted that secondary endpoints are usually not considered to be sufficient to influence B/R assessment, however, results from the two submitted studies, based on the secondary endpoints, are considered clinically meaningful. Efficacy endpoints were analysed in all patients who received at least 1 dose of crizotinib with measurable or evaluable disease at baseline by Investigator assessment or per central review.

Study A8081013, is an ongoing supportive study aiming to assess the efficacy, safety, and PK of crizotinib in patients whose tumours were found to have a translocation, mutation, or amplification involving the ALK gene locus, in tumour types other than NSCLC.

This study is also part of the PIP that has been agreed for crizotinib with the PDCO in 2019 for the treatment of ALCL and treatment of IMT.

Efficacy data and additional analyses

The efforts made by the MAH in order to collect and analyse the audit findings are acknowledged. It should be noted that the findings are more qualifying to "deficiencies" than protocol deviations that can be collected in a more standardized trial. Four Major disease outcome/Response Deficiency deviations that could impact the efficacy results analysis were reported. When looking into the details of these deficiencies within the annex provided by the MAH, it seems that only one major deficiency could have an impact since the CT scan done for one patient reports measurable lesions when only non-measurable disease is reported for this patient. The 3 other major deficiencies concern the absence of signature of the spreadsheet of disease response by the investigator, a dose interruption due to scan delays and the change of imaging method during the study for one patient. In one hand and since the search for such information was done retrospectively, the MAH states that it has been done "to the extent possible", which can lead to some bias in the analysis. On the other hand, when assessing the detailed list of major deviations provided in appendix with a potential impact on efficacy, which was the major concern for discussion, none of the deviations appear to question study results' reliability.

Two starting doses were evaluated: 165 mg/m² BID and 280 mg/m² BID. A total of the 22 paediatric patients who received at least 1 dose of crizotinib were enrolled in ALCL Group, from which 20 patients had discontinued from study and 2 were on treatment at the date of study closure and were switched to commercial supplies. Around 20% of patients discontinued treatment after physician decision or refusal of further protocol therapy. The MAH couldn't detail the reasons of treatment discontinuation upon physician decision since the study was not designed to collect such details.

Fourteen paediatric patients who received at least 1 dose of crizotinib were enrolled in IMT Group, from which 11 had discontinued from the study and 3 were on treatment at the date of study closure. The most frequent reasons for discontinuation were adverse event and physician decision. Overall, patients had a median age of 11 years (from 3 to 16 years, patients over 21 years old excluded from this analyses) and 86.4% of them had measurable disease at baseline. All patients had received prior therapies, as per inclusion criteria. The most frequently reported prior therapies were multi-agent chemotherapy (22 patients in the ALCL group, 100%), surgery, and radiation. No satisfactory responses were provided regarding censoring rules. These latter couldn't be implemented for the pivotal study ADVL0912 with no sensitivity nor supportive applicable analyses.

Given the design of the study and the low number of patients enrolled, it is hard to draw clear conclusions from a statistical point of view, however, efficacy results are quite outstanding:

ORR:

The ORR for the 22 enrolled ALCL patients was 86.4% (95% CI: 66.7, 95.3) for both dose level groups (6 patients received 165 mg/m² BID with an ORR of 83.3% and 16 patients received 280 mg/m² BID and achieved an ORR of 87.5%).

The ORR for the 14 patients in the IMT group was 85.7% (95%CI: 60.1, 96.0) across all dose levels; 1 patient enrolled at the 100 mg/m2 BID dose level and did not have an objective response, 1 patient enrolled at 165 mg/m² BID and had an objective response, and 12 patients enrolled at 280 mg/m² BID and had an ORR of 91.7%.

CR:

CRs were quite high across study groups and observed in 77.3% (17/22) of patients in the ALCL group across both dose levels, and in 83.3% (5/6) and 75.0% (12/16) of patients at the 165 mg/m² BID and 280 mg/m² BID dose levels, respectively.

In the IMT group, CRs were observed in 35.7% (5/14) of paediatric patients across dose levels. No patient at 100 mg/m² BID and 165 mg/m² BID dose levels had a CR; at the 280 mg/m² BID dose level, CRs were observed in 41.7% (5/12) of patients.

ORR and CR results remained stable across all age groups, despite the absence of patients under the age of 3, also including ALCL patients between 18 and 21.

These results are very encouraging despite the small number of patients enrolled. It is to be noted that 100% of patients between 18 and 21 years-old treated with crizotinib for ALCL achieved CR.

DR:

The median DR was 3.6 months (range: 0.0 to 15.0 months) for the responders across both dose levels in the ALCL group; 5 patients with objective tumour response at the 165 mg/m² BID dose level had a median DR of 6.9 months and 14 patients with objective tumour response at the 280 mg/m² BID dose level had a median DR of 2 months. The DR is quite underestimated here because of the 10 patients who proceeded to HSCT after completing objective response (2 at the 165 mg/m² BID dose

level and 8 at the 280 mg/m² BID dose level). A longer median DR (9.2 months) is noted for ALCL patients who did not receive a HSCT.

DR for patients with IMT were more durable, with a median DR of 14.8 months (range: 2.8 to 48.9 months) for the 12 responders. Eight of the 11 enrolled patients in the 280 mg/m² BID completed the study without any event.

TR:

Rapid responses were observed in the ALCL group with a median time to response (TTR) of 0.9 months (0.8 to 2.1 months) across both dose levels. Median TTR was comparable between the 165 mg/m² BID and the 280 mg/m² BID dose level groups (0.9 months and 1 month, respectively).

Some patients in the ALCL group have quickly been in CR but did not receive HSCT before 20 months of treatment. Reasons for not receiving HSCT are not clear. Moreover, it is unclear for how long the patients were followed before censoring occurred in the IMT group. The MAH was asked to provide post-transplant efficacy and safety data, 100-day mortality and GvHD rates and is mainly stating that no such requested data could be provided since the pivotal study was completed 10 years ago when standards and clinical practices were much different and that no guidance was planned for proceeding to HSCT within the protocols. No such data were thus collected, which also applies for patients for whom crizotinib was used as a bridge to HSCT. From the supportive study A8081013, very scarce data were available

For IMT group, the responses were also quite rapid and comparable to those observed in ALCL group, with a median TTR of 1 month (0.8 to 4.6 months) across the two dose levels.

Dosing recommendations:

In both dose levels, crizotinib presents similar efficacy results. Meanwhile, data at 280 mg/m² BID are more robust considering the larger number of enrolled patients (most patients with ALCL (16 of 22) and most patients with IMT (12 of 14) were treated at 280 mg/m² BID). Moreover, due to the paediatric-inadequate dosage form, dose adjustments below 200 mg are not possible and the 280 mg/m² BID dose is allowing dose reduction recommendations. These results should be interpreted with caution since the number of patients in each of the groups is small and would be sensitive to shifts in the data.

Moreover, two different formulations were used within the submitted studies including the oral solution which is not available on the market but were determined as bioequivalent during product development. An efficacy analysis by formulation was also provided but no clear conclusions regarding formulation-effect could be drawn for efficacy parameters compared to the previously assessed pooled data considering the very limited number of patients especially for the oral solution group (6 each in the ALCL and the IMT group). Overall, 7 patients switched formulations during the study with 1 patient switching from capsules to liquid. No reasons for the reported switches were provided by the MAH stressing that these information were not collected within the CRF. The MAH though confirmed that a paediatric microsphere encapsulated formulation is under development with 3 strengths: 20 mg, 50 mg, and 150 mg and a type 2 variation is planned for Q2 2023 in order to seek the line extension.

Patients with CNS involvement were not eligible in the submitted studies. CNS involvement are rare in children and adolescents with ALK+ ALCL and since there is no evidence of anti-leukemic activity of crizotinib in the excluded population of patients with CNS involvement/tumours/metastases, the MAH was asked to add a paragraph in section 5.1 of the SmPC in order to appropriately reflect this exclusion criteria which has been provided and the issue is then solved.

Supportive study

A8081013 study enrolled a total of 5 paediatric patients (3 with relapsed or refractory systemic ALK-positive ALCL and 2 with unresectable, recurrent, or refractory ALK-positive IMT) as of the data cut-off date of 03 September 2019. Paediatric patients represent ~ 11.4% (5/44) of the population enrolled in this study.

Given the inclusion criteria, the paediatric population is represented by adolescents, among the 3 patients with ALK-positive ALCL, 2 were males aged 15 years and 1 was female aged 16 years. Two patients with ALK-positive IMT were also enrolled, one was a 16 years old male and the other one was a 17 years old female patient.

At time of date cut-off, all patients (but one treated for IMT) received at least one prior therapy. For the 3 ALCL patients, median duration of treatment was 77.1 months (range: 2.9 to 77.7 months) and dosing interruption was reported in one patient after a dose reduction from 250 mg BID to 200 mg BID. The durations of treatment for the 2 IMT patients were 75.7 months and 76.3 months.

Of the 2 paediatric patients with ALK-positive IMT in Study A8081013, one patient achieved a PR (DR: 69 months, PFS: 70.4 months) and 1 patient had a best overall response of stable disease with a PFS of 51 months at data cut-off date. Both patients were still on treatment as of the data cut-off date. Of the 3 patients enrolled with ALCL, two patients had objective responses with one patient having a CR (DR: 31.2 months, PFS: 32 months) while the second had a PR (27.6 months, PFS: 28.8 months). Both patients were still on treatment at data cut-off date while the third patient had a best overall response of stable disease with a PFS of 2.8 months.

Efficacy data from this supportive study do not allow to draw robust conclusions for efficacy given the limitations in study design (even though it includes OS and PFS as secondary endpoints) and the limited number of paediatric patients enrolled. This being said, efficacy results from Study A8081013 are consistent and supportive of those reported within the pivotal study.

Historical Control:

The MAH provided a short literature review of alternative treatment options in paediatric R/R ALCL and IMT. Despite the absence of comparability due to study design, this is informative.

Complex high-dose therapies associations including irradiation, etoposide, cyclophosphamide, busulfan, carmustine, melphalan, cytarabine and vinblastine followed by HSCT are currently used for paediatric patients in the R/R ALCL setting with significant toxicities considering the targeted population.

There is no standard of care regimen for the treatment of R/R paediatric ALCL and ORRs are of approximately 30-83% for currently used multiagent chemotherapy and 53-83% for monotherapy regimens (brentuximab and vinblastrine).

For ALCL patients, the MAH elaborates on the results from the French AcSé program. Since Crizotinib has shown significant clinical activity in relapsed/refractory ALK+ ALCL in small cohorts of patients and in order to avoid a generalized off-label use and allow for an equal and nationwide access to crizotinib, the French National Cancer Institute (INCa, state organization) launched the AcSé program in patients aged 1 year and older with advanced ALK+ ALCL. Median age was 21 years and the median number of prior chemotherapy lines was 2 including brentuximab in 66% of patients. Among the 15 evaluable patients, 10 achieved an OR (67%, 95% CI [42%-85%]) (9CR, 1PR) and 5 experienced a disease progression. The response rate was similar in paediatric patients (67%, 95% CI [24%, 94%]) and in adults (6/9, 67%, 95% CI [31%, 91%]) and with a median follow-up of 12 months, the median PFS was 11.6 months (95% CI [1.41, NA]). A compassionate use program where Crizotinib was administered as monotherapy to 11 ALK+ lymphoma patients who were resistant/refractory to

cytotoxic therapy also pointed out very encouraging results as the ORR was of 90.9%; (95% CI = 58.7% to 99.8%).

All these results are in line with the ADVL0912 pivotal study findings where the ORR for the 22 enrolled ALCL patients was 86.4% (95% CI: 66.7, 95.3) for both dose level groups with high CR rates. It should be noted that 100% of patients between 18 and 21 years-old treated with crizotinib for ALCL achieved CR.

Efficacy results obtained within the small cohorts of patients treated for IMT report comparable ORR even though the 2018's results presented by the MAH for the EORTC 90101 CREATE study are not up to date since the final analysis as of data cut-off on 28th January 2021 describe an ORR reaching 66.7% (95% CI 34.9-90.1%) in ALK+ IMT patients and a 3-year OS rates of 83.3% (95% CI 48.2-95.6).

These supplementary historical data for the IMT indication are as well very encouraging and altogether in line with the results provided within this application where the ORR for the 14 patients in the IMT group was of 85.7% (95%CI: 60.1, 96.0) across all dose levels.

The MAH discussed in depth the 5 literature references provided describing two abrupt relapses cases from which one patient was switched to ceritinib with rapid clinical improvement and a durable CR. The other patient resumed crizotinib and remained in CR. There was an additional case of a patient progressing while receiving crizotinib, the MAH broadly discussed this case which was not an abrupt relapse one. The data provided regarding abrupt relapses in ALCL and IMT patients are limited at this time and definitely need more characterization since the mechanism is not known yet. Minimum inhibition duration and thus treatment duration to avoid such early relapses after treatment discontinuation also need to be better characterized. It is highly recommended that the MAH closely monitors documented abrupt relapses cases in the PSURs.

The final approved indication was as follows: " The treatment of paediatric patients (age ≥ 6 to < 18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and for the treatment of paediatric patients (age ≥6 to <18 years) recurrent or refractory anaplastic lymphoma kinase (ALK)-positive unresectable inflammatory myofibroblastic tumour (IMT)".

In order to address the expressed concerns regarding the small number of patients enrolled and possible data gaps, the MAH proposed to implement PAMs requested by the FDA to further assess the PK and efficacy of crizotinib at the lower dose of 165 mg/m^2 BID in paediatric patients. Although it was difficult to amend the study protocols, these additional data are highly expected, the MAH confirmed that paediatric patients will also be enrolled at 280 mg/m^2 BID and efficacy analysis performed in this setting.

As the MAH has processed and provided the audit findings as a surrogate to non processed protocol deviations, since these latter do not appear to challenge the reproducibility nor the reliability of the efficacy results, and since all published results from the supportive studies and supplementary cohorts still confirm the quite outstanding tumour activity of crizotinib in the sought indications, as revised above.

2.4.4 Conclusions on the clinical efficacy

The results of a single pivotal non-comparative study shows a clinically relevant activity of crizotinib in the two claimed indications and in view of the unmet medical need in the targeted paediatric setting, the combined phase 1/2 study design is considered appropriate. Data obtained from historical comparator studies were also submitted and could serve to assist with the interpretation of efficacy data from the submitted single-arm studies. Efficacy results (ORR, CR and rapid and durable) were quite outstanding

and remained stable across all age groups including ALCL patients between 18 and 21. The MAH provided an exhaustive review of all published data for crizotinib within the two claimed indications in the paediatric setting and all results from the small provided cohort were supportive of the pivotal study results.
The available data regarding abrupt relapses in ALCL and IMT patients are limited and definitely need more characterization since the mechanism is not known yet. Minimum inhibition duration and thus treatment duration to avoid such early relapses after treatment discontinuation also need to be better characterized. It is highly recommended that the MAH closely monitors documented abrupt relapses cases in the PSURs.

Lastly, as two different formulations were used within the submitted studies including the oral solution which is not available on the market, an efficacy analysis by formulation was provided but no clear conclusions regarding formulation-effect could be drawn for efficacy parameters. It should be noted that a paediatric microsphere encapsulated formulation is under development with 3 strengths: 20 mg, 50 mg, and 150 mg and a type 2 variation is planned for Q2 2023 in order to seek a line extension.

The following measures are considered necessary to address issues related to efficacy:

1. The MAH will further assess the PK and efficacy of crizotinib at the lower dose of 165 mg/m^2 BID and in paediatric patients enrolled at 280 mg/m^2 BID and efficacy analysis performed in this setting.

2.5 Clinical safety

2.5.1 Introduction

Crizotinib (Xalkori) as monotherapy is approved in Europe for the following indications:

• 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 anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)

• The treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC)

Therefore, the safety profile is characterized in adult population with solid ALK positive or ROS-1 positive NSCLC.

The most common adverse reactions in adult patients with either ALK-positive or ROS1-positive NSCLC are vision disorder, nausea, diarrhoea, vomiting, oedema, constipation, elevated transaminases, fatigue, decreased appetite, dizziness, and neuropathy.

In this application for an extension of indication in children with ALK-positive anaplastic large cell lymphoma (ALCL) or Inflammatory myofibroblastic tumour (IMT), the safety analysis population includes 25 paediatric patients with ALK-positive ALCL and 16 paediatric patients with ALK-positive IMT.

To support this application, safety data of 69 paediatric patients with other tumour types were further provided.

These data were retrieved from the two following non comparatives studies:

- ADVL0912, a Phase 1/2 Study of PF-02341066, An Oral Small Molecule Inhibitor of Anaplastic Lymphoma Kinase and c-MET, in Children with Relapsed or Refractory Solid Tumors and Anaplastic Large Cell Lymphoma, which included 22 patients with ALK+ ALCL, 14 Patients with ALK+ IMT and 69 patients with other tumour types.

At the time of the submission, this study was completed (last patient last visit: 19 January 2018)

- A8081013, a Phase 1b Open-Label Study of the Safety and Clinical Activity of Crizotinib (PF-02341066) in Tumors with Genetic Events Involving the Anaplastic Lymphoma Kinase Gene Locus, which included 3 patients with ALK+ ALCL and 2 Patients with ALK+ IMT.

At the time of this submission, this study was ongoing (data cutoff date: 03 September 2019).

Patients received the treatment until disease progression or as long as there was evidence of clinical benefit in the judgment of the Investigator.

The data were presented separately by study as well as pooled sets.

- The term "pool" is only used when data are combined between the 2 studies (Study ADVL0912 and Study A8081013)

- The term "group" is only used when data are from an individual study, ie either Study ADVL0912 or Study A8081013.

4 pooled dataset were described: "Pooled ALCL", "Pooled IMT", "Pooled ALCL+IMT" and "Pooled All tumour types".

Additional informations in the summary of safety data are provided from study ANHL12PI. Study ANHL12P1 is a randomized Phase 2 NCI-sponsored trial of brentuximab vedotin (BV) or crizotinib (CZ) in combination with chemotherapy for newly diagnosed patients with ALCL. Patients were <22 years of age at the time of study enrollment.

Patient exposure

Study ADVL0912

- **ALCL group**

The median duration of treatment was 5.11 months (range: 1.8 to 82.3 months) with a median of 4.21 months (range: 1.8 to 17.2 months) at 280 mg/m^2 BID (N = 16). Of note, 11 paediatric patients permanently discontinued crizotinib treatment to undergo HSCT. Median RD was 92.72% (range: 63.9% to 101.0%) (*Table 34*).

Table 34 Duration of Treatment by Dose Level (ALCL, Age < 18 years) – Safety Analysis Set (Protocol ADVL0912)

	Crizotinib 165 mg/m^2 BID (N=6)	Crizotinib 280 mg/m^2 BID (N=16)	Total (N=22)
Duration of Treatment (Months)			
n	6	16	22
Mean	39.29	5.69	14.85
Median	33.00	4.21	5.11
Std Dev	37.815	4.828	24.326
Range (min, max)	(3.8, 82.3)	(1.8, 17.2)	(1.8, 82.3)
Category (Months)			
< 3	0	7 (43.8)	7 (31.8)
3 - < 6	2 (33.3)	4 (25.0)	6 (27.3)
6 - < 12	1 (16.7)	2 (12.5)	3 (13.6)
≥ 12	3 (50.0)	3 (18.8)	6 (27.3)

Duration of Treatment (in Months) = (Last Treatment Date - First Treatment Date + 1) / 30.4375

Table 35 Relative Dose and Average Daily Dose of Crizotinib by Dose Level (ALCL, Age < 18 years) - Safety Analysis Set (Protocol ADVL0912)

	Crizotinib 165 mg/m² BID (N=6)	Crizotinib 280 mg/m² BID (N=16)	Total (N=22)
Relative Dose (RD) (%) Based on Dose in Unit mg/m²			
n	6	16	22
Mean	90.49	88.68	89.17
Median	92.76	92.60	92.72
Std Dev	7.938	11.224	10.280
Range (min, max)	(80.1, 98.4)	(63.9, 101.0)	(63.9, 101.0)
Relative Dose (RD) (%) Based on Dose in Unit mg			
n	6	16	22
Mean	90.42	89.38	89.66
Median	92.54	91.56	92.17
Std Dev	8.545	9.364	8.958
Range (min, max)	(78.4, 99.6)	(66.1, 99.7)	(66.1, 99.7)
Average Daily Dose (mg/m²/day)			
n	6	16	22
Mean	338.76	522.78	472.59
Median	328.90	533.44	524.97
Std Dev	29.317	50.663	95.260
Range (min, max)	(313.0, 394.3)	(385.4, 583.9)	(313.0, 583.9)
Average Daily Dose (mg/day)			
n	6	16	22
Mean	387.38	731.88	637.92
Median	402.92	717.80	590.02
Std Dev	127.158	211.199	245.703
Range (min, max)	(212.6, 550.1)	(436.6, 1082.3)	(212.6, 1082.3)

Relative Dose (RD) (%) = 100 * [Overall Cumulative Dose] / [Intended Cumulative Dose]
Average Daily Dose = Overall Cumulative Dose / Total Days on Treatment

- **IMT group**

The Median duration of treatment for patients with IMT at the dose level of 280 mg/m² BID (N = 12) was 18.86 months (range 2.8 to 41.6 months, Table *36*). Median RD was 93.30% (range: 65.4% to 100.7%)

Table 36 Duration of Treatment by Dose Level (IMT, Age < 18 years) – Safety Analysis Set (Protocol ADVL0912)

	Crizotinib 100 mg/m² BID (N=1)	Crizotinib 165 mg/m² BID (N=1)	Crizotinib 280 mg/m² BID (N=12)	Total (N=14)
Duration of Treatment (Months)				
n	1	1	12	14
Mean	22.01	73.63	18.73	22.88
Median	22.01	73.63	18.86	20.52
Std Dev	NE	NE	11.233	17.912
Range (min, max)	(22.0, 22.0)	(73.6, 73.6)	(2.8, 41.6)	(2.8, 73.6)
Category (Months)				
< 3	0	0	1 (8.3)	1 (7.1)
3 - < 6	0	0	1 (8.3)	1 (7.1)
6 - < 12	0	0	2 (16.7)	2 (14.3)
≥ 12	1 (100)	1 (100)	8 (66.7)	10 (71.4)

Duration of Treatment (in Months) = (Last Treatment Date - First Treatment Date + 1) / 30.4375

Table 37 Relative Dose and Average Daily Dose of Crizotinib by Dose Level (IMT, Age < 18 years) - Safety Analysis Set (Protocol ADVL0912)

	Crizotinib 100 mg/m² BID (N=1)	Crizotinib 165 mg/m² BID (N=1)	Crizotinib 280 mg/m² BID (N=12)	Total (N=14)
Relative Dose (RD) (%) Based on Dose in Unit mg/m²				
n	1	1	12	14
Mean	100.68	100.17	85.52	87.65
Median	100.68	100.17	89.52	93.30
Std Dev	NE	NE	12.180	12.444
Range (min, max)	(100.7, 100.7)	(100.2, 100.2)	(65.4, 99.2)	(65.4, 100.7)
Relative Dose (RD) (%) Based on Dose in Unit mg				
n	1	1	12	14
Mean	100.71	100.07	84.61	86.86
Median	100.71	100.07	89.15	92.99
Std Dev	NE	NE	12.518	12.862
Range (min, max)	(100.7, 100.7)	(100.1, 100.1)	(64.5, 98.5)	(64.5, 100.7)
Average Daily Dose (mg/m²/day)				
n	1	1	12	14
Mean	201.67	428.25	497.72	471.62
Median	201.67	428.25	518.65	488.49
Std Dev	NE	NE	55.140	94.615
Range (min, max)	(201.7, 201.7)	(428.2, 428.2)	(418.2, 558.5)	(201.7, 558.5)
Average Daily Dose (mg/day)				
n	1	1	12	14
Mean	296.76	420.59	499.08	479.02
Median	296.76	420.59	463.36	438.80
Std Dev	NE	NE	163.917	161.010
Range (min, max)	(296.8, 296.8)	(420.6, 420.6)	(264.1, 804.8)	(264.1, 804.8)

Relative Dose (RD) (%) = 100 * [Overall Cumulative Dose] / [Intended Cumulative Dose]
Average Daily Dose = Overall Cumulative Dose / Total Days on Treatment

Study A8081013

For the 3 paediatric patients in ALCL group, median duration of treatment was 335.10 weeks (77.06 months) (range: 12.6 to 338.0 weeks [2.90 to 77.73 months]). For the 2 paediatric patients, the durations of treatments were 329.10 weeks (75.68 months) and 331.6 weeks (76.26 months) (Table *38*).

Table 38 Duration of Crizotinib Treatment (Summary of Weeks on Drug), Paediatric Subjects - Safety Analysis Population (Protocol A8081013)

	ALCL (N=3)	IMT (N=2)	ALCL+IMT (N=5)
Duration of Treatment (Weeks)			
n	3	2	5
Mean	228.57	330.35	269.28
Median	335.10	330.35	331.60
Std Dev	187.038	1.768	143.528
Range (min,max)	(12.6, 338.0)	(329.1, 331.6)	(12.6, 338.0)
Category (Weeks)			
≤ 4	0	0	0
> 4 – ≤ 12	0	0	0
> 12 – ≤ 24	1 (33.3)	0	1 (20.0)
> 24 – ≤ 52	0	0	0
> 52 – ≤ 104	0	0	0
> 104 – ≤ 156	0	0	0
> 156 – ≤ 208	0	0	0
> 208 – ≤ 260	0	0	0
> 260 – ≤ 312	0	0	0
> 312	2 (66.7)	2 (100.0)	4 (80.0)

Table 39 Dose Intensity of Crizotinib, Overall, Paediatric Subjects - Safety Analysis Population (Protocol A8081013)

	ALCL	IMT	ALCL+IMT
Cumulative Dose (mg)			
n	3	2	5
Mean	749016.7	1137375	904360.0
SD	615103.9	10429.83	484200.6
Median	1030800	1137375	1130000
Range (min,max)	(43500, 1172750)	(1130000, 1144750)	(43500, 1172750)
Actual Dose Intensity (mg/day)			
n	3	2	5
Mean	476.6	491.8	482.7
SD	35.58	1.95	26.52
Median	494.3	491.8	493.2
Range (min,max)	(436, 500)	(490, 493)	(436, 500)
Relative Dose Intensity (%)			
n	3	2	5
Mean	95.3	98.4	96.5
SD	7.12	0.39	5.31
Median	98.9	98.4	98.6
Range (min,max)	(87, 100)	(98, 99)	(87, 100)

Cumulative Dose is the actual total dose received in study. Intended Dose Intensity (per day) is the intended total dose per cycle divided by the intended number of days in a cycle; for this study it is 500 mg/day. Actual Dose Intensity (per day) is the actual total dose per cycle divided by the actual number of days in cycle. Relative Dose Intensity is the actual dose intensity divided by the intended dose intensity multiplied by the 100%.
Date of Data Snapshot: 18OCT2019 and Date of Data Cutoff: 03SEP2019

Pooled Data (Study ADVL0912 and Study A8081013)

In the ALCL pool, the median duration of treatment was 5.1 months (range 1.8-82.3 months). In the IMT pool, the median duration of treatment was 21.8 months (range 2.8-76.3 months) (Table *40*).

Table 40 Crizotinib Paediatric Submission Duration of Treatment by Tumour Type (All Tumour Types, Age < 18 years) - Safety Analysis Population (Paediatric Pool)

	ALCL (N=25)	IMT (N=16)	ALCL + IMT (N=41)	All Tumor Types (N=110)
Duration of Treatment (Months)				
n	25	16	41	110
Mean	19.38	29.52	23.33	12.17
Median	5.13	21.75	10.71	2.76
Std Dev	28.784	24.636	27.382	21.412
Range (min, max)	(1.8, 82.3)	(2.8, 76.3)	(1.8, 82.3)	(0.1, 88.8)
Category (Months)				
< 3	8 (32.0)	1 (6.3)	9 (22.0)	60 (54.5)
3 -< 6	6 (24.0)	1 (6.3)	7 (17.1)	13 (11.8)
6 -< 12	3 (12.0)	2 (12.5)	5 (12.2)	10 (9.1)
12 -< 18	3 (12.0)	0	3 (7.3)	6 (5.5)
18 -< 30	0	8 (50.0)	8 (19.5)	9 (8.2)
30 -< 54	0	1 (6.3)	1 (2.4)	2 (1.8)
54 -< 78	3 (12.0)	3 (18.8)	6 (14.6)	7 (6.4)
≥ 78	2 (8.0)	0	2 (4.9)	3 (2.7)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 03SEP2019)
Duration of Treatment (in Months) = (Last Treatment Date - First Treatment Date + 1) / 30.4375

Demographic and other characteristics of study population

Study ADVL0912

The majority of the patients were White and most of the patients' age ranged from 6 years to <12 years old (Table *41*). The most frequently reported (>30% of patients) prior therapies for paediatric patients in the total group (patients with ALCL, IMT, or other tumours) were multi-agent systemic chemotherapy, surgery, and limited radiation (Table *42*).

The most frequently reported (>30% of patients) prior therapies for paediatric patients by tumour group were the same as those for all patients: multi-agent systemic chemotherapy (ALCL group), surgery (IMT group), and multi-agent systemic chemotherapy, surgery, limited radiation, bone marrow transplant, and single agent systemic chemotherapy (Other Tumours group).

Table 41 Demographic Characteristics by Tumour Type (All Tumour Types, All Dose Levels, Age < 18 years) - Safety Analysis Set (Protocol ADVL0912)

	ALCL (N=22)	IMT (N=14)	Other Tumors (N=69)	Total (N=105)
Age, years				
Mean (SD)	9.7 (3.78)	7.1 (3.53)	8.4 (4.00)	8.5 (3.93)
Median	11.0	6.5	8.0	8.0
Range (min, max)	(3, 16)	(2, 13)	(1, 17)	(1, 17)
Age Category, n (%)				
<2	0	0	1 (1.4)	1 (1.0)
2-<6	4 (18.2)	4 (28.6)	18 (26.1)	26 (24.8)
6-<12	11 (50.0)	8 (57.1)	32 (46.4)	51 (48.6)
12-<18	7 (31.8)	2 (14.3)	18 (26.1)	27 (25.7)
Gender, n (%)				
Male	17 (77.3)	5 (35.7)	30 (43.5)	52 (49.5)
Female	5 (22.7)	9 (64.3)	39 (56.5)	53 (50.5)
Race, n (%)				
White	11 (50.0)	10 (71.4)	53 (76.8)	74 (70.5)
Black or African American	5 (22.7)	1 (7.1)	5 (7.2)	11 (10.5)
Asian	2 (9.1)	0	4 (5.8)	6 (5.7)
Unknown	4 (18.2)	3 (21.4)	7 (10.1)	14 (13.3)
Ethnicity, n (%)				
Hispanic or Latino	3 (13.6)	3 (21.4)	6 (8.7)	12 (11.4)
Not Hispanic or Latino	18 (81.8)	8 (57.1)	58 (84.1)	84 (80.0)
Unknown	1 (4.5)	3 (21.4)	5 (7.2)	9 (8.6)

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each tumor type.
Age is derived by Date of Enrollment and Birth Date.

Table 42 Prior Therapy by Tumour Type (All Tumour Types, All Dose Levels, Age < 18 years) - Safety Analysis Set (Protocol ADVL0912)

Number (%) of Subjects	ALCL (N=22) n (%)	IMT (N=14) n (%)	Other Tumors (N=69) n (%)	Total (N=105) n (%)
Prior Therapy Type: [1]				
Bone Marrow Transplant	2 (9.1)	0	24 (34.8)	26 (24.8)
Chemotherapy Multi-Agent Systemic	22 (100)	3 (21.4)	61 (88.4)	86 (81.9)
Chemotherapy Non-Cytotoxic	0	0	7 (10.1)	7 (6.7)
Chemotherapy Not Otherwise Specified (NOS)	1 (4.5)	1 (7.1)	2 (2.9)	4 (3.8)
Chemotherapy Single Agent Systemic	2 (9.1)	0	24 (34.8)	26 (24.8)
Extensive Radiation	0	0	8 (11.6)	8 (7.6)
Immunotherapy	1 (4.5)	0	19 (27.5)	20 (19.0)
Limited Radiation	1 (4.5)	0	35 (50.7)	36 (34.3)
Oncolytic Virotherapy	0	0	1 (1.4)	1 (1.0)
Prior Therapy NOS	4 (18.2)	4 (28.6)	20 (29.0)	28 (26.7)
Radiotherapy Not Otherwise Specified	0	0	15 (21.7)	15 (14.3)
Surgery	2 (9.1)	8 (57.1)	49 (71.0)	59 (56.2)

[1] Prior therapy type is pre-filled on CRF page "Prior Therapy".

Study A8081013

ALCL group: Among the 3 paediatric patients in the ALCL group, 2 were males and both were 15 years old (1 White and 1 Asian), and 1 was female aged 16 years (Asian)

All 3 paediatric patients received at least 1 regimen of prior systemic therapy (Table 14.1.4.3.1 of the CSR). No paediatric patient had prior radiation therapy or surgery (Table 16.2.5.3.1.3.2 interim_compliance).

IMT group: The 2 paediatric patients in the IMT group were Asian, 1 female aged 17 years and 1 male aged 16 years

One (50.0%) paediatric patient received prior systemic therapy, and no patient received prior radiation therapy (Table 14.1.4.3.1 of the CSR). All the paediatric patients had prior surgery (Table 16.2.5.3.1.3.2 interim_compliance).

Table 43 Demographic Characteristics, Paediatric Subjects - Safety Analysis Population (Protocol A8081013)

	ALCL (N=3)	IMT (N=2)	ALCL+IMT (N=5)
Age, years			
Mean (SD)	15.3 (0.58)	16.5 (0.71)	15.8 (0.84)
Median	15.0	16.5	16.0
Range	(15.0, 16.0)	(16.0, 17.0)	(15.0, 17.0)
Age Category, n (%)			
<18	3 (100.0%)	2 (100.0%)	5 (100.0%)
Sex, n (%)			
Male	2 (66.7%)	1 (50.0%)	3 (60.0%)
Female	1 (33.3%)	1 (50.0%)	2 (40.0%)
Race, n (%)			
White	1 (33.3%)	0	1 (20.0%)
Black	0	0	0
Asian	2 (66.7%)	2 (100.0%)	4 (80.0%)
Other	0	0	0
Racial Designation for Asian, n (%)			
Japanese	1 (33.3%)	0	1 (20.0%)
Korean	0	0	0
Chinese	1 (33.3%)	2 (100.0%)	3 (60.0%)
Other	0	0	0

Pooled Data (Study ADVL0912 and Study A8081013)

The median (range) age of the patients across all tumour types was 8.0 (1, 17) years, with the majority being White across all 4 pools (ALCL pool, IMT pool, ALCL+IMT pool, All Tumour Types pool) (Table *44*).

Table 44 Crizotinib Paediatric Submission Demographic Characteristics by Tumour Type (All Tumour Types, Age < 18 years) - Safety Analysis Population (Paediatric Pool)

	ALCL (N=25)	IMT (N=16)	ALCL + IMT (N=41)	All Tumor Types (N=110)
Age, years				
Mean (SD)	10.4 (4.01)	8.3 (4.59)	9.6 (4.31)	8.8 (4.14)
Median	11.0	7.5	10.0	8.0
Range (min, max)	(3, 16)	(2, 17)	(2, 17)	(1, 17)
Age Category, n (%)				
<2	0	0	0	1 (0.9)
2-<6	4 (16.0)	4 (25.0)	8 (19.5)	26 (23.6)
6-<12	11 (44.0)	8 (50.0)	19 (46.3)	51 (46.4)
12-<18	10 (40.0)	4 (25.0)	14 (34.1)	32 (29.1)
Gender, n (%)				
Male	19 (76.0)	6 (37.5)	25 (61.0)	55 (50.0)
Female	6 (24.0)	10 (62.5)	16 (39.0)	55 (50.0)
Race, n (%)				
White	12 (48.0)	10 (62.5)	22 (53.7)	75 (68.2)
Black or African American	5 (20.0)	1 (6.3)	6 (14.6)	11 (10.0)
Asian	4 (16.0)	2 (12.5)	6 (14.6)	10 (9.1)
Unknown	4 (16.0)	3 (18.8)	7 (17.1)	14 (12.7)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 03SEP2019)
The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each tumor type.
Age is derived by Date of Enrollment and Birth Date.

Adverse events

A summary of treatment-emergent AEs of all-causality and treatment-related were presented by SOC and PT. In addition, AE summaries by PT or cluster terms in descending frequency were reported for all AEs (all-causality and treatment-related), and AEs with Grade ≥3 (Grades 3, or 4 and Grade 5, separately).

Cluster terms were created because the frequency of certain medical concepts or conditions were underestimated by the reliance on single MedDRA PTs (Table *45*). Thus, certain PTs were analysed in aggregate using cluster terms. Patients having more than 1 AE PT within a cluster term contributed 1 event to the cluster term at the highest grade observed. Cluster terms are presented using capital letters throughout this CSR while MedDRA PTs are written with only the first letter capitalised.

Table 45 Preferred Terms Included Per Cluster Term – Study ADVL0912 and Study A8081013

Cluster Number	Cluster Term	Preferred Terms (PTs)
1	VISION DISORDER	Chromatopsia, Diplopia, Halo vision, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual brightness, Visual impairment, Visual perseveration, Vitreous floaters
2	OESOPHAGITIS	Erosive oesophagitis, Necrotising oesophagitis, Oesophageal perforation, Oesophageal rupture, Oesophageal ulcer, Oesophageal ulcer haemorrhage, Oesophageal ulcer perforation, Oesophagitis, Oesophagitis haemorrhagic, Oesophagitis ulcerative
3	ABDOMINAL PAIN	Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness
4	STOMATITIS	Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis
5	OEDEMA	Eye swelling, Face oedema, Generalised oedema, Localised oedema, Oedema, Oedema peripheral, Periorbital oedema, Swelling
6	CHEST PAIN	Chest discomfort, Chest pain, Musculoskeletal chest pain, Non-cardiac chest pain
7	INTERSTITIAL LUNG DISEASE (ILD)	Acute interstitial pneumonitis, Acute lung injury, Acute respiratory distress syndrome, Alveolitis, Alveolitis necrotising, Diffuse alveolar damage, Eosinophilic pneumonia, Eosinophilic pneumonia acute, Hypersensitivity pneumonitis, Idiopathic pulmonary fibrosis, Interstitial lung disease, Pneumonitis, Pulmonary toxicity

Cluster Number	Cluster Term	Preferred Terms (PTs)
8	RADIATION INDUCED ILD	Pulmonary radiation injury, Radiation alveolitis, Radiation fibrosis - lung, Radiation pneumonitis
9	UPPER RESPIRATORY INFECTION	Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Upper respiratory tract infection
10	DYSPNOEA	Dyspnoea, Dyspnoea at rest, Dyspnoea exertional, Dyspnoea paroxysmal nocturnal, Nocturnal dyspnoea, Orthopnoea
11	COUGH	Cough, Productive cough
12	DIZZINESS	Balance disorder, Dizziness, Dizziness exertional, Dizziness postural, Presyncope
13	NEUROPATHY	Acute polyneuropathy, Amyotrophy, Areflexia, Autoimmune neuropathy, Autonomic failure syndrome, Autonomic neuropathy, Axonal neuropathy, Biopsy peripheral nerve abnormal, Burning feet syndrome, Burning sensation, Decreased vibratory sense, Demyelinating polyneuropathy, Dysaesthesia, Electromyogram abnormal, Formication, Gait disturbance, Genital hypoaesthesia, Guillain-Barre syndrome, Hyperaesthesia, Hypoaesthesia, Hyporeflexia, Hypotonia, Ischaemic neuropathy, Loss of proprioception, Miller Fisher syndrome, Mononeuritis, Mononeuropathy, Mononeuropathy multiplex, Motor dysfunction, Multifocal motor neuropathy, Muscle atrophy, Muscular weakness, Myelopathy, Nerve conduction studies abnormal, Nerve degeneration, Neuralgia, Neuritis, Neuromuscular toxicity, Neuromyopathy, Neuronal neuropathy, Neuropathy peripheral, Neuropathy vitamin B6 deficiency, Neurotoxicity, Paraesthesia, Peripheral motor neuropathy, Peripheral nerve lesion, Peripheral nerve palsy, Peripheral nervous system function test abnormal, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Peroneal nerve palsy, Phrenic nerve paralysis, Polyneuropathy, Polyneuropathy chronic, Polyneuropathy idiopathic progressive, Radiation neuropathy, Sensorimotor disorder, Sensory disturbance, Sensory loss, Skin burning sensation, Small fibre neuropathy, Temperature perception test decreased, Tinel's sign, Toxic neuropathy, Ulnar neuritis
14	ELEVATED TRANSAMINASES	Alanine aminotransferase, Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Gamma-glutamyltransferase abnormal, Gamma-glutamyltransferase increased, Hepatic enzyme abnormal, Hepatic enzyme increased, Hepatic function abnormal, Hypertransaminasaemia, Liver function test abnormal, Liver function test increased, Transaminases, Transaminases abnormal, Transaminases increased
15	HEPATOTOXICITY	Acute hepatic failure, Cholestatic liver injury, Coma hepatic, Drug-induced liver injury, Hepatic encephalopathy, Hepatic failure, Hepatic necrosis, Hepatic steatosis, Hepatitis fulminant, Hepatocellular injury, Hepatorenal failure, Hepatorenal syndrome, Hepatotoxicity, Liver disorder, Liver injury, Mixed liver injury, Subacute hepatic failure

Number		
16	CHOLESTASIS	Bilirubin conjugated, Bilirubin conjugated abnormal, Bilirubin conjugated increased, Bilirubin excretion disorder, Blood bilirubin, Blood bilirubin abnormal, Blood bilirubin increased, Cholestasis, Cholestatic liver injury, Hepatitis cholestatic, Hyperbilirubinaemia, Jaundice, Jaundice cholestatic, Jaundice hepatocellular, Ocular icterus, Yellow skin
17	NEUTROPENIA	Febrile neutropenia, Neutropenia, Neutrophil count decreased
18	THROMBOCYTOPENIA	Platelet count decreased, Thrombocytopenia
19	LYMPHOPENIA	Lymphocyte count decreased, Lymphopenia
20	ANAEMIA	Anaemia, Anaemia macrocytic, Anaemia megaloblastic, Haemoglobin, Haemoglobin decreased, Hyperchromic anaemia, Hypochromic anaemia, Hypoplastic anaemia, Microcytic anaemia, Normochromic normocytic anaemia
21	BRADYCARDIA	Bradyarrhythmia, Bradycardia, Heart rate decreased, Sinus arrest, Sinus bradycardia
22	RENAL CYST	Renal abscess, Renal cyst, Renal cyst excision, Renal cyst haemorrhage, Renal cyst infection, Renal cyst ruptured
23	PULMONARY EMBOLISM	Pulmonary artery thrombosis, Pulmonary embolism, Pulmonary thrombosis
24	LEUKOPENIA	Leukopenia, White blood cell count decreased
25	BLOOD TESTOSTERONE DECREASED	Androgen deficiency, Blood gonadotrophin abnormal, Blood gonadotrophin decreased, Blood gonadotrophin increased, Blood testosterone abnormal, Blood testosterone decreased, Blood testosterone free decreased, Gonadotrophin deficiency, Hypogonadism, Hypogonadism male, Saliva testosterone abnormal, Saliva testosterone decreased, Secondary hypogonadism
26	GASTRO INTESTINAL PERFORATION	Anastomotic ulcer perforation, Diverticular perforation, Duodenal perforation, Duodenal ulcer perforation, Duodenal ulcer perforation, obstructive, Gastric perforation, Gastric ulcer perforation, Gastric ulcer perforation, obstructive, Gastrointestinal anastomotic leak, Gastrointestinal perforation, Gastrointestinal ulcer perforation, Ileal perforation, Ileal ulcer perforation, Intestinal perforation, Intestinal ulcer perforation, Jejunal perforation, Jejunal ulcer perforation, Large intestinal ulcer perforation, Large intestine perforation, Peptic ulcer perforation, Peptic ulcer perforation, obstructive, Perforated Peptic ulcer oversewing, Perforated ulcer, Rectal perforation, Small intestinal perforation, Small intestinal ulcer perforation
27	BLOOD CREATININE INCREASED	Blood creatinine abnormal, Blood creatinine increased, Creatinine renal clearance abnormal, Creatinine renal clearance decreased, Glomerular filtration rate abnormal, Glomerular filtration rate decreased
28	VISUAL LOSS	Amaurosis, Amaurosis fugax, Blindness, Blindness cortical, Blindness day, Blindness transient, Blindness unilateral, Hemianopia, Hemianopia heteronymous, Hemianopia homonymous, Night blindness, Optic atrophy, Optic ischaemic neuropathy, Optic nerve disorder, Optic neuropathy, Quadrantanopia, Retinopathy, Sudden visual loss, Toxic optic neuropathy, Tunnel vision, Visual cortex atrophy, Visual field defect, Visual pathway disorder

Cluster Number	Cluster Term	Preferred Terms (PTs)
29	CARDIAC FAILURE	Acute left ventricular failure, Acute right ventricular failure, Cardiac failure, Cardiac failure acute, Cardiac failure chronic, Cardiac failure congestive, Cardiac failure high output, Cardiopulmonary failure, Chronic left ventricular failure, Chronic right ventricular failure, Ejection fraction decreased, Left ventricular failure, Pulmonary oedema, Right ventricular failure, Ventricular failure

Source: Crizotinib-PF-02341066 (A808-ALCL PLUS IMT) Integrated Analysis Plan for Safety, Appendix 1

Study ADVL0912

Data are presented for phase 2 part (crizotinib administered at the intended dose) + patients with ALK+ ALCL/IMT patients from phase 1 (dose escalation).

All causality adverse events

- *Summary*

All-causality AEs were reported in all 105 paediatric patients (Table 46). Grade 3 or 4 AEs were reported in 80 patients (76.2%).

Table 46 Treatment-Emergent Adverse Events by Tumour Type (All Tumour Types, All Dose Levels, Age < 18 years, All Causality) - CTCAE Grade – Safety Analysis Set (Protocol ADVL0912)

Number (%) of Subjects	ALCL n (%)	IMT n (%)	ALCL+IMT n (%)	Other Tumors n (%)	Total n (%)
Subjects evaluable for adverse events	22	14	36	69	105
Number of adverse events	626	416	1042	1437	2479
Subjects with adverse events	22 (100)	14 (100)	36 (100)	69 (100)	105 (100)
Subjects with Maximum Grade 3 or 4 adverse events	21 (95.5)	11 (78.6)	32 (88.9)	48 (69.6)	80 (76.2)
Subjects with Maximum Grade 5 adverse events	0	0	0	5 (7.2)	5 (4.8)

Except for the Number of Adverse Events subjects are counted only once per tumor type in each row.
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table, but are included in the supporting listing.
One grade 5 AE of disease progression was not entered into database due to site oversight.
MedDRA v22.1 coding dictionary applied and CTCAE version 4.0 applied.

- **ALCL Group**: All-causality AEs were reported in all 22 paediatric patients and Grade 3 or 4 AEs in 21 (95.5%) paediatric patients: 5/6 (83.3%) at the 165 mg/m^2 BID dose level and all 16 at the 280 mg/m^2 BID dose level (Table 14.3.1.2.1.1.1 of the CSR).
- **IMT Group**: All-causality AEs were reported in all 14 paediatric patients and Grade 3 or 4 AEs in 11 (78.6%) paediatric patients: none at the 100 mg/m^2 BID dose level, 1 at the 165 mg/m^2 BID dose level and 10/12 (83.3%) at the 280 mg/m^2 BID dose level.
- **Other Tumours Group**: All-causality AEs were reported in all 69 paediatric patients and Grade 3 or 4 AEs in 48 (69.6%) paediatric patients.

- *Incidence*

The most frequently reported (≥60% of patients) all-causality AEs in all paediatric patients were elevated transaminases, Vomiting, neutropenia, Nausea, Diarrhoea, and leukopenia. The most frequently reported (≥30% of patients) all-causality Grade 3 or 4 AE in all paediatric patients was neutropenia.

The most frequent Grade 3 or 4 all-causality AEs for all patients (≥20% of Total patients) were neutropenia and lymphopenia. While both AEs were reported in the ALCL group, lymphopenia was not reported in the IMT group. Neutropenia is currently listed as a very common ADR for crizotinib

ALCL Group Most frequently reported (≥60% of patients) AEs were Vomiting, Diarrhoea, elevated transaminases, neutropenia, leukopenia, Nausea, vision disorder, and Headache. The most frequently reported (≥30% of patients) all-causality Grade 3 or 4 AEs were neutropenia, lymphopenia, and leukopenia.

IMT Group: Most frequently reported (≥60% of patients) AEs were neutropenia, Vomiting, Nausea, elevated transaminases, leukopenia, blood creatinine increased, cough, Diarrhoea, Hypoalbuminaemia, Hypocalcaemia, and upper respiratory infection. The most frequently reported (≥30% of patients) all-causality Grade 3 or 4 AE was neutropenia.

Other Tumours Group: Most frequently reported (≥60% of patients) AEs were elevated transaminases, Vomiting, Nausea, and neutropenia (Table 47). The most frequently reported (≥30% of patients) all-causality Grade 3 or 4 AE was neutropenia.

Table 47 TEAEs by PT (or Cluster), Tumour Type in Descending Order of Frequency (All Tumour Types, All Dose Levels, Age < 18 years, All Causality) in ≥ 30 % of Subjects - Safety Analysis Set (Protocol ADVL0912)

Number of Subjects Evaluable for AEs	ALCL (N=22)	IMT (N=14)	ALCL+IMT (N=36)	Other Tumors (N=69)	Total (N=105)
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event*	22 (100)	14 (100)	36 (100)	69 (100)	105 (100)
ELEVATED TRANSAMINASES [14]	21 (95.5)	11 (78.6)	32 (88.9)	61 (88.4)	93 (88.6)
Vomiting	22 (100)	13 (92.9)	35 (97.2)	46 (66.7)	81 (77.1)
NEUTROPENIA [17]	21 (95.5)	13 (92.9)	34 (94.4)	41 (59.4)	75 (71.4)
Nausea	17 (77.3)	12 (85.7)	29 (80.6)	44 (63.8)	73 (69.5)
Diarrhoea	22 (100)	9 (64.3)	31 (86.1)	41 (59.4)	72 (68.6)
LEUKOPENIA [24]	18 (81.8)	10 (71.4)	28 (77.8)	37 (53.6)	65 (61.9)
Hypoalbuminaemia	12 (54.5)	9 (64.3)	21 (58.3)	40 (58.0)	61 (58.1)
Hypocalcaemia	13 (59.1)	9 (64.3)	22 (61.1)	38 (55.1)	60 (57.1)
LYMPHOPENIA [19]	13 (59.1)	7 (50.0)	20 (55.6)	39 (56.5)	59 (56.2)
ANAEMIA [20]	9 (40.9)	7 (50.0)	16 (44.4)	40 (58.0)	56 (53.3)
Fatigue	9 (40.9)	6 (42.9)	15 (41.7)	35 (50.7)	50 (47.6)
Hyperglycaemia	9 (40.9)	8 (57.1)	17 (47.2)	33 (47.8)	50 (47.6)
BLOOD CREATININE INCREASED [27]	7 (31.8)	9 (64.3)	16 (44.4)	32 (46.4)	48 (45.7)
COUGH [11]	8 (36.4)	9 (64.3)	17 (47.2)	31 (44.9)	48 (45.7)
ABDOMINAL PAIN [3]	12 (54.5)	8 (57.1)	20 (55.6)	25 (36.2)	45 (42.9)
VISION DISORDER [1]	15 (68.2)	7 (50.0)	22 (61.1)	23 (33.3)	45 (42.9)
Pyrexia	9 (40.9)	7 (50.0)	16 (44.4)	26 (37.7)	42 (40.0)
Decreased appetite	8 (36.4)	4 (28.6)	12 (33.3)	28 (40.6)	40 (38.1)
Headache	14 (63.6)	5 (35.7)	19 (52.8)	17 (24.6)	36 (34.3)
Hypophosphataemia	2 (9.1)	3 (21.4)	5 (13.9)	28 (40.6)	33 (31.4)
Pain in extremity	8 (36.4)	5 (35.7)	13 (36.1)	20 (29.0)	33 (31.4)
Constipation	7 (31.8)	5 (35.7)	12 (33.3)	20 (29.0)	32 (30.5)

Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table, but are included in the supporting listing.
MedDRA v22.1 coding dictionary applied.
* "With Any Adverse Event" row is without consideration for the minimum 30 % frequency cutoff used in this table.
Includes preferred terms (or clusters) reported by ≥ 30 % of subjects in the total column.

Table 48 Max Grade ≥ 3 TEAEs by PTs (or Cluster), Max CTCAE Grade, Tumour Type in Descending Order of Frequency (All Tumour Types, All Dose Levels, Age < 18 yr, All Causality) in ≥ 2 % of Subjects - Safety Analysis Set (Protocol ADVL0912)

Number of Subjects Evaluable for AEs	ALCL (N=22)		IMT (N=14)		ALCL+IMT (N=36)		Other Tumors (N=69)		Total (N=105)	
	Grade 3-4	Grade 5	Grade 3-4	Grade 5	Grade 3-4	Grade 5	Grade 3-4	Grade 5	Grade 3-4	Grade 5
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event*	21 (95.5)	0	11 (78.6)	0	32 (88.9)	0	48 (69.6)	5 (7.2)	80 (76.2)	5 (4.8)
NEUTROPENIA [17]	17 (77.3)	0	8 (57.1)	0	25 (69.4)	0	30 (43.5)	0	55 (52.4)	0
LYMPHOPENIA [19]	9 (40.9)	0	0	0	9 (25.0)	0	17 (24.6)	0	26 (24.8)	0
LEUKOPENIA [24]	9 (40.9)	0	0	0	9 (25.0)	0	8 (11.6)	0	17 (16.2)	0
ANAEMIA [20]	1 (4.5)	0	0	0	1 (2.8)	0	9 (13.0)	0	10 (9.5)	0
THROMBOCYTOPENIA [18]	5 (22.7)	0	0	0	5 (13.9)	0	5 (7.2)	0	10 (9.5)	0
ELEVATED TRANSAMINASES [14]	3 (13.6)	0	0	0	3 (8.3)	0	6 (8.7)	0	9 (8.6)	0
Diarrhoea	3 (13.6)	0	1 (7.1)	0	4 (11.1)	0	2 (2.9)	0	6 (5.7)	0
Death	0	0	0	0	0	0	0	4 (5.8)	0	4 (3.8)
Hypokalaemia	1 (4.5)	0	0	0	1 (2.8)	0	3 (4.3)	0	4 (3.8)	0
Hypoxia	0	0	0	0	0	0	4 (5.8)	0	4 (3.8)	0
Pain in extremity	3 (13.6)	0	0	0	3 (8.3)	0	1 (1.4)	0	4 (3.8)	0
Pyrexia	0	0	0	0	0	0	4 (5.8)	0	4 (3.8)	0
Vomiting	1 (4.5)	0	0	0	1 (2.8)	0	3 (4.3)	0	4 (3.8)	0
Back pain	0	0	0	0	0	0	3 (4.3)	0	3 (2.9)	0
Blood alkaline phosphatase increased	0	0	0	0	0	0	3 (4.3)	0	3 (2.9)	0
Device related infection	1 (4.5)	0	0	0	1 (2.8)	0	2 (2.9)	0	3 (2.9)	0
Hypotension	2 (9.1)	0	1 (7.1)	0	3 (8.3)	0	0	0	3 (2.9)	0
NEUROPATHY [13]	0	0	0	0	0	0	3 (4.3)	0	3 (2.9)	0
Pain	0	0	0	0	0	0	3 (4.3)	0	3 (2.9)	0
Skin infection	1 (4.5)	0	0	0	1 (2.8)	0	2 (2.9)	0	3 (2.9)	0

Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table, but are included in the supporting listing.
MedDRA v22.1 coding dictionary applied.
* "With Any Adverse Event" row is without consideration for the minimum 2 % frequency cutoff used in this table.
Includes preferred terms (or clusters) reported by ≥ 2 % of subjects in the total column.
One grade 5 AE of disease progression was not entered into database due to site oversight.

Treatment-Related Adverse Events

- *Summary*

Treatment-related AEs were reported in 104/105 (99.0%) paediatric patients in the total group (Table *49*). Grade 3 or 4 treatment-related AEs were reported in 62 (59.0%) paediatric patients.

Table 49 Treatment-Emergent Adverse Events by Tumour Type (All Tumour Types, All Dose Levels, Age < 18 years, Treatment Related) - CTCAE Grade - Safety Analysis Set (Protocol ADVL0912)

Number (%) of Subjects	ALCL n (%)	IMT n (%)	ALCL+IMT n (%)	Other Tumors n (%)	Total n (%)
Subjects evaluable for adverse events	22	14	36	69	105
Number of adverse events	322	226	548	758	1306
Subjects with adverse events	22 (100)	14 (100)	36 (100)	68 (98.6)	104 (99.0)
Subjects with Maximum Grade 3 or 4 adverse events	15 (68.2)	9 (64.3)	24 (66.7)	38 (55.1)	62 (59.0)
Subjects with Maximum Grade 5 adverse events	0	0	0	1 (1.4)	1 (1.0)

Except for the Number of Adverse Events subjects are counted only once per tumor type in each row.
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table, but are included in the supporting listing.
Treatment Related Adverse Events are Adverse Events collected with attribution of Possible, Probable, Definite.
MedDRA v22.1 coding dictionary applied and CTCAE version 4.0 applied.

- **ALCL Group**: Treatment-related AEs were reported in all 22 paediatric patients (Table *49*). Grade 3 or 4 treatment-related AEs were reported in 15 (68.2%) paediatric patients: 2/6 (33.3%) at the 165 mg/m^2 BID dose level and 13/16 (81.3%) at the 280 mg/m^2 BID dose level.
- **IMT Group**: Treatment-related AEs were reported in all 14 paediatric patients (Table *49*). Grade 3 or 4 treatment-related AEs were reported in 9 (64.3%) paediatric patients: 1/1 (100%) at the 165 mg/m^2 BID dose level and 8/12 (66.7%) at the 280 mg/m^2 BID dose level. No Grade 3 or 4 all-causality AE was reported for the 1 paediatric patient at the 100 mg/m2 BID dose level.
- **ALCL + IMT Group**: Treatment-related AEs were reported in all 36 paediatric patients (Table *49*). Grade 3 or 4 treatment-related AEs were reported in 24 (66.7%) paediatric patients: 3/7 (42.9%) at the 165 mg/m^2 BID dose level and 21/28 (75.0%) at the 280 mg/m^2 BID dose level.
- **Other Tumours Group**: Treatment-related AEs were reported in 68/69 paediatric patients (98.6%) (Table *49*) Grade 3 or 4 treatment-related AEs were reported in 38 (55.1%) paediatric patients

➢ *Incidence*

The most frequently reported (≥50% of patients) treatment-related AEs for paediatric patients (total group) were elevated transaminases, Vomiting, neutropenia, Nausea, Diarrhoea, and leukopenia. The most frequently reported (≥40% of patients) treatment-related Grade 3 or 4 AE for paediatric patients in the total group was neutropenia (43.8%) (Table 51). The most frequent Grade 3 or Grade 4 treatment-related AEs (>10% of Total patients) were neutropenia and lymphopenia. Lymphopenia was not reported as a Grade 3 or Grade 4 treatment-related AE in the ALCL+IMT group (Table 51)

Table 50 TEAEs by PT (or Cluster), Tumour Type in Descending Order of Frequency (All Tumour Types, All Dose Levels, Age < 18 years, Treatment Related) in ≥ 30 % of Subjects - Safety Analysis Set (Protocol ADVL0912)

Number of Subjects Evaluable for AEs	ALCL (N=22)	IMT (N=14)	ALCL+IMT (N=36)	Other Tumors (N=69)	Total (N=105)
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event*	22 (100)	14 (100)	36 (100)	68 (98.6)	104 (99.0)
ELEVATED TRANSAMINASES [14]	20 (90.9)	11 (78.6)	31 (86.1)	56 (81.2)	87 (82.9)
Vomiting	21 (95.5)	13 (92.9)	34 (94.4)	42 (60.9)	76 (72.4)
NEUTROPENIA [17]	21 (95.5)	13 (92.9)	34 (94.4)	37 (53.6)	71 (67.6)
Nausea	17 (77.3)	12 (85.7)	29 (80.6)	39 (56.5)	68 (64.8)
Diarrhoea	21 (95.5)	6 (42.9)	27 (75.0)	37 (53.6)	64 (61.0)
LEUKOPENIA [24]	18 (81.8)	7 (50.0)	25 (69.4)	34 (49.3)	59 (56.2)
Hypoalbuminaemia	8 (36.4)	8 (57.1)	16 (44.4)	29 (42.0)	45 (42.9)
VISION DISORDER [1]	15 (68.2)	6 (42.9)	21 (58.3)	22 (31.9)	43 (41.0)
Hypocalcaemia	10 (45.5)	8 (57.1)	18 (50.0)	24 (34.8)	42 (40.0)
LYMPHOPENIA [19]	7 (31.8)	6 (42.9)	13 (36.1)	28 (40.6)	41 (39.0)
BLOOD CREATININE INCREASED [27]	5 (22.7)	8 (57.1)	13 (36.1)	25 (36.2)	38 (36.2)
Fatigue	7 (31.8)	5 (35.7)	12 (33.3)	26 (37.7)	38 (36.2)
ANAEMIA [20]	6 (27.3)	6 (42.9)	12 (33.3)	25 (36.2)	37 (35.2)

Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table, but are included in the supporting listing.
Treatment Related Adverse Events are Adverse Events collected with attribution of Possible, Probable, Definite.
MedDRA v22.1 coding dictionary applied.
* "With Any Adverse Event" row is without consideration for the minimum 30 % frequency cutoff used in this table.
Includes preferred terms (or clusters) reported by ≥ 30 % of subjects in the total column.

Table 51 Max Grade ≥ 3 TEAEs by PTs (or Cluster), Max CTCAE Grade, Tumour Type in Descending Order of Frequency (All Tumour Types, All Dose Levels, Age < 18 years, Treatment Related) in ≥ 2 % of Subjects – Safety Analysis Set (Protocol ADVL0912)

Number of Subjects Evaluable for AEs	ALCL (N=22)		IMT (N=14)		ALCL+IMT (N=36)		Other Tumors (N=69)		Total (N=105)	
	Grade 3-4	Grade 5	Grade 3-4	Grade 5	Grade 3-4	Grade 5	Grade 3-4	Grade 5	Grade 3-4	Grade 5
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event*	15 (68.2)	0	9 (64.3)	0	24 (66.7)	0	38 (55.1)	1 (1.4)	62 (59.0)	1 (1.0)
NEUTROPENIA [17]	14 (63.6)	0	7 (50.0)	0	21 (58.3)	0	25 (36.2)	0	46 (43.8)	0
LYMPHOPENIA [19]	0	0	0	0	0	0	12 (17.4)	0	12 (11.4)	0
LEUKOPENIA [24]	2 (9.1)	0	0	0	2 (5.6)	0	5 (7.2)	0	7 (6.7)	0
ELEVATED TRANSAMINASES [14]	1 (4.5)	0	0	0	1 (2.8)	0	5 (7.2)	0	6 (5.7)	0
ANAEMIA [20]	1 (4.5)	0	0	0	1 (2.8)	0	2 (2.9)	0	3 (2.9)	0
Diarrhoea	1 (4.5)	0	1 (7.1)	0	2 (5.6)	0	1 (1.4)	0	3 (2.9)	0
Vomiting	1 (4.5)	0	0	0	1 (2.8)	0	2 (2.9)	0	3 (2.9)	0

Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table, but are included in the supporting listing.
Treatment Related Adverse Events are Adverse Events collected with attribution of Possible, Probable, Definite.
MedDRA v22.1 coding dictionary applied.
* "With Any Adverse Event" row is without consideration for the minimum 2 % frequency cutoff used in this table.
Includes preferred terms (or clusters) reported by ≥ 2 % of subjects in the total column.

Study A8081013

All causality Adverse events

- *Summary*

All-causality AEs were reported in all the paediatric patients; 3 (60.0%) of those patients had SAEs (Table 52). All the paediatric patients had Grade 3 or 4 AEs. There were no Grade 5 AEs, or AEs associated with permanent treatment discontinuation reported.

Table 52 Treatment-Emergent Adverse Events (All Causality), Paediatric Subjects - Safety Analysis Population (Protocol A8081013)

Number (%) of Subjects	ALCL n (%)	IMT n (%)	ALCL+IMT n (%)
Subjects evaluable for adverse events	3	2	5
Number of adverse events	83	26	109
Subjects with adverse events	3 (100.0)	2 (100.0)	5 (100.0)
Subjects with serious adverse events	2 (66.7)	1 (50.0)	3 (60.0)
Subjects with Maximum Grade 3 or 4 adverse events	3 (100.0)	2 (100.0)	5 (100.0)
Subjects with Maximum Grade 5 adverse events	0	0	0
Subjects discontinued study drug due to AE and continue Study (a)	0	0	0
Subjects with dose reduced due to adverse events	0	0	0
Subjects with temporary discontinuation due to adverse events	2 (66.7)	2 (100.0)	4 (80.0)

Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table, but are included in the supporting listing.
(a) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be discontinued
from Study.
Serious Adverse Events - according to the investigator's assessment. MedDRA v22.0 coding dictionary applied.
Date of Data Snapshot: 18OCT2019 and Date of Data Cutoff: 03SEP2019

- *Incidence*

  - **ALCL group**

All-causality AEs of Diarrhoea, elevated transaminases, leukopenia, Nausea, Pyrexia, upper respiratory infection, vision disorder and Vomiting were reported in all 3 paediatric patients. Grade 3 AEs were reported in 1 (33.3%) patient. These Grade 3 AEs were elevated transaminases, leukopenia, Vomiting, neutropenia, Blood lactate dehydrogenase increased and Hypoalbuminaemia. Grade 4 AEs were reported in 2 (66.7%) patients and were Blood creatine phosphokinase increased and LYMPHOPENIA (1 patient each, 33.3%). Of note, Grade 4 LYMPHOPENIA was present at baseline.

  - **IMT Group**

All-causality AE of Nausea was reported in both paediatric patients. Grade 3 NEUTROPENIA was reported in another paediatric patient. There were no Grade 4 AEs reported.

Treatment related Adverse events

- *Summary*

Treatment-related AEs were reported in all the 5 paediatric patients; 3 (60.0%) of those patients had treatment-related SAEs (Table 53). Treatment-related Grade 3 or 4 AEs were reported in 3 (60.0%) paediatric patients. There were no treatment-related Grade 5 AEs or AEs associated with permanent treatment discontinuation reported.

Table 53 Treatment-Emergent Adverse Events (Treatment Related), Paediatric Subjects - Safety Analysis Population (Protocol A8081013)

Number (%) of Subjects	ALCL n (%)	IMT n (%)	ALCL+IMT n (%)
Subjects evaluable for adverse events	3	2	5
Number of adverse events	49	11	60
Subjects with adverse events	3 (100.0)	2 (100.0)	5 (100.0)
Subjects with serious adverse events	2 (66.7)	1 (50.0)	3 (60.0)
Subjects with Maximum Grade 3 or 4 adverse events	2 (66.7)	1 (50.0)	3 (60.0)
Subjects with Maximum Grade 5 adverse events	0	0	0
Subjects discontinued study drug due to AE and continue Study (a)	0	0	0
Subjects with dose reduced due to adverse events	0	0	0
Subjects with temporary discontinuation due to adverse events	1 (33.3)	1 (50.0)	2 (40.0)

Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table, but are included in the supporting listing.
(a) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be discontinued
from Study.
Serious Adverse Events - according to the investigator's assessment. MedDRA v22.0 coding dictionary applied.
Date of Data Snapshot: 18OCT2019 and Date of Data Cutoff: 03SEP2019

- *Incidence*

  - **ALCL group**

Treatment-related AEs of Diarrhoea, ELEVATED TRANSAMINASES, LEUKOPENIA, Nausea, VISION DISORDER and Vomiting were reported in all 3 paediatric patients.

Treatment-related Grade 3 AEs of ELEVATED TRANSAMINASES, Vomiting and NEUTROPENIA were reported in 1 paediatric patient. Grade 4 AE of Blood creatine phosphokinase increased was reported in 1 paediatric patient (Table 54); this AE was considered to be possibly related to physical activity by the investigator.

Table 54 Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Clustered Term and Maximum CTCAE Grade in Descending Order of Frequency (Treatment Related, All Cycles), Paediatric Subjects - Safety Analysis Population (Protocol A8081013)

Number of Subjects Evaluable for AEs	ALCL (N=3)							
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-4	Grade ≥3	Total
Number (%) of Subjects: by Clustered / Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	0	1 (33.3)	1 (33.3)	1 (33.3)	0	2 (66.7)	2 (66.7)	3 (100.0)
Diarrhoea	3 (100.0)	0	0	0	0	0	0	3 (100.0)
ELEVATED TRANSAMINASES [14]	1 (33.3)	1 (33.3)	1 (33.3)	0	0	1 (33.3)	1 (33.3)	3 (100.0)
LEUKOPENIA [24]	1 (33.3)	2 (66.7)	0	0	0	0	0	3 (100.0)
Nausea	3 (100.0)	0	0	0	0	0	0	3 (100.0)
VISION DISORDER [1]	2 (66.7)	1 (33.3)	0	0	0	0	0	3 (100.0)
Vomiting	2 (66.7)	0	1 (33.3)	0	0	1 (33.3)	1 (33.3)	3 (100.0)
NEUTROPENIA [17]	0	1 (33.3)	1 (33.3)	0	0	1 (33.3)	1 (33.3)	2 (66.7)
Rash	2 (66.7)	0	0	0	0	0	0	2 (66.7)
ABDOMINAL PAIN [3]	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Amnesia	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Asthenia	1 (33.3)	0	0	0	0	0	0	1 (33.3)
BLOOD CREATININE INCREASED [27]	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Blood creatine phosphokinase increased	0	0	0	1 (33.3)	0	1 (33.3)	1 (33.3)	1 (33.3)
Blood phosphorus decreased	0	1 (33.3)	0	0	0	0	0	1 (33.3)
Constipation	1 (33.3)	0	0	0	0	0	0	1 (33.3)
DIZZINESS [12]	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Decreased appetite	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Dermatitis	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Erythema	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Fatigue	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Gastroenteritis	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Hand dermatitis	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Headache	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Insomnia	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Myalgia	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Nail discolouration	1 (33.3)	0	0	0	0	0	0	1 (33.3)
OEDEMA [5]	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Peripheral swelling	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Pyrexia	1 (33.3)	0	0	0	0	0	0	1 (33.3)
Swelling face	1 (33.3)	0	0	0	0	0	0	1 (33.3)

- **IMT Group**

Treatment-related AE of Nausea was reported in both paediatric patients. Treatment-related Grade 3 AE of NEUTROPENIA was reported in 1 paediatric patient. There were no Grade 4 AEs reported.

Table 55 Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Clustered Term and Maximum CTCAE Grade in Descending Order of Frequency (Treatment Related, All Cycles), Paediatric Subjects – Safety Analysis Population (Protocol A8081013)

Number of Subjects Evaluable for AEs	IMT (N=2)							
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-4	Grade ≥3	Total
Number (%) of Subjects: by Clustered / Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	0	1 (50.0)	1 (50.0)	0	0	1 (50.0)	1 (50.0)	2 (100.0)
Nausea	2 (100.0)	0	0	0	0	0	0	2 (100.0)
ABDOMINAL PAIN [3]	1 (50.0)	0	0	0	0	0	0	1 (50.0)
ANAEMIA [20]	0	1 (50.0)	0	0	0	0	0	1 (50.0)
Bone marrow failure	0	1 (50.0)	0	0	0	0	0	1 (50.0)
Decreased appetite	1 (50.0)	0	0	0	0	0	0	1 (50.0)
Diarrhoea	0	1 (50.0)	0	0	0	0	0	1 (50.0)
LEUKOPENIA [24]	0	1 (50.0)	0	0	0	0	0	1 (50.0)
NEUTROPENIA [17]	0	0	1 (50.0)	0	0	1 (50.0)	1 (50.0)	1 (50.0)
Vomiting	0	1 (50.0)	0	0	0	0	0	1 (50.0)

Pooled data ADVL0912 + A8081013

All-Causality Adverse events

- *Summary*

Across the 4 pools, all patients had at least 1 all-causality AE. No all-causality Grade 5 AEs were reported in the ALCL or IMT pools (Table 56). Five Grade 5 AEs were reported in the Other Tumours group. Of note, 1 all-causality Grade 5 AE of Disease progression in the Other Tumours group was not entered into the database due to site reporting oversight.

Table 56 Crizotinib Paediatric Submission Treatment-Emergent Adverse Events by Tumour Type (All Tumour Types, Age < 18 years, All Causality) – CTCAE Grade - Safety Analysis Population (Paediatric Pool)

Number (%) of Subjects	ALCL n (%)	IMT n (%)	ALCL + IMT n (%)	All Tumor Types n (%)
Subjects evaluable for adverse events	25	16	41	110
Number of adverse events	709	442	1151	2588
Subjects with adverse events	25 (100)	16 (100)	41 (100)	110 (100)
Subjects with Maximum Grade 3 or 4 adverse events	24 (96.0)	13 (81.3)	37 (90.2)	85 (77.3)
Subjects with Maximum Grade 5 adverse events	0	0	0	5 (4.5)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 03SEP2019)
Except for the Number of Adverse Events subjects are counted only once per tumor type in each row.
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.
One grade 5 AE of disease progression was not entered into database due to site oversight.
MedDRA v22.1 coding dictionary applied and CTCAE version 4.0 applied.

- *Incidence*

Although the frequencies varied slightly across the 4 pools, the most frequent all-causality AEs reported were Diarrhoea, Vomiting, ELEVATED TRANSAMINASES, NEUTROPENIA, LEUKOPENIA, and Nausea (Table 57 and Table 58).

- **ALCL Group**

Table 57 Crizotinib Paediatric Submission TEAEs by PTs (or Cluster), Max CTCAE Grade, in Descending Order of Frequency (ALCL Types, Age < 18 years, All Causality) in ≥ 30 % of Subjects - Safety Analysis Population (Paediatric Pool)

Number of Subjects Evaluable for AEs	ALCL (N=25)							
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-4	Grade ≥3	Total
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event*	0	1 (4.0)	7 (28.0)	17 (68.0)	0	24 (96.0)	24 (96.0)	25 (100)
Diarrhoea	16 (64.0)	6 (24.0)	3 (12.0)	0	0	3 (12.0)	3 (12.0)	25 (100)
Vomiting	12 (48.0)	11 (44.0)	2 (8.0)	0	0	2 (8.0)	2 (8.0)	25 (100)
ELEVATED TRANSAMINASES [14]	17 (68.0)	3 (12.0)	4 (16.0)	0	0	4 (16.0)	4 (16.0)	24 (96.0)
NEUTROPENIA [17]	1 (4.0)	3 (12.0)	5 (20.0)	14 (56.0)	0	19 (76.0)	19 (76.0)	23 (92.0)
LEUKOPENIA [24]	7 (28.0)	4 (16.0)	3 (12.0)	7 (28.0)	0	10 (40.0)	10 (40.0)	21 (84.0)
Nausea	17 (68.0)	2 (8.0)	1 (4.0)	0	0	1 (4.0)	1 (4.0)	20 (80.0)
VISION DISORDER [1]	16 (64.0)	2 (8.0)	0	0	0	0	0	18 (72.0)
Headache	11 (44.0)	5 (20.0)	0	0	0	0	0	16 (64.0)
LYMPHOPENIA [19]	2 (8.0)	2 (8.0)	1 (4.0)	9 (36.0)	0	10 (40.0)	10 (40.0)	14 (56.0)
ABDOMINAL PAIN [3]	10 (40.0)	3 (12.0)	0	0	0	0	0	13 (52.0)
Hypoalbuminaemia	4 (16.0)	8 (32.0)	1 (4.0)	0	0	1 (4.0)	1 (4.0)	13 (52.0)
Hypocalcaemia	9 (36.0)	4 (16.0)	0	0	0	0	0	13 (52.0)
Pyrexia	8 (32.0)	4 (16.0)	0	0	0	0	0	12 (48.0)
Decreased appetite	5 (20.0)	5 (20.0)	0	0	0	0	0	10 (40.0)
Fatigue	8 (32.0)	2 (8.0)	0	0	0	0	0	10 (40.0)
ANAEMIA [20]	4 (16.0)	4 (16.0)	1 (4.0)	0	0	1 (4.0)	1 (4.0)	9 (36.0)
COUGH [11]	9 (36.0)	0	0	0	0	0	0	9 (36.0)
Hyperglycaemia	7 (28.0)	2 (8.0)	0	0	0	0	0	9 (36.0)
BLOOD CREATININE INCREASED [27]	3 (12.0)	5 (20.0)	0	0	0	0	0	8 (32.0)
Constipation	8 (32.0)	0	0	0	0	0	0	8 (32.0)

Pain in extremity	4 (16.0)	1 (4.0)	3 (12.0)	0	0	3 (12.0)	3 (12.0)	8 (32.0)
Hypophosphataemia	2 (8.0)	0	0	0	0	0	0	2 (8.0)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 03SEP2019)
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.
MedDRA v22.1 coding dictionary applied.
* "With Any Adverse Event" row is without consideration for the minimum 30 % frequency cutoff used in this table.
Includes preferred terms (or clusters) reported by ≥ 30 % of subjects in the total column for all the tumor types.

- **IMT Group**

Table 58 Crizotinib Paediatric Submission TEAEs by PTs (or Cluster), Max CTCAE Grade, in Descending Order of Frequency (IMT, Age < 18 years, All Causality) in ≥ 30 % of Subjects - Safety Analysis Population (Paediatric Pool)

Number of Subjects Evaluable for AEs	IMT (N=16)							
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-4	Grade ≥3	Total
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event*	0	3 (18.8)	9 (56.3)	4 (25.0)	0	13 (81.3)	13 (81.3)	16 (100)
NEUTROPENIA [17]	2 (12.5)	3 (18.8)	5 (31.3)	4 (25.0)	0	9 (56.3)	9 (56.3)	14 (87.5)
Nausea	14 (87.5)	0	0	0	0	0	0	14 (87.5)
Vomiting	9 (56.3)	5 (31.3)	0	0	0	0	0	14 (87.5)
ELEVATED TRANSAMINASES [14]	10 (62.5)	1 (6.3)	0	0	0	0	0	11 (68.8)
LEUKOPENIA [24]	7 (43.8)	4 (25.0)	0	0	0	0	0	11 (68.8)
Diarrhoea	6 (37.5)	3 (18.8)	1 (6.3)	0	0	1 (6.3)	1 (6.3)	10 (62.5)
ABDOMINAL PAIN [3]	8 (50.0)	1 (6.3)	0	0	0	0	0	9 (56.3)
BLOOD CREATININE INCREASED [27]	7 (43.8)	2 (12.5)	0	0	0	0	0	9 (56.3)
COUGH [11]	7 (43.8)	2 (12.5)	0	0	0	0	0	9 (56.3)
Hypoalbuminaemia	4 (25.0)	5 (31.3)	0	0	0	0	0	9 (56.3)
Hypocalcaemia	5 (31.3)	4 (25.0)	0	0	0	0	0	9 (56.3)
ANAEMIA [20]	4 (25.0)	4 (25.0)	0	0	0	0	0	8 (50.0)
Hyperglycaemia	8 (50.0)	0	0	0	0	0	0	8 (50.0)
LYMPHOPENIA [19]	6 (37.5)	1 (6.3)	0	0	0	0	0	7 (43.8)
Pyrexia	4 (25.0)	3 (18.8)	0	0	0	0	0	7 (43.8)
VISION DISORDER [1]	5 (31.3)	2 (12.5)	0	0	0	0	0	7 (43.8)
Constipation	5 (31.3)	1 (6.3)	0	0	0	0	0	6 (37.5)
Fatigue	6 (37.5)	0	0	0	0	0	0	6 (37.5)
Decreased appetite	5 (31.3)	0	0	0	0	0	0	5 (31.3)
Headache	5 (31.3)	0	0	0	0	0	0	5 (31.3)
Pain in extremity	5 (31.3)	0	0	0	0	0	0	5 (31.3)
Hypophosphataemia	3 (18.8)	0	0	0	0	0	0	3 (18.8)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 03SEP2019)
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.
MedDRA v22.1 coding dictionary applied.
* "With Any Adverse Event" row is without consideration for the minimum 30 % frequency cutoff used in this table.
Includes preferred terms (or clusters) reported by ≥ 30 % of subjects in the total column for all the tumor types.

Across the 4 pools, the most frequent Grade 3 or 4 all-causality AE reported was NEUTROPENIA (ALCL pool: 19 [76.0%] patients; IMT pool: 9 [56.3%] patients; ALCL+IMT pool: 28 [68.3%]; All Tumour Types pool: 58 [52.7%] patients).

Treatment-Related Adverse events

Although the frequency of the AEs varied slightly across the 4 pools, the most frequent treatment-related AEs were Diarrhoea, Vomiting, ELEVATED TRANSAMINASES, NEUTROPENIA, LEUKOPENIA, and Nausea.

A summary of treatment-related AEs by PTs (or cluster term) in descending order of frequency for ≥30% of the patients for each pool is provided in Table 59 (ALCL pool), Table 60 (IMT pool) and Table 61 (ALCL+IMT pool).

Table 59 Crizotinib Paediatric Submission TEAEs by PTs (or Cluster), Max CTCAE Grade, in Descending Order of Frequency (ALCL, Age < 18 years, Treatment Related) in ≥ 30 % of Subjects - Safety Analysis Population (Paediatric Pool)

Number of Subjects Evaluable for AEs	ALCL (N=25)							
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-4	Grade ≥3	Total
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event*	1 (4.0)	7 (28.0)	7 (28.0)	10 (40.0)	0	17 (68.0)	17 (68.0)	25 (100)
Diarrhoea	19 (76.0)	4 (16.0)	1 (4.0)	0	0	1 (4.0)	1 (4.0)	24 (96.0)
Vomiting	14 (56.0)	8 (32.0)	2 (8.0)	0	0	2 (8.0)	2 (8.0)	24 (96.0)
ELEVATED TRANSAMINASES [14]	19 (76.0)	2 (8.0)	2 (8.0)	0	0	2 (8.0)	2 (8.0)	23 (92.0)
NEUTROPENIA [17]	1 (4.0)	7 (28.0)	7 (28.0)	8 (32.0)	0	15 (60.0)	15 (60.0)	23 (92.0)
LEUKOPENIA [24]	12 (48.0)	7 (28.0)	2 (8.0)	0	0	2 (8.0)	2 (8.0)	21 (84.0)
Nausea	18 (72.0)	2 (8.0)	0	0	0	0	0	20 (80.0)
VISION DISORDER [1]	16 (64.0)	2 (8.0)	0	0	0	0	0	18 (72.0)
ABDOMINAL PAIN [3]	8 (32.0)	2 (8.0)	0	0	0	0	0	10 (40.0)

Hypocalcaemia	8 (32.0)	2 (8.0)	0	0	0	0	0	10 (40.0)
Fatigue	6 (24.0)	2 (8.0)	0	0	0	0	0	8 (32.0)
Hypoalbuminaemia	3 (12.0)	5 (20.0)	0	0	0	0	0	8 (32.0)
LYMPHOPENIA [19]	4 (16.0)	3 (12.0)	0	0	0	0	0	7 (28.0)
ANAEMIA [20]	3 (12.0)	2 (8.0)	1 (4.0)	0	0	1 (4.0)	1 (4.0)	6 (24.0)
BLOOD CREATININE INCREASED [27]	2 (8.0)	4 (16.0)	0	0	0	0	0	6 (24.0)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 03SEP2019)
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.
Treatment Related Adverse Events are Adverse Events collected with attribution of Possible, Probable, Definite.
MedDRA v22.1 coding dictionary applied.
Includes preferred terms (or clusters) reported by ≥ 30 % of subjects in the total column for all the tumor types.
* "With Any Adverse Event" row is without consideration for the minimum 30 % frequency cutoff used in this table.

Table 60 Crizotinib Paediatric Submission TEAEs by PTs (or Cluster), Max CTCAE Grade, in Descending Order of Frequency (IMT, Age < 18 years, Treatment Related) in ≥ 30 % of Subjects - Safety Analysis Population (Paediatric Pool)

Number of Subjects Evaluable for AEs	IMT (N=16)							
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-4	Grade ≥3	Total
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event*	1 (6.3)	5 (31.3)	6 (37.5)	4 (25.0)	0	10 (62.5)	10 (62.5)	16 (100)
NEUTROPENIA [17]	2 (12.5)	4 (25.0)	4 (25.0)	4 (25.0)	0	8 (50.0)	8 (50.0)	14 (87.5)
Nausea	14 (87.5)	0	0	0	0	0	0	14 (87.5)
Vomiting	9 (56.3)	5 (31.3)	0	0	0	0	0	14 (87.5)
ELEVATED TRANSAMINASES [14]	10 (62.5)	1 (6.3)	0	0	0	0	0	11 (68.8)
BLOOD CREATININE INCREASED [27]	6 (37.5)	2 (12.5)	0	0	0	0	0	8 (50.0)
Hypoalbuminaemia	4 (25.0)	4 (25.0)	0	0	0	0	0	8 (50.0)
Hypocalcaemia	6 (37.5)	2 (12.5)	0	0	0	0	0	8 (50.0)
LEUKOPENIA [24]	4 (25.0)	4 (25.0)	0	0	0	0	0	8 (50.0)
ABDOMINAL PAIN [3]	6 (37.5)	1 (6.3)	0	0	0	0	0	7 (43.8)
ANAEMIA [20]	4 (25.0)	3 (18.8)	0	0	0	0	0	7 (43.8)
Diarrhoea	4 (25.0)	2 (12.5)	1 (6.3)	0	0	1 (6.3)	1 (6.3)	7 (43.8)
LYMPHOPENIA [19]	5 (31.3)	1 (6.3)	0	0	0	0	0	6 (37.5)
VISION DISORDER [1]	5 (31.3)	1 (6.3)	0	0	0	0	0	6 (37.5)
Fatigue	5 (31.3)	0	0	0	0	0	0	5 (31.3)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 03SEP2019)
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.
Treatment Related Adverse Events are Adverse Events collected with attribution of Possible, Probable, Definite.
MedDRA v22.1 coding dictionary applied.
Includes preferred terms (or clusters) reported by ≥ 30 % of subjects in the total column for all the tumor types.
* "With Any Adverse Event" row is without consideration for the minimum 30 % frequency cutoff used in this table.

Table 61 Crizotinib Paediatric Submission TEAEs by PTs (or Cluster), Max CTCAE Grade, in Descending Order of Frequency (ALCL and IMT, Age < 18 years, Treatment Related) in ≥ 30 % of Subjects - Safety Analysis Population (Paediatric Pool

Number of Subjects Evaluable for AEs	ALCL + IMT (N=41)							
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-4	Grade ≥3	Total
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event*	2 (4.9)	12 (29.3)	13 (31.7)	14 (34.1)	0	27 (65.9)	27 (65.9)	41 (100)
Vomiting	23 (56.1)	13 (31.7)	2 (4.9)	0	0	2 (4.9)	2 (4.9)	38 (92.7)
NEUTROPENIA [17]	3 (7.3)	11 (26.8)	11 (26.8)	12 (29.3)	0	23 (56.1)	23 (56.1)	37 (90.2)
ELEVATED TRANSAMINASES [14]	29 (70.7)	3 (7.3)	2 (4.9)	0	0	2 (4.9)	2 (4.9)	34 (82.9)
Nausea	32 (78.0)	2 (4.9)	0	0	0	0	0	34 (82.9)
Diarrhoea	23 (56.1)	6 (14.6)	2 (4.9)	0	0	2 (4.9)	2 (4.9)	31 (75.6)
LEUKOPENIA [24]	16 (39.0)	11 (26.8)	2 (4.9)	0	0	2 (4.9)	2 (4.9)	29 (70.7)
VISION DISORDER [1]	21 (51.2)	3 (7.3)	0	0	0	0	0	24 (58.5)
Hypocalcaemia	14 (34.1)	4 (9.8)	0	0	0	0	0	18 (43.9)
ABDOMINAL PAIN [3]	14 (34.1)	3 (7.3)	0	0	0	0	0	17 (41.5)
Hypoalbuminaemia	7 (17.1)	9 (22.0)	0	0	0	0	0	16 (39.0)
BLOOD CREATININE INCREASED [27]	8 (19.5)	6 (14.6)	0	0	0	0	0	14 (34.1)
ANAEMIA [20]	7 (17.1)	5 (12.2)	1 (2.4)	0	0	1 (2.4)	1 (2.4)	13 (31.7)
Fatigue	11 (26.8)	2 (4.9)	0	0	0	0	0	13 (31.7)
LYMPHOPENIA [19]	9 (22.0)	4 (9.8)	0	0	0	0	0	13 (31.7)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 03SEP2019)
Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table.
Treatment Related Adverse Events are Adverse Events collected with attribution of Possible, Probable, Definite.
MedDRA v22.1 coding dictionary applied.
Includes preferred terms (or clusters) reported by ≥ 30 % of subjects in the total column for all the tumor types.
* "With Any Adverse Event" row is without consideration for the minimum 30 % frequency cutoff used in this table.

The most frequently reported Grade 3 or 4 treatment-related AE across all 4 pools was NEUTROPENIA (ALCL pool: 15 [60.0%] patients; IMT pool: 8 [50.0%] patients; ALCL+IMT pool: 23 [56.1%]; All Tumour Types pool: 48 [43.6%] patients).

In conclusion, Crizotinib–related AEs were most frequently hematological, gastrointestinal, and hepatic in nature.

ADRs from the ALCL+IMT pool were compared to adult patients with ALK-positive or ROS1-positive NSCLC (Table 62). There were no changes in the ADR listing since the last regulatory submission for a new indication.

The Grade 3 or 4 ADRs of NEUTROPENIA and LEUKOPENIA were reported with higher frequency (difference of ≥10%) in the ALCL+IMT pool than the adult population with ALK-positive or ROS1-positive NSCLC (Table 62). Of note, the number of adult patients (N=1722) is about 15 times higher than the number of paediatric patients (N=110); the age, comorbidities and underlying conditions are also very different in these 2 populations, and this could explain the differences in the frequencies.

Although not all ADRs identified in the adult population have been observed in clinical studies of paediatric patients, the same ADRs for adults should be considered for paediatric patients.

Table 62 Crizotinib Adverse Drug Reactions by SOC and Severity - Frequency of All-Causality Adverse Events – Safety Analysis Population (ALCL and IMT Pool and Adult Pool)

Number of Subjects Evaluable for AEs	ALCL (N=25)		IMT (N=16)		ALCL + IMT (N=41)		Pooled ROS1 Positive NSCLC and ALK Positive NSCLC Adult Patients N=1722	
Number (%) of Subjects: by System Organ Class and Preferred Term	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
With Any Adverse Drug Reaction	25 (100)	22 (88.0)	16 (100)	11 (68.8)	41 (100)	33 (80.5)	1710 (99.3)	786 (45.6)
Blood and Lymphatic System Disorders								
NEUTROPENIA [c]	23 (92.0)	19 (76.0)	14 (87.5)	9 (56.3)	37 (90.2)	28 (68.3)	374 (21.7)	212 (12.3)
LEUKOPENIA [c]	21 (84.0)	10 (40.0)	11 (68.8)	0	32 (78.0)	10 (24.4)	250 (14.5)	48 (2.8)
Metabolism and Nutrition Disorders								
Decreased appetite	10 (40.0)	0	5 (31.3)	0	15 (36.6)	0	511 (29.7)	30 (1.7)
Nervous System Disorders								
Dysgeusia	5 (20.0)	0	2 (12.5)	0	7 (17.1)	0	364 (21.1)	0
NEUROPATHY [c]	6 (24.0)	0	4 (25.0)	0	10 (24.4)	0	435 (25.3)	22 (1.3)
DIZZINESS [c]	5 (20.0)	0	2 (12.5)	0	7 (17.1)	0	442 (25.7))	9 (0.5)
Eye Disorders								
VISION DISORDER [c]	18 (72.0)	0	7 (43.8)	0	25 (61.0)	0	1084 (63.0)	6 (0.3)
Cardiac Disorders								
BRADYCARDIA [c]	5 (20.0)	0	2 (12.5)	1 (6.3)	7 (17.1)	1 (2.4)	219 (12.7)	7 (0.4)
Electrocardiogram QT prolonged	2 (8.0)	0	1 (6.3)	0	3 (7.3)	0	64 (3.7)	27 (1.6)
Syncope	0	0	0	0	0	0	44 (2.6)	42 (2.4)
Respiratory, Thoracic and Mediastinal Disorders								
INTERSTITIAL LUNG DISEASE (ILD) [c]	0	0	0	0	0	0	50 (2.9)	18 (1.0)
Gastrointestinal Disorders								
Diarrhoea	25 (100)	3 (12.0)	10 (62.5)	1 (6.3)	35 (85.4)	4 (9.8)	930 (54.0)	21 (1.2)
Nausea	20 (80.0)	1 (4.0)	14 (87.5)	0	34 (82.9)	1 (2.4)	974 (56.6)	38 (2.2)
Vomiting	25 (100)	2 (8.0)	14 (87.5)	0	39 (95.1)	2 (4.9)	874 (50.8)	34 (2.0)
Constipation	8 (32.0)	0	6 (37.5)	0	14 (34.1)	0	743 (43.1)	15 (0.9)

Dyspepsia	5 (20.0)	0	2 (12.5)	0	7 (17.1)	0	144 (8.4)	0
OESOPHAGITIS [c]	1 (4.0)	0	1 (6.3)	0	2 (4.9)	0	30 (1.7)	3 (0.2)
Hepatobiliary Disorders								
ELEVATED TRANSAMINASES [c]	24 (96.0)	4 (16.0)	11 (68.8)	0	35 (85.4)	4 (9.8)	553 (32.1)	178 (10.3)
Blood alkaline phosphatase increased	4 (16.0)	0	7 (43.8)	0	11 (26.8)	0	112 (6.5)	16 (0.9)
Hepatic Failure	0	0	0	0	0	0	5 (0.3)	4 (0.2)
Skin and Subcutaneous Tissue Disorders								
Rash	2 (8.0)	0	1 (6.3)	0	3 (7.3)	0	227 (13.2)	5 (0.3)
Renal and Urinary Disorders								
RENAL CYST [c]	0	0	0	0	0	0	52 (3.0)	10 (0.6)
BLOOD CREATININE INCREASED [c]	8 (32.0)	0	9 (56.3)	0	17 (41.5)	0	138 (8.0)	4 (0.2)
General Disorders and Administration Site Conditions								
OEDEMA [c]	7 (28.0)	0	5 (31.3)	1 (6.3)	12 (29.3)	1 (2.4)	815 (47.3)	36 (2.1)
Fatigue	10 (40.0)	0	6 (37.5)	0	16 (39.0)	0	514 (29.8)	56 (3.3)
Investigations								
Blood testosterone decreased	0	0	0	0	0	0	24 (1.4)	1 (0.1)

ALCL, IMT, AND ALCL+IMT Pediatric Pool columns include data from ADVL0912, A8081013 (Date of Data Cutoff: 03SEP2019). MedDRA version 22.1 coding dictionary and CTCAE version 4.0 were used.
Pooled ROS1 Positive NSCLC and ALK Positive NSCLC Adult Patients column includes data from A8081001(RP2D, NSCLC, ALK+), A8081005, A8081007 (Crizotinib only) and A8081014 (Crizotinib only, including patients crossed over to Crizotinib)with a data cutoff of 30NOV2013 and A8081001 (ROS1+, NSCLC) patients with a data cutoff of 30NOV2014. MedDRA (v17.1) coding dictionary applied.
c Includes Preferred Terms reported within the CLUSTERED TERMS.

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

Analysis of Adverse Events by Organ System or Syndrome

For comparative purposes, the all-causality frequency of **AESIs** are from adult patients.The number of adult patients (N=1722) is about 40 times higher that the number of paediatric patients (ALCL+IMT pool, N=41); the age, comorbidities and underlying conditions are different in these 2 populations, and this could explain, in part, the differences in the frequencies.

Diarrhoea, ELEVATED TRANSAMINASES, Nausea, Vomiting, and BLOOD CREATININE INCREASED occurred in a higher frequency (>10%) in the paediatric population (ALCL+IMT pool) compared to the adult population

ELEVATED TRANSAMINASES were reported in 85.4% (35/41) of the ALCL+IMT pool and in 32.1% (553/1722) of adult patients

Nausea was reported in 82.9% (34/41) of the ALCL+IMT pool and in 56.6% (974/1722) of adult patients

Diarrhoea was reported in 85.4% (35/41) of the ALCL+IMT pool and in 54.0% (930/1722) of adult patients

Vomiting was reported in 95.1% (39/41) of the ALCL+IMT pool and in 50.8% (874/1722) of adult patients

Electrocardiogram QT prolonged was reported in 7.3% (3/41) patients of the ALCL+IMT pool and in 3.7% (64/1722) of adult patients

BRADYCARDIA was reported in 17.1% (7/41) patients of the ALCL+IMT pool and in 12.7 % (219/1722) of adult patients

OEDEMA occurred in a higher frequency (>10%) in the adult population that in the paediatric population (ALCL+IMT pool).

HEPATOTOXICITY was reported in 0 patients of the ALCL+IMT pool and in 2.2% (38/1722) of adult patients

INTERSTITIAL LUNG DISEASE was reported in 0 patients of the ALCL+IMT pool and in 2.9% (50/1722) of adult patients

VISION DISORDER was reported in 61.0% (25/41) of the ALCL+IMT pool and in 63.0% (1084/1722) of adult patients. Of note, there was 1 patient with Grade 3 AE from the VISUAL LOSS cluster in the

ALCL+IMT pool. This paediatric patient with IMT had an Optic nerve disorder which was present at baseline and reported to be related to myopia; severity fluctuated from Grade 1 to Grade 3 while on crizotinib treatment.

Constipation was reported in 34.1% (14/41) of the ALCL+IMT pool and in 43.1% (743/1722) of adult patients

RENAL CYST was reported in 0 patients of the ALCL+IMT pool and in 3.0% (52/1722) of adult patients

OEDEMA was reported in 29.3% (12/41) of the ALCL+IMT pool and in 47.3% (815/1722) of adult patients

BLOOD CREATININE INCREASED was reported in 41.5% (17/41) patients of the ALCL+IMT pool and in 8.0% (138/1722) of adult patients

Syncope was reported in 0 patients of the ALCL+IMT pool and in 2.6 % (44/1722) of adult patients

The MAH has added PT of abdominal pain and hypophosphatemia in Table 8 of the SmPC (ADR, section 4.8).

Serious adverse event/deaths/other significant events

Serious adverse events

Study ADVL0912

All-causality SAEs were reported in 42 paediatric patients (40.0%) in the total group (Table 63). The most frequently reported (≥5% of patients) all-causality SAE for paediatric patients was neutropenia (15 patients [14.3%]). Treatment-related SAEs were reported in 22 paediatric patients (21.0%). The most frequently reported (≥5% of patients) treatment-related SAE was neutropenia (10 patients [9.5%]).

- **ALCL Group**: SAEs were reported in 7 paediatric patients (31.8%): 3/6 (50.0%) at the 165 mg/m^2 BID dose level and 4/16 (25.0%) at the 280 mg/m^2 BID dose level. The most frequently reported (≥5% of patients) SAEs were neutropenia and Hypotension.
- **IMT Group**: SAEs were reported in 1 paediatric patient (7.1%) at the 280 mg/m^2 BID dose level. This patient reported SAEs of bradycardia, Hypotension, Myocarditis, and neutropenia.

- *All causality SAE*

Table 63 SAEs from Pfizer Global Safety Database by PT (or Cluster), Tumour Type in Descending Order of Frequency (All Tumour Types, All Dose Levels, Age < 18 years, All Causality) in ***≥ 2 %*** *of Subjects - Safety Analysis Set (Protocol ADVL0912)*

Number of Subjects Evaluable for SAEs	ALCL (N=22)	IMT (N=14)	ALCL+IMT (N=36)	Other Tumors (N=69)	Total (N=105)
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Serious Adverse Event*	7 (31.8)	1 (7.1)	8 (22.2)	34 (49.3)	42 (40.0)
NEUTROPENIA [17]	3 (13.6)	1 (7.1)	4 (11.1)	11 (15.9)	15 (14.3)
BLOOD CREATININE INCREASED [27]	1 (4.5)	0	1 (2.8)	3 (4.3)	4 (3.8)
Hypotension	2 (9.1)	1 (7.1)	3 (8.3)	1 (1.4)	4 (3.8)
LEUKOPENIA [24]	0	0	0	4 (5.8)	4 (3.8)
ANAEMIA [20]	0	0	0	3 (4.3)	3 (2.9)
Disease progression	0	0	0	3 (4.3)	3 (2.9)
ELEVATED TRANSAMINASES [14]	0	0	0	3 (4.3)	3 (2.9)
Hypokalaemia	0	0	0	3 (4.3)	3 (2.9)
Hypoxia	0	0	0	3 (4.3)	3 (2.9)
Pain in extremity	1 (4.5)	0	1 (2.8)	2 (2.9)	3 (2.9)
Pyrexia	0	0	0	3 (4.3)	3 (2.9)
Skin infection	1 (4.5)	0	1 (2.8)	2 (2.9)	3 (2.9)
Vomiting	0	0	0	3 (4.3)	3 (2.9)

Serious Adverse Events - according to the investigator's assessment. Source of Serious Adverse Events are all the Adverse Events from Pfizer Global Safety Database.
Serious adverse events starting after new anticancer therapy (including transplant) begins are not counted in this table, but are included in the supporting listing.
MedDRA v.22.1J coding dictionary applied.
* "With Any Serious Adverse Event" row is without consideration for the minimum 2 % frequency cutoff used in this table.
Includes preferred terms (or clusters) reported by ≥ 2 % of subjects in the total column.

*Table 64 Serious Adverse Events from Pfizer Global Safety Database by Preferred Term (or Cluster), Dose Level, Age Group in Descending Order of Frequency (**ALCL**, Age < 18 years, All Causality) - Safety Analysis Set (Protocol ADVL0912)*

Number of Subjects Evaluable for SAEs	Crizotinib 165 mg/m² BID (N=6)	Crizotinib 280 mg/m² BID (N=16)	Total (N=22)
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)
With Any Serious Adverse Event	3 (50.0)	4 (25.0)	7 (31.8)
NEUTROPENIA [17]	2 (33.3)	1 (6.3)	3 (13.6)
Hypotension	0	2 (12.5)	2 (9.1)
BLOOD CREATININE INCREASED [27]	1 (16.7)	0	1 (4.5)
Cyanopsia	1 (16.7)	0	1 (4.5)
Dehydration	0	1 (6.3)	1 (4.5)
Device related infection	1 (16.7)	0	1 (4.5)
Femur fracture	1 (16.7)	0	1 (4.5)
Hypoalbuminaemia	1 (16.7)	0	1 (4.5)
Infective myositis	0	1 (6.3)	1 (4.5)
Kidney enlargement	1 (16.7)	0	1 (4.5)
Nausea	0	1 (6.3)	1 (4.5)
Obesity	0	1 (6.3)	1 (4.5)
Pain in extremity	0	1 (6.3)	1 (4.5)
Skin infection	0	1 (6.3)	1 (4.5)
Tumour lysis syndrome	0	1 (6.3)	1 (4.5)
Wheezing	0	1 (6.3)	1 (4.5)

*Table 65 Serious Adverse Events from Pfizer Global Safety Database by Preferred Term (or Cluster), Dose Level, Age Group in Descending Order of Frequency (**IMT**, Age < 18 years, All Causality) - Safety Analysis Set (Protocol ADVL0912)*

Number of Subjects Evaluable for SAEs	Crizotinib 100 mg/m² BID (N=1)	Crizotinib 165 mg/m² BID (N=1)	Crizotinib 280 mg/m² BID (N=12)	Total (N=14)
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)	n (%)
With Any Serious Adverse Event	0	0	1 (8.3)	1 (7.1)
BRADYCARDIA [21]	0	0	1 (8.3)	1 (7.1)
Hypotension	0	0	1 (8.3)	1 (7.1)
Myocarditis	0	0	1 (8.3)	1 (7.1)
NEUTROPENIA [17]	0	0	1 (8.3)	1 (7.1)

- *Treatment related SAE*

ALCL group Treatment-related SAEs were reported in 5 paediatric patients (22.7%) (Table 67): 3 (50.0%) at 165 mg/m^2 BID and 2 (12.5%) at 280 mg/m^2 BID. The most frequently reported (≥5% of patients) treatment-related SAE was NEUTROPENIA.

IMT group: The event of BRADYCARDIA was treatment-related. (Table 65)

Table 66 SAEs from Pfizer Global Safety Database by PT (or Cluster), Tumour Type in Descending Order of Frequency (All Tumour Types, All Dose Levels, Age < 18 years, Treatment Related) in ≥ 2 % of Subjects -Safety Analysis Set (Protocol ADVL0912).

Number of Subjects Evaluable for SAEs	ALCL (N=22)	IMT (N=14)	ALCL+IMT (N=36)	Other Tumors (N=69)	Total (N=105)
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Serious Adverse Event*	5 (22.7)	1 (7.1)	6 (16.7)	16 (23.2)	22 (21.0)
NEUTROPENIA [17]	2 (9.1)	0	2 (5.6)	8 (11.6)	10 (9.5)
LEUKOPENIA [24]	0	0	0	4 (5.8)	4 (3.8)

Serious Adverse Events - according to the investigator's assessment. Source of Serious Adverse Events are all the Adverse Events from Pfizer Global Safety Database.
Serious adverse events starting after new anticancer therapy (including transplant) begins are not counted in this table, but are included in the supporting listing.
Treatment Related Adverse Events are Adverse Events collected with attribution of Related.
MedDRA v.22.1J coding dictionary applied.
* "With Any Serious Adverse Event" row is without consideration for the minimum 2 % frequency cutoff used in this table.
Includes preferred terms (or clusters) reported by > 2 % of subjects in the total column.

Table 67 Serious Adverse Events from Pfizer Global Safety Database by Preferred Term (or Cluster), Dose Level, Age Group in Descending Order of Frequency (ALCL, Age < 18 years, Treatment Related) - Safety Analysis Set (Protocol ADVL0912)

Number of Subjects Evaluable for SAEs	Crizotinib 165 mg/m² BID (N=6)	Crizotinib 280 mg/m² BID (N=16)	Total (N=22)
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)
With Any Serious Adverse Event	3 (50.0)	2 (12.5)	5 (22.7)
NEUTROPENIA [17]	2 (33.3)	0	2 (9.1)
BLOOD CREATININE INCREASED [27]	1 (16.7)	0	1 (4.5)
Cyanopsia	1 (16.7)	0	1 (4.5)
Hypoalbuminaemia	1 (16.7)	0	1 (4.5)
Infective myositis	0	1 (6.3)	1 (4.5)
Kidney enlargement	1 (16.7)	0	1 (4.5)
Skin infection	0	1 (6.3)	1 (4.5)
Tumour lysis syndrome	0	1 (6.3)	1 (4.5)

Table 68 Serious Adverse Events from Pfizer Global Safety Database by Preferred Term (or Cluster), Dose Level, Age Group in Descending Order of Frequency (IMT, Age < 18 years, Treatment Related) - Safety Analysis Set (Protocol ADVL0912)

Number of Subjects Evaluable for SAEs	Crizotinib 100 mg/m² BID (N=1)	Crizotinib 165 mg/m² BID (N=1)	Crizotinib 280 mg/m² BID (N=12)	Total (N=14)
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)	n (%)
With Any Serious Adverse Event	0	0	1 (8.3)	1 (7.1)
BRADYCARDIA [21]	0	0	1 (8.3)	1 (7.1)

Study A8081013

All-causality SAEs were reported in 3 (60.0%) paediatric patients (Table 69). Each of these SAEs was only reported in 1 (20.0%) patient. All the SAEs were considered to be treatment related (Table *70*).

- *All causality and treatment related SAE*

- **ALCL group**

All-causality SAEs were reported in 2 (66.7%) paediatric patients (Table 69). Treatment-related SAEs of Blood creatine phosphokinase increased and Nausea were reported in 1 patient each (Table *70*).

- **IMT group**

All-causality SAEs were reported in 1 paediatric patient (Table 69). Treatment-related SAEs of Vomiting and Diarrhoea were reported in this patient (Table *70*).

Table 69 Summary of Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term and Clustered Term in Descending Order of Frequency (All Causality, All Cycles), Paediatric Subjects - Safety Analysis Population (Protocol A8081013)

Number of Subjects Evaluable for SAEs	ALCL (N=3)	IMT (N=2)	ALCL+IMT (N=5)
Number (%) of Subjects: by Clustered / Preferred Term	**n (%)**	**n (%)**	**n (%)**
With Any Serious Adverse Event	2 (66.7)	1 (50.0)	3 (60.0)
Blood creatine phosphokinase increased	1 (33.3)	0	1 (20.0)
Diarrhoea	0	1 (50.0)	1 (20.0)
Nausea	1 (33.3)	0	1 (20.0)
Vomiting	0	1 (50.0)	1 (20.0)

Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table, but are included in the supporting listing.
MedDRA v22.0 coding dictionary applied.
Date of Data Snapshot: 18OCT2019 and Date of Data Cutoff: 03SEP2019

Table 70 Summary of Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term and Clustered Term in Descending Order of Frequency (Treatment Related, All Cycles), Paediatric Subjects - Safety Analysis Population (Protocol A8081013)

Number of Subjects Evaluable for SAEs	ALCL (N=3)	IMT (N=2)	ALCL+IMT (N=5)
Number (%) of Subjects: by Clustered / Preferred Term	n (%)	n (%)	n (%)
With Any Serious Adverse Event	2 (66.7)	1 (50.0)	3 (60.0)
Blood creatine phosphokinase increased	1 (33.3)	0	1 (20.0)
Diarrhoea	0	1 (50.0)	1 (20.0)
Nausea	1 (33.3)	0	1 (20.0)
Vomiting	0	1 (50.0)	1 (20.0)

Treatment-Emergent Adverse Events starting after new anticancer therapy (including transplant) begins are not counted in this table, but are included in the supporting listing.
MedDRA v22.0 coding dictionary applied.
Date of Data Snapshot: 18OCT2019 and Date of Data Cutoff: 03SEP2019

Pooled data ADVL0912 + A8081013

All-Causality Serious Adverse events

The most frequent all-causality SAE across the 4 pools was NEUTROPENIA (Table *71*)

Table 71 Crizotinib Paediatric Submission SAEs from Pfizer Global Safety Database by PT (or Cluster), Tumour Type in Descending Order of Frequency (All Tumour Types, Age < 18 years, All Causality) in ≥ 2 % of Subjects – Safety Analysis Population (Paediatric Pool)

Number of Subjects Evaluable for SAEs	ALCL (N=25)	IMT (N=16)	ALCL + IMT (N=41)	All Tumor Types (N=110)
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)	n (%)
With Any Serious Adverse Event*	9 (36.0)	2 (12.5)	11 (26.8)	45 (40.9)
NEUTROPENIA [17]	3 (12.0)	1 (6.3)	4 (9.8)	15 (13.6)
BLOOD CREATININE INCREASED [27]	1 (4.0)	0	1 (2.4)	4 (3.6)
Hypotension	2 (8.0)	1 (6.3)	3 (7.3)	4 (3.6)
LEUKOPENIA [24]	0	0	0	4 (3.6)
Vomiting	0	1 (6.3)	1 (2.4)	4 (3.6)
ANAEMIA [20]	0	0	0	3 (2.7)
Disease progression	0	0	0	3 (2.7)
ELEVATED TRANSAMINASES [14]	0	0	0	3 (2.7)
Hypokalaemia	0	0	0	3 (2.7)
Hypoxia	0	0	0	3 (2.7)
Nausea	2 (8.0)	0	2 (4.9)	3 (2.7)
Pain in extremity	1 (4.0)	0	1 (2.4)	3 (2.7)
Pyrexia	0	0	0	3 (2.7)
Skin infection	1 (4.0)	0	1 (2.4)	3 (2.7)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 03SEP2019)
Serious Adverse Events - according to the investigator's assessment. Source of Serious Adverse Events are all the Adverse Events from Pfizer Global Safety Database.
Serious adverse events starting after new anticancer therapy (including transplant) begins are not counted in this table.
* "With Any Serious Adverse Event" row is without consideration for the minimum 2 % frequency cutoff used in this table.
MedDRA v.22.1J coding dictionary applied.
Includes preferred terms (or clusters) reported by ≥ 2 % of subjects in the all tumor types column.

No new safety issues were identified from a review of the SAEs reported across the 4 pools (ALCL pool, IMT pool, ALCL+IMT pool, and All Tumour Types pool).

Treatment-Related Serious Adverse Events

Similar to the all-causality SAEs across the 4 pools, NEUTROPENIA was the most frequently reported treatment-related SAE (Table *72*).

Table 72 Crizotinib Paediatric Submission SAEs from Pfizer Global Safety Database by PT (or Cluster), Tumour Type in Descending Order of Frequency (All Tumour Types, Age < 18 years, Treatment Related) in ≥ 2 % of Subjects - Safety Analysis Population (Paediatric Pool)

Number of Subjects Evaluable for SAEs	ALCL (N=25)	IMT (N=16)	ALCL + IMT (N=41)	All Tumor Types (N=110)
Number (%) of Subjects: by Preferred Term (or Cluster)	n (%)	n (%)	n (%)	n (%)
With Any Serious Adverse Event*	7 (28.0)	2 (12.5)	9 (22.0)	25 (22.7)
NEUTROPENIA [17]	2 (8.0)	0	2 (4.9)	10 (9.1)
LEUKOPENIA [24]	0	0	0	4 (3.6)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 03SEP2019)
Serious Adverse Events - according to the investigator's assessment. Source of Serious Adverse Events are all the Adverse Events from Pfizer Global Safety Database.
Serious adverse events starting after new anticancer therapy (including transplant) begins are not counted in this table.
* "With Any Serious Adverse Event" row is without consideration for the minimum 2 % frequency cutoff used in this table.
Treatment Related Adverse Events are Adverse Events collected with attribution of Related.
MedDRA v.22.1J coding dictionary applied.
Includes preferred terms (or clusters) reported by ≥ 2 % of subjects in the all tumor types column.

Deaths

Study ADVL0912

In the ALCL+IMT group, there were no deaths related to crizotinib treatment and similarly, there were no Grade 5 AEs (Table *73*).

A total of 8 deaths (all in the Other Tumours group) were reported in the clinical database (Study ADVL0912). Of these, 2 occurred more than 30 days after the last dose of crizotinib. In addition, 1 death due to non-treatment related sepsis occurred more than 30 days after the last dose of crizotinib but was reported only in the Pfizer Global Safety database (Study ADVL0912). Of the 6 patients who died within 30 days after the last dose of crizotinib, 5 deaths were due to disease under study and 1 was reported as due to both disease progression and protocol treatment (cause of death Haemorrhage intracranial)

Table 73 Summary of Deaths by Tumour Type (Age < 18 years, All Tumour Types) - Safety Analysis Set (Protocol ADVL0912)

Number (%) of Subjects	ALCL (N=22) n (%)	IMT (N=14) n (%)	ALCL + IMT (N=36) n (%)	Other Tumors (N=69) n (%)	Total (N=105) n (%)
Death within 30 days after last dose of study drug	0	0	0	6 (8.7)	6 (5.7)
Cause of Death [1]					
Due to this disease	0	0	0	6 (8.7)	6 (5.7)
Due to protocol treatment	0	0	0	1 (1.4)	1 (1.0)

Data is based on CRF page "Death".
[1] More than one cause of death, including primary cause of death and contributing cause of death, may be reported.

In study ADVL0912, no death due to the protocol treatment nor the disease occurred in the intended population.

Study A8081013

- **ALCL group**

No Grade 5 all-causality AEs or treatment-related AEs were reported for patients with ALCL or IMT

No paediatric patients died as of the data cutoff date. No Grade 5 AEs were reported in any paediatric patient

- **IMT group**

No paediatric patients died as of the data cutoff date. There were no Grade 5 all-causality AEs reported

In study A8081013, no death occurred in the intended population.

Other significant events

Thrombotic events were reported in study ANHL12P1 in patients receiving crizotinib in association with chemotherapy.

Study ANHL12P1 is a randomised Phase 2 NCI-sponsored trial of brentuximab vedotin (BV) or crizotinib (CZ) in combination with chemotherapy for newly diagnosed patients with ALCL. Patients were <22 years of age at the time of study enrollment. Patients in Arm BV received brentuximab vedotin plus a chemotherapy regimen and patients in Arm CZ received crizotinib plus a chemotherapy regimen. The protocol involved 6 cycles of treatment, and the chemotherapy regimen included cyclophosphamide, dexamethasone, ifosfamide, methotrexate, etoposide, cytarabine, methotrexate and doxorubicin.

Pfizer was notified on 08 July 2016 that NCI temporarily suspended enrollment in the Arm CZ of Study ANHL12P1 due to a higher incidence of thromboembolic events in Arm CZ compared to Arm BV, which included 5 events versus 1 event, respectively. On 23 June 2017, FDA placed Study ANHL12P1 on partial clinical hold because of the higher than expected rates of thromboembolic events in patients receiving crizotinib in combination with chemotherapy. Subsequently, the protocol for Study ANHL12P1 was amended in order to re-open enrollment in Arm CZ and included required implementation of prophylactic

anticoagulation in this arm of the study. Additional stopping rules for Arm CZ were also added with this amendment. Specifically, further enrollment into the Arm CZ would be discontinued if any of the following occurred in patients enrolled after Amendment 6A:

2 CVL-associated thrombotic events:

- Any one event of:
    - Thromboembolic event requiring surgical intervention, or
    - Pulmonary embolism
- 2 bleeding events, defined as Grade 2 or higher hemorrhage events corresponding to bleeding events which required intervention and consisted of major bleeding and clinically relevant minor bleeding.

The stopping rules were met with 2 additional thrombotic events in Arm CZ, and patients on this arm were instructed to permanently discontinue crizotinib in February 2019; however, patients in Arm CZ could continue treatment on chemotherapy alone. As of 30 June 2019, 137 patients had been enrolled (Arm BV, n=68; Arm CZ, n=69) (ANHL12P1 Study Progress Report 2019).

A total of 13 cases of thromboembolic events were reported in the 66 patients treated in Arm CZ of Study ANHL12P1. Upon review of these cases from the Pfizer Global Safety database and information provided by COG, it was noted that most cases were related to indwelling venous catheters used for multiple chemotherapy agents which may have had a contributory role. In addition, 2 of the 13 patients had genetic mutations which predisposed them to thrombotic events. It was also noted that potentially serious thrombocytopenia is a known ADR of brentuximab vedotin and this may explain the lower number of thromboembolic events in the BV arm.

Laboratory findings

Laboratory test data in this study consisted of hematology values (hemoglobin, neutrophils [abs], platelets, and white blood cell count), chemistry tests (ALT, albumin, creatinine, calcium, magnesium, phosphate, and total bilirubin), and urine tests. Laboratory test results were entered in the clinical database at baseline and weekly for the first cycle of treatment.

After Cycle 1, the corresponding laboratory test results were not entered into the clinical database and therefore are not included in the CSR. According to COG's procedures, any abnormalities in laboratory test results that were considered clinically relevant were to be reported as AEs.

Normal ranges were implemented to identify values that were outside the normal ranges and programmatically created the NCI toxicity grade using the CTCAE v 4.0.

For patients with Grade ≥3 laboratory test values, a by-patient data listing was presented to display data including visit label, assessment date (day), laboratory test value, normal range flag (low, normal, and high), and change from baseline value. The baseline value was flagged in this data listing.

Hematology laboratory evaluations

Study ADVL0912

Neutrophils (abs) was the most frequent shift from Grade ≤2 at baseline to Grade 3 or 4 postbaseline in paediatric patients and was most apparent at the 280 mg/m^2 BID dose level in paediatric patients (ALCL group in Table *74*, IMT group in Table 75).

- **ALCL group**

Table 74 Shift Summary Results of Labs from Grade ≤ 2 at Baseline to Grade 3 or 4 Postbaseline by Dose Level (Hematology, ALCL, Cycle 1 Only, Age < 18 years) - Safety Analysis Set (Protocol ADVL0912)

Subjects with Shift from Grade ≤ 2 at Baseline to Grade 3 or 4:	Crizotinib 165 mg/m² BID (N=6)		Crizotinib 280 mg/m² BID (N=16)		Total (N= 22)	
	N*	n(%)	N*	n(%)	N*	n(%)
Anemia	6	0	16	0	22	0
Hemoglobin increased	6	0	16	0	22	0
Neutrophils (abs)	6	1 (16.7)	16	10 (62.5)	22	11 (50)
Platelets	6	0	16	0	22	0
White blood cells	6	0	16	1 (6.3)	22	1 (4.5)

n=number of subjects, N* includes subjects with a post-baseline value during study treatment
Includes unplanned laboratory test results.
CTCAE version 4 criteria have been used.

- **IMT group**

Table 75 Shift Summary Results of Labs from Grade ≤ 2 at Baseline to Grade 3 or 4 Postbaseline by Dose Level (Hematology, IMT, Cycle 1 Only, Age < 18 years) - Safety Analysis Set (Protocol ADVL0912)

Subjects with Shift from Grade ≤ 2 at Baseline to Grade 3 or 4:	Crizotinib 100 mg/m² BID (N=1)		Crizotinib 165 mg/m² BID (N=1)		Crizotinib 280 mg/m² BID (N=12)		Total (N= 14)	
	N*	n(%)	N*	n(%)	N*	n(%)	N*	n(%)
Anemia	1	0	1	0	12	0	14	0
Hemoglobin increased	1	0	1	0	12	0	14	0
Neutrophils (abs)	1	0	1	0	12	5 (41.7)	14	5 (35.7)
Platelets	1	0	1	0	12	0	14	0
White blood cells	1	0	1	0	12	0	14	0

n=number of subjects, N* includes subjects with a post-baseline value during study treatment
Includes unplanned laboratory test results.
CTCAE version 4 criteria have been used.

Study A8081013

- **ALCL group**

Two (66.7%) paediatric patients had shifts from Grade ≤2 at baseline to Grade 3 or 4 post-baseline for neutrophil count decreased, 1 (33.3%) for lymphocyte count decreased and 1 (33.3%) for white blood cell decreased (Table 76).

- **IMT group**

One (50%) paediatric patient had shifts from Grade ≤2 at baseline to Grade 3 or 4 post-baseline for neutrophil count decreased (Table 76)

Table 76 Shift Summary Results of Labs from Grade ≤ 2 at Baseline to Grade 3 or 4 Postbaseline by Tumour Group, Paediatric Subjects (Hematology, All Cycles) – Safety Analysis Population (Protocol A8081013)

	ALCL (N=3)		IMT (N=2)	
Subjects with Shift from Grade ≤ 2 at Baseline to Grade 3 or 4:	**N***	**n(%)**	**N***	**n(%)**
ANEMIA	3	0	2	0
HEMOGLOBIN INCREASED	3	0	2	0
LYMPHOCYTE COUNT DECREASED	3	1 (33.3)	2	0
LYMPHOCYTE COUNT INCREASED	3	0	2	0
NEUTROPHIL COUNT DECREASED	3	2 (66.7)	2	1 (50)
PLATELET COUNT DECREASED	3	0	2	0
WHITE BLOOD CELL DECREASED	3	1 (33.3)	2	0

n=number of subjects, N* includes subjects with a post-baseline value during study treatment
Includes unplanned laboratory test results.
CTCAE version 4 criteria have been used.
Date of Data Snapshot: 18OCT2019 and Date of Data Cutoff: 03SEP2019

Chemistry laboratory evaluations

Study ADVL0912

No paediatric patients in either of the ALCL, IMT, or ALCL + IMT groups had a shift in chemistry laboratory test results from Grade ≤2 at baseline to Grade 3 or 4 postbaseline.

Laboratory tests were only collected for Cycle 1 and thus, in order to evaluate potential Hy's law cases for Study ADVL0912 after Cycle 1, the AEs associated with Blood bilirubin increased/ Hyperbilirubinaemia (Grade ≥2) that occurred concurrently with AST increased and/or ALT increased (Grade ≥1) were evaluated. There were no potential Hy's Law cases reported for paediatric patients of Study ADVL0912 or in Study A8081013.

Study A8081013

- **ALCL group**

One (33.3%) paediatric patient had shifts from Grade ≤2 at baseline to Grade 3 or 4 post-baseline for aspartate aminotransferase increased, 1 (33.3%) for hypoglycaemia and 1 (33.3%) for hypophosphatemia).

- **IMT group**

There were no shifts from Grade ≤2 at baseline to Grade 3 or 4 post-baseline for chemistry laboratory results

Table 77 Shift Summary Results of Labs from Grade ≤ 2 at Baseline to Grade 3 or 4 Postbaseline by Tumour Group, Paediatric Subjects (Chemistries, All Cycles) – Safety Analysis Population (Protocol A8081013)

	ALCL (N=3)		IMT (N=2)	
Subjects with Shift from Grade ≤ 2 at Baseline to Grade 3 or 4:	**N***	**n(%)**	**N***	**n(%)**
ALANINE AMINOTRANSFERASE INCREASED	3	0	2	0
ALKALINE PHOSPHATASE INCREASED	3	0	2	0
ASPARTATE AMINOTRANSFERASE INCREASED	3	1 (33.3)	2	0
BLOOD BILIRUBIN INCREASED	3	0	2	0
CREATININE INCREASED	3	0	2	0
HYPERCALCEMIA	3	0	2	0
HYPERGLYCEMIA	3	0	2	0
HYPERKALEMIA	3	0	2	0
HYPERMAGNESEMIA	3	0	2	0
HYPERNATREMIA	3	0	2	0
HYPOALBUMINEMIA	3	0	2	0
HYPOCALCEMIA	3	0	2	0
HYPOGLYCEMIA	3	1 (33.3)	2	0
HYPOKALEMIA	3	0	2	0
HYPOMAGNESEMIA	3	0	2	0
HYPONATREMIA	3	0	2	0
HYPOPHOSPHATEMIA	3	1 (33.3)	2	0

n=number of subjects, N* includes subjects with a post-baseline value during study treatment
Includes unplanned laboratory test results.
CTCAE version 4 criteria have been used.
Date of Data Snapshot: 18OCT2019 and Date of Data Cutoff: 03SEP2019

Vital Signs, Electrocardiograms, and Other Observations Related to Safety (Growth plate and vision disorders)

Study ADVL0912

- *Vital Signs (Body Weight only) and ECG*

Only body weight (kg), height (cm) and BSA (m^2) were collected on the CRF for Study ADVL0912. According to COG's procedures, any clinically relevant findings related to vital signs data were reported as AEs. For this reason, no pooling of vital sign data was performed. ECGs were not collected post-

baseline in Study ADVL0912. Thus, ECG parameter data on treatment are only available for Study A8081013.

No changes in body weight were considered clinically relevant. As this was a study in paediatric patients, increases body weight over time were expected. 9/22 patients in the ALCL group had a maximum increase in body weight from baseline of ≥7% and 6/22 patients had a maximum decrease in body weight from baseline of ≥ 3.5%. All patients in the IMT group had a maximum increase in body weight from baseline of ≥7%.

- *Growth Plate Alterations*

Thirty-one patients had tibial growth plate status assessments at baseline (10 patients in the ALCL group, 6 patients in the IMT group, and 15 patients in the Other Tumours group). Of these patients, 27 had open growth plates at baseline and were assessed in subsequent cycles.

No growth plate abnormalities were observed in paediatric patients overall.

- *Ophthalmic Examination*

Due to limitations in how data were collected on the CRF, summarizations of visual acuity data could not be performed. Of the 105 paediatric patients who had visual acuity evaluations at baseline, 42 patients were only recorded with "Yes/No".

Study A8081013

- *Vital Signs*

No vital sign changes were reported as AEs

- *Electrocardiograms*

Of the 3 patients in the ALCL group, 2 had maximum post-dose QTcF <480 msec and 1 had QTcF ≥500 msec and also a maximum increase from baseline in QTcF ≥60 msec on treatment (See Study A8081013 CSR Section 12.5.2.1.2). No AEs of all-causality Electrocardiogram QT prolonged were reported.

Of the 2 patients in the IMT group, none had a QTcF ≥500 msec or a maximum increase from baseline in QTcF ≥60 msec.

No patients met the pre-specified categorical criteria for a clinical significant change on QRS complex or PR interval

- *Ophthalmic Examination*

For biomicroscope examinations, the 3 patients in the ALCL group had normal results at baseline and no changes from baseline. The 2 paediatric patients in the IMT group had normal results at baseline but with no follow-up examinations. For ocular characteristics, the 3 patients in the ALCL group had no changes from baseline, with 2 having normal results and 1 with nevi or freckles on conjunctiva bulbi at baseline. The 2 paediatric patients in the IMT group had normal results at baseline but with no follow-up examinations.

Safety in special populations

Intrinsic Factors (Age, gender, race)

Data were examined for the effects of age, gender and race, by dose, and tumour type on crizotinib in patients of Study ADVL0912 and Study A8081013 as shown in the following sections. The small number of patients in the different subgroups does not allow for definitive conclusions to be made. However, the most frequent AEs (elevated transaminases, Vomiting, neutropenia, Nausea, Diarrhoea and leukopenia)

were reported in all subgroups, independent of age, gender, race or tumour types. The frequencies of each of these AEs slightly varied among subgroups.

The MAH provided numerous tables by age range for treatment duration, relative dose and average daily dose, treatment related adverse events, all causality serious adverse, treatment-related serious adverse events by PT or cluster term, dose reduction, dosing interruption, permanent treatment discontinuation, Shift Summary Results of Laboratory Tests by Maximum CTCAE Grade (hematology and chemistry, categorisation of body weight). However, it is difficult to draw any conclusion considering low number of patients included and multiple data.

In order to have a more general view of data by age ranges, the MAH completed the following table for each indication at 280 mg/m² BID including age range 2-<6 years given the requested enlargement of age range. Although no difference between classes of age can be evidenced at this time, no conclusion can be drawn considering the low number of subjects in each category (see table below).

Table 78 ALCL Safety Data at 280 mg/m² BID:

MedDRA Terms	Age 2-<6 years number (percentage) N=0	Age 6-<12 years number (percentage) N=10	Age 12-<18 years number (percentage) N=6
Total AEs	N/A	N/A	N/A
Treatment-emergent Adverse Events (TEAEs)	N/A	10 (100)	6 (100)
Serious AEs – Total	N/A	2 (20)	2 (33)
Serious AEs related to DFP	N/A	0	2 (33)
- Fatal	N/A	0	0
- Hospitalisation/prolong existing hospitalisation	N/A	0	1
- Life-threatening	N/A	0	0
- Disability/incapacity	N/A	0	0
- Other (medically significant)	N/A	0	1
AE leading to discontinuation	N/A	1	0
Diarrhoea	N/A	10 (100)	6 (100)
Vomiting	N/A	10 (100)	6 (100)
Nausea	N/A	7 (70)	4 (67)
NEUTROPENIA	N/A	10 (100)	5 (83)
ELEVATED TRANSAMINASES	N/A	10 (100)	5 (83)
LEUKOPENIA	N/A	7 (70)	6 (100)
BLOOD CREATININE INCREASED	N/A	3 (30)	0
VISION DISORDER	N/A	8 (80)	5 (83)

N/A= not available

MedDRA Terms	Age 2-<6 years number (percentage) N=0	Age 6-<12 years number (percentage) N=10	Age 12-<18 years number (percentage) N=6
Total AEs	N/A	N/A	N/A
Treatment-emergent Adverse Events (TEAEs)	N/A	10 (100)	6 (100)
Serious AEs – Total	N/A	2 (20)	2 (33)
Serious AEs related to DFP	N/A	0	2 (33)
- Fatal	N/A	0	0
- Hospitalisation/prolong existing hospitalisation	N/A	0	1
- Life-threatening	N/A	0	0
- Disability/incapacity	N/A	0	0
- Other (medically significant)	N/A	0	1
AE leading to discontinuation	N/A	1	0
Diarrhoea	N/A	10 (100)	6 (100)
Vomiting	N/A	10 (100)	6 (100)
Nausea	N/A	7 (70)	4 (67)
NEUTROPENIA	N/A	10 (100)	5 (83)
ELEVATED TRANSAMINASES	N/A	10 (100)	5 (83)
LEUKOPENIA	N/A	7 (70)	6 (100)
BLOOD CREATININE INCREASED	N/A	3 (30)	0
VISION DISORDER	N/A	8 (80)	5 (83)

N/A= not available

Extrinsic factors

No new information relevant to the effect of extrinsic factors is available for inclusion in this submission.

Use in Pregnancy and Lactation

In Study A8081013, 1 patient in the IMT group (17 years of age at the time of enrollment) had an AE of pregnancy reported on Day 1891 as an 'exposure during pregnancy"

Overdose

In Study ADVL0912, no AEs resulting from medication error were reported, or overdose.

In Study A8081013, an AE of Injury, poisoning and procedural complications/Overdose' was reported in 1 patient. No AEs were associated with the overdose. No action was taken following the overdose of 1 x 250 mg capsule.

Safety related to drug-drug interactions and other interactions

There is no new information on drug-drug interactions. In Study ADVL0912 and Study A8081013, no AEs of drug interactions were reported

Discontinuation due to adverse events

Study ADVL0912

Permanent treatment discontinuation

In Study ADVL0912, the AE CRF page did not include a field for 'action taken with study drug'. Thus, this did not allow for the generation of tables for AEs leading to permanent treatment discontinuation, dose reduction or temporary discontinuation of treatment. From the patient disposition CRF page, it could be determined whether a permanent treatment discontinuation was associated with an AE(s). However, the specific AE(s) was not provided on this CRF page and thus, in most cases, the specific AE(s) associated with the permanent treatment of crizotinib could not be determined. A listing of AEs that were ongoing at the time of permanent treatment discontinuation as well as a listing of SAEs that were present within 20 days of permanent treatment discontinuation are provided. Because of the nature of these data, no summary tables could be produced. The information on permanently discontinued treatment associated with AE(s) for Study ADVL0912 provided in this section was based on the patient disposition CRF page.

A total of 105 paediatric patients (22 in the ALCL group, 14 in the IMT group, and 69 in the Other Tumours group) received at least 1 dose of crizotinib (Table *79*). As of the date of study closure, all patients who received at least 1 dose of crizotinib were off study as follows:

- **ALCL Group**: Of the 22 paediatric patients who received at least 1 dose of crizotinib, 20 (90.9%) paediatric patients had discontinued from study and 2 (9.1%) paediatric patients on treatment at the date of study closure were switched to commercial supplies (Table *79*).

The most frequent (> 20% of patients) reasons for discontinuation were physician decision and refusal of further protocol therapy by patient/parent/guardian.

In addition, 11 patients in the ALCL group permanently discontinued crizotinib due to HSCT

- **IMT Group**: Of the 14 paediatric patients who received at least 1 dose of crizotinib, 11 (78.6%) paediatric patients had discontinued from the study and 3 (21.4%) paediatric patients on treatment at the date of study closure were switched to commercial supplies (Table *79*). The most frequent (> 20% of patients) reasons for discontinuation were adverse event and physician decision.

The most frequent (>20% of patients) reason for discontinuation was physician decision Permanent discontinuation from treatment associated with an AE occurred in 11 (10.5%) patients (1 patient in the ALCL group associated with NEUTROPENIA, 4 patients in the IMT group and 6 patients in the other tumour Group).

Table 79 Disposition Events Summary by Tumour Type (All Tumour Types, All Dose Levels, Age < 18 years) - Safety Analysis Set (Protocol ADVL0912)

Number (%) of Subjects	ALCL (N=22) n (%)	IMT (N=14) n (%)	Other Tumors (N=69) n (%)	Total (N=105) n (%)
Disposition Phase: Treatment				
Subjects Not Entered:	0	0	0	0
Subjects Entered:	22 (100)	14 (100)	69 (100)	105 (100)
Discontinued [1]	20 (90.9)	11 (78.6)	69 (100)	100 (95.2)
Adverse Event	1 (4.5)	4 (28.6)	6 (8.7)	11 (10.5)
Lost to Follow-Up	1 (4.5)	0	0	1 (1.0)
Non-Compliance With Study Drug	1 (4.5)	2 (14.3)	0	3 (2.9)
Physician Decision	7 (31.8)	4 (28.6)	1 (1.4)	12 (11.4)
Progressive Disease	2 (9.1)	0	54 (78.3)	56 (53.3)
No Longer Meets Eligibility Criteria	1 (4.5)	0	0	1 (1.0)
Refusal of Further Protocol Therapy by Patient/Parent/Guardian [2]	6 (27.3)	1 (7.1)	8 (11.6)	15 (14.3)
Withdrawal of Consent	1 (4.5)	0	0	1 (1.0)
Completed [3]	2 (9.1)	3 (21.4)	0	5 (4.8)

[1] Based on primary off protocol therapy reason.
[2] Patients did not receive further treatment, but continued to be followed for safety.
[3] Patients on treatment at study closure, moved to commercial/donated supplies.

In ALCL group, 3 paediatric patients (13.6%) had a dose reduction; 1 from 280 mg/m^2 BID to 200 mg/m^2 BID and 2 from 280 mg/m^2 BID to 215 mg/m^2 BID (Table *80*).

In IMT group, 4 paediatric patients (28.6%) had a dose reduction; all from 280 mg/m^2 BID to 215 mg/m^2 BID (Table *80*).

Table 80 Crizotinib Dose Reductions by Tumour Type (All Tumour Types, Age < 18 years) - Safety Analysis Set (Protocol ADVL0912)

	ALCL (N=22) n (%)	IMT (N=14) n (%)	ALCL + IMT (N=36) n (%)	Other Tumors (N=69) n (%)	Total (N=105) n (%)
Number of Subjects with at least one Dose Reduction [1]	3 (13.6)	4 (28.6)	7 (19.4)	7 (10.1)	14 (13.3)
Treatment duration with dose reduced (weeks) [2]					
n	3	4	7	7	14
Mean	4.05	36.29	22.47	59.73	41.10
SD	0.082	32.915	28.960	138.584	98.107
Median	4.00	37.14	4.14	8.00	6.07
Range (min, max)	(4.0, 4.1)	(3.7, 67.1)	(3.7, 67.1)	(0.9, 373.7)	(0.9, 373.7)
Total number of subjects with dose reduction duration of: [3]					
≤ 2 weeks	0	0	0	2 (28.6)	2 (14.3)
> 2 - ≤ 4weeks	2 (66.7)	1 (25.0)	3 (42.9)	1 (14.3)	4 (28.6)
> 4 - ≤ 6 weeks	1 (33.3)	0	1 (14.3)	0	1 (7.1)
> 6 - ≤ 12 weeks	0	0	0	1 (14.3)	1 (7.1)
> 12 - ≤ 18 weeks	0	1 (25.0)	1 (14.3)	2 (28.6)	3 (21.4)
> 18 - ≤ 24 weeks	0	0	0	0	0
> 24 - ≤ 52 weeks	0	0	0	0	0
> 52 weeks	0	2 (50.0)	2 (28.6)	1 (14.3)	3 (21.4)

[1] A dose reduction is defined as any reduction below the starting dose of prescribed dose per day. Dosing interruptions are not counted as reductions.
[2] Treatment duration is the sum of all different dosing periods with reductions.
[3] Percentages are based on the number of subjects with at least one dose reduction.

- *Time to first dose reduction*

Of the **105 patients** in safety analysis set, 14 (13.3%) experienced at least 1 crizotinib dose reduction. The overall median (range) time to first dose reduction was 9.64 (4.0-201.1) weeks. There were 2/20, 1/8, 9/56, and 2/8 patients who experienced at least one dose reduction at 165 mg/m^2 BID, 215 mg/m^2 BID, 280 mg/m^2 BID, and 365 mg/m^2 BID, respectively.

No patients had a dose reduction at 100 mg/m^2 BID or 130 mg/m^2 BID

Dosing interruption

Only in the ALCL group, IMT group, and ALCL+IMT group did the majority of patients have at least 1 dosing interruption (Table *81*).

Table 81 Crizotinib Dosing Interruptions by Tumour Type (All Tumour Types, Age < 18 years) - Safety Analysis Set (Protocol ADVL0912)

	ALCL (N=22)	IMT (N=14)	ALCL + IMT (N=36)	Other Tumors (N=69)	Total (N=105)
	n (%)	n (%)	n (%)	n (%)	n (%)
Number(%) of Subjects with at least one Dosing Interruption [1]	16 (72.7)	10 (71.4)	26 (72.2)	18 (26.1)	44 (41.9)
Total Number of Subjects with Maximum Dosing Interruptions of [2]:					
< 1 week	10 (62.5)	3 (30.0)	13 (50.0)	7 (38.9)	20 (45.5)
1 - < 2 weeks	5 (31.3)	2 (20.0)	7 (26.9)	11 (61.1)	18 (40.9)
2 - < 3 weeks	1 (6.3)	4 (40.0)	5 (19.2)	0	5 (11.4)
3 - < 4 weeks	0	0	0	0	0
≥ 4 weeks	0	1 (10.0)	1 (3.8)	0	1 (2.3)

[1] A dosing interruption is defined as patient not treated for more than 1 day in a cycle.
[2] Percent is based on the total number of subjects with at least one dosing interruption.

- *Time to first dosing interruption*

Of the 105 patients in safety analysis set, 44 (41.9%) experienced at least 1 dosing interruption. The overall median (range) time to first dosing interruptions was 7.93 (1.1- 176.1) weeks. There were 2/6, 9/20, 2/8, 29/56, and 2/8 patients who experienced at least 1 dosing interruption at 100 mg/m^2 BID, 165 mg/m^2 BID, 215 mg/m^2 BID, 280 mg/m^2 BID, and 365 mg/m^2 BID, respectively. No patients had a dosing interruption at crizotinib 130 mg/m^2 BID.

Study A8081013

Permanent treatment discontinuation

No patient was permanently discontinued from study treatment associated with AEs

Dose reduction

No patients had a dose reduction associated with AEs in this study

Dosing interruption

A total of 4 (80.0%) patients (2 ALCL patients and 2 IMT patients) had a dosing interruption.

The most frequently reported AEs (in ≥40% of patients) associated with dosing interruption for both ALCL and IMT patients were Blood creatine phosphokinase increased and NEUTROPENIA (in 2 [40.0%] patients each).

Treatment-related AEs associated with dosing interruptions were reported in 1 patient in the ALCL group (Nausea, Vomiting, AST increased, and CPK increased) and in 1 patient in the IMT group (NEUTROPENIA and Myelosuppression)

Pooled data (study ADVL0912 and Study A8081013)

Permanent treatment discontinuation

Of the 110 patients with all tumour types, permanent discontinuation from treatment associated with an AE occurred in 11 (10.0%) patients (of which 1 [4.0%] patient in the ALCL pool, and 4 [25.0%] patients in the IMT pool) all from study ADVL0912. As mentioned above, patient in the ALCL pool permanently discontinued treatment associated with NEUTROPENIA (study ADVL0912)

Dose reductions

Across the 4 pools, the number of patients with at least one dose reduction was low (Table *82*)

Table 82 Crizotinib Paediatric Submission Dose Reductions by Tumour Type (All Tumour Types, Age < 18 years) - Safety Analysis Population (Paediatric Pool)

	ALCL (N=25) n (%)	IMT (N=16) n (%)	ALCL + IMT (N=41) n (%)	All Tumor Types (N=110) n (%)
Number of Subjects with at least one Dose Reduction [1]	4 (16.0)	4 (25.0)	8 (19.5)	15 (13.6)
Treatment duration with dose reduced (weeks) [2]				
n	4	4	8	15
Mean	44.89	36.29	40.59	49.52
SD	81.691	32.915	57.840	100.007
Median	4.07	37.14	8.21	8.00
Range (min, max)	(4.0, 167.4)	(3.7, 67.1)	(3.7, 167.4)	(0.9, 373.7)
Total number of subjects with dose reduction duration of: [3]				
≤ 2 weeks	0	0	0	2 (13.3)
> 2 - ≤ 4weeks	2 (50.0)	1 (25.0)	3 (37.5)	4 (26.7)
> 4 - ≤ 6 weeks	1 (25.0)	0	1 (12.5)	1 (6.7)
> 6 - ≤ 12 weeks	0	0	0	1 (6.7)
> 12 - ≤ 18 weeks	0	1 (25.0)	1 (12.5)	3 (20.0)
> 18 - ≤ 24 weeks	0	0	0	0
> 24 - ≤ 52 weeks	0	0	0	0
> 52 weeks	1 (25.0)	2 (50.0)	3 (37.5)	4 (26.7)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 03SEP2019)
[1] A dose reduction is defined as any reduction below the starting dose of prescribed dose per day. Dosing interruptions are not counted as reductions.
[2] Treatment duration is the sum of all different dosing periods with reductions.
[3] Percentages are based on the number of subjects with at least one dose reduction.

Dosing interruptions

The percentage of patients having a dosing interruption is higher in the ALCL+IMT pool than in the All Tumour Types pool (Table *83*). However, the median duration of treatment was longer in the ALCL+IMT pool than the All Tumour Types pool (Table *40*).

Table 83 Crizotinib Paediatric Submission Dosing Interruptions by Tumour Type (All Tumour Types, Age < 18 years) - Safety Analysis Population (Paediatric Pool)

	ALCL (N=25) n (%)	IMT (N=16) n (%)	ALCL + IMT (N=41) n (%)	All Tumor Types (N=110) n (%)
Number(%) of Subjects with at least one Dosing Interruption [1]	17 (68.0)	12 (75.0)	29 (70.7)	47 (42.7)
Total Number of Subjects with Maximum Dosing Interruptions of [2]:				
< 1 week	10 (58.8)	4 (33.3)	14 (48.3)	21 (44.7)
1 -< 2 weeks	5 (29.4)	2 (16.7)	7 (24.1)	18 (38.3)
2 -< 3 weeks	2 (11.8)	4 (33.3)	6 (20.7)	6 (12.8)
3 -< 4 weeks	0	0	0	0
≥ 4 weeks	0	2 (16.7)	2 (6.9)	2 (4.3)

Includes data for: ADVL0912, A8081013 (Date of Data Cutoff: 03SEP2019)
[1] A dosing interruption is defined as patient not treated for more than 1 day in a cycle.
[2] Percent is based on the total number of subjects with at least one dosing interruption.

Post marketing experience

Not applicable

2.5.1 Discussion on clinical safety

Xalkori as single agent has been approved in Europe in 2012 and is indicated for adult patients with ALK-positive and ROS-1-positive NSCLC. The MAH has applied for an extension of indication in paediatric patients with resistant/refractory ALK-positive ALK + ALCL and ALK-positive IMT.

Safety data for this application are mainly based on 2 non comparative studies. Study ADVL0912 was a phase I/II trial with a dose-escalation part and a dose expansion part. Safety population of study ADVL0912 includes 22 paediatric patients with ALK-positive ALCL and 14 paediatric patients with ALK-positive IMT. In addition, study ADVL0912 includes 69 patients in the "other tumour group" with tumours presenting ALK or MET alterations and are considered as supportive data. Study A8081013 is a phase Ib trial in which 3 paediatric patients with ALK-positive ALCL and 2 paediatric patients with ALK-positive IMT were included.

Both studies provided data for a limited number of patients which is expected due to the rarity of the targeted indications. Data are presented by study and indication and also as pooled data, which is an acceptable strategy given the small number of patients.

Study A8081013 was ongoing at the time of the MAA submission and updated data are expected to be provided under Article 46 of Regulation (EC) No 1901/2006

Patient exposure

In Study ADVL0912, the intended dose (280 mg/m² BID) was received by 28 patients in the targeted indications while all 5 patients from study A801013 received the intended dose. Limited data are available

to assess lower doses (7 patients received the dose of 165 mg/m² BID and only 1 patient received 100mg/m² BID) in Study ADVL0912.

The median duration of treatment for patients with IMT in study ADVL0912 was 22.88 months overall and 18.86 months at the intended dose. The majority of patients at 280 mg/m² BID 8/12) had a duration of treatment ≥ 12 months. In addition, both patients with IMT study A801013 had a treatment duration ≥ 12 months.

On the other hand, the median duration of treatment for patients with ALCL in study ADVL0912 was 5.11 months overall and 4.21 months at the intended dose. The shorter median duration of treatment in ALCL patients compared to IMT patients can be attributed in part to the fact that 11 of these patients permanently discontinued crizotinib to undergo HSCT. Only 5 ALCL patients within both studies treated at the intended dose had a treatment duration≥ 12 months. Overall, long term data are scarce, especially for patients with ALCL.

Mean relative dose at the intended posology was 88.68% and 85.52% for ALCL and IMT respectively in study ADL0912. Dose reductions and dosing interruptions in case of toxicities were allowed by protocol, which may explain the relative dose results. However, considering the unclear informations on the formulations received by the patients, it could not be excluded that a poor observance in young patients may have contributed to these data. The MAH discussed these data with regards to the observance and a potential issue was not evidenced.

Demographic

The safety population reflects the population of the claimed indication with patients between 6 and 18 years old, a majority of white patients, a majority of males in ALCL indication and a majority of women in IMT indication. Younger patients were included providing data for patients < 6 years old.

Adverse events

The MAH reported TEAE by SOC and PT and further created "cluster terms" (in capital letters) to address the reliance on single MedDRA PT. This methodology was previously used in initial application of XALKORI.

In both studies ADVL0912 and A8081013, TEAEs were observed in 100% of the safety population. In both indications, at the intended dose of 280mg/m² BID, the majority of patients experienced grade 3 or 4 AEs (95.5% of ALCL patients and 78.5 % of IMT patients). No grade 5 AE were reported in ALCL or IMT patients.

The nature of the most frequently reported TEAEs in paediatric patients are consistent with the nature of most frequently reported TEAEs of crizotinib in adult patients (elevated transaminases, Vomiting, neutropenia, Nausea, Diarrhoea, and leukopenia). The most frequently reported all-causality grade 3 or 4 AE in all paediatric patients was neutropenia. Furthermore, all grade 3/4 AE from paediatric population were observed with the same severity (as grade 3/4 AE) in the adults population except for neutropenia (see below). These TEAE are listed in the SmPC of Xalkori (elevated transaminases, neutropenia, leukopenia, bradycardia, Diarrhoea, nausea, vomiting and oedema).

In study ADVL0912, the most frequently reported Grade 3 or 4 treatment-related AE was neutropenia in ALCL (63.6 %) and IMT (50.0%) population.

In study A8081013, grade 3/4 treatment-related TEAE were reported in 2/3 ALCL patients and 1/2 IMT patient (neutropenia, vomiting, elevated transaminases and blood creatine phosphokinase (CPK) increase. The grade 4 AE of CPK increase was considered as a SAE. This event resolved after a temporarily withdrawal of crizotinib which was then resumed at a reduce dose. Moreover, three other grade 4 CPK increase were observed in the adult population, 2 of which were considered as SAE. However, all SAE of CPK increase were reported from the same site where it is routine practice to test CPK for cancer patients. Moreover, for 5 of the 6 patients in both studies, CPK increase occurred in a context of strenuous physical activity. Events of blood CPK increase and rhabdomyolisis are currently followed in the PSUR and a review of both events is expected in the next PSUR.

Regarding frequency of AE, it appears that gastrointestinal toxicities occurred at a higher frequency in the paediatric population compared to the adult population (nausea: 82.9% vs 56.6%, diarrhoea: 85.4% vs 54.0% and vomiting: 95.1% vs 50.8). Recommendations for the management of gastrointestinal toxicities specifically for paediatric population have been added in section 4.4 of the proposed SmPC which is acknowledged considering the higher risk of dehydration in children.

In addition, ELEVATED TRANSAMINASES were observed at a higher frequency in the paediatric population compared to the adult population (85.4% vs 32.1 %). Dose modifications as well as the recommendations for monitoring in the SmPC appear currently acceptable since very frequent. Of note, hepatotoxicity is listed as an important identified risk in the RMP.

Blood creatinine increase was also observed at a higher frequency in paediatric population relative to adult population (41.5% vs 8.0%). Although monitoring of blood creatinine was already recommended in the SmPC, it seems that additional recommendations for paediatric population are needed. Indeed, although acute renal failure, an expected AE in adult population, was not observed in paediatric population, the limited number of patients does not allow to exclude this AE in paediatrics. In response to a request, the MAH agreed to a close monitoring through PSUR of renal toxicity in post-marketing setting provided favourable outcome of the marketing authorisation from the CHMP.

Considering adverse reactions listed in the SmPC for adult population, some PTs were not reported in paediatrics. Among them, syncope, interstitial lung disease, hepatic failure and renal cyst will be closely monitored in post marketing setting in PSUR through the corresponding safety concerns listed in the RMP and renal failure will be closely monitored through PSUR as requested above. Additional data on blood testosterone decrease are currently collected in the ongoing study ITCC 053 'CRISP' study (protocol title: A phase 1B of crizotinib either in combination or as single agent in pediatric patients with ALK, ROS1 or MET positive malignancies) proposed as PAM provided a favourable outcome of the CHMP in addition to tanner stage to assess the impact of crizotinib on puberty.

PT of abdominal pain was observed in 18/41 patients of pooled ALCL + IMT patients. No other information was provided. Abdominal pain was included in table 8 of the SmPC (see SmPC section 4.8)

Serious adverse events

In study ADVL0912, SAEs were reported in 31.8% and 7.1% of ALCL and IMT patient respectively.

Treatment-related SAEs were experienced by 5 ALCL patients: 3 patients at 165 mg/m² BID and 2 patients at 280 mg/m² BID. 2 patients at 165mg/m² were 5 years old (hypoalbuminemia and blood creatinine increase for one patient and kidney enlargement for the other patient) while the third patient was 13 years old and experienced neutropenia and cyanopsia. Both patients at 280 mg/m² BID were 14 years old and experienced infective myositis and skin infection for 1 patient and tumour lysis syndrome (TLS) for the other patient. In IMT patients, only one patient experienced a treatment related SAE of bradycardia at 280 mg/m² BID.

Kidney enlargement did not recovered at the end of therapy. However, it is not clear from the provided documents if this AE led to discontinuation of treatment. Indeed, kidney enlargement is not reported at the last patient visit. However, as agreed by the MAH, renal toxicity will be closely monitored through PSUR in post marketing setting provided favourable outcome of the marketing authorisation from the CHMP, which will allow further characterization of renal toxicity.

Laboratory test findings

Neutrophil count decrease was the most frequent haematological laboratory finding which is consistent with adverse events data.

Importantly, it is to be noted that in study ADVL0912, laboratory evaluations were reported in the CRF only for Cycle 1 and reported afterwards only if laboratory test results were considered clinically relevant. In that case, they were to be reported as AEs. This issue raises concerns about the comprehensiveness of data for cycles ≥ 2 and about cumulative toxicity. Supplemental analysis could not resolved these concern. However, laboratory test data grade 3/4 are collected in ongoing CRISP study proposed as PAM provided a favourable outcome of the CHMP.

Grade 3/4 thrombocytopenia and anemia were not reported in the pooled data of study ADVL0912 and are not reported as adverse reaction in the specific table 8 of the SmPC for paediatric patients section 4.8. However, dosing modifications are provided in Table 5 of the SmPC section 4.2 in case of grade 3 and 4 platelet count decrease and anemia. The MAH was requested to clarify the need for these recommendations and for inclusion of PT of thrombocytopenia and anemia in table 8 of the SmPC. The MAH agreed to update the SmPC regarding anemia since it is a known ADR in adult patients and has been reported in children.

Other observations related to safety

Visual acuity

In study ADVL0912, due to limitations in how data were collected on the CRF, a comprehensive assessment is not possible. For this reason and considering any potential difficulties to explain and verbalize ocular acuity disorders in younger patients, additional monitoring and dose modifications recommendations were requested and agreed by the MAH.

Bone growth

Non-clinical data evidenced a decrease in bone formation and in study ADVL0912, only 31/105 patients (29.5%) of the safety paediatric population (all tumour types) had tibial growth plate status assessments at baseline. In addition, bone fracture case reports have been reported with crizotinib including in paediatric patients. The MAH was requested to discuss measures to better identify and characterize the risk of bone toxicities and on bone growth in post-marketing setting provided favorable outcome of the MA by the CHMP. Inclusion of this safety concern in the RMP was to be discussed.

Overall, while it is endorsed that cases of bone toxicity reported in clinical studies have confounding factors, a pharmacological mechanism and non-clinical data of crizotinib supported by non-clinical data of other ALK inhibitors do not allow to exclude a risk in human. The MAH agreed to add "bone toxicities and impaired bone growth" in the RMP as an important potential risk in paediatric population. In addition, tibial growth plate is assessed in ongoing study CRZ-NBALCL (Protocol WI218627. Title: 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) while bone toxicities will be reported as AEs.

Safety in special groups and situation

The MAH provided numerous tables by age range making difficult to draw any conclusion considering low number of patients and multiple data. In order to have a more general view of data by age ranges. The MAH was requested to complete an adequate table. Although no difference between classes of age can be evidenced at this time, no conclusion can be drawn considering the low number of subjects in each category.

Discontinuation due to adverse events

In study ADVL0912, only 1/22 patient in ALCL group and 4/14 patients in IMT group discontinued treatment due to an adverse event. This difference may be attributed to the shorter duration of treatment for patients in ALCL group who received HSCT. Dose reductions occurred in 3/22 patients in ALCL group and in 4/14 patients in IMT group. Median dose reduction were shorter in ALCL group compared to IMT group with 4.00 and 37.14 weeks in ALCL and IMT group respectively. No discontinuation or dose reduction occurred in study A8081013.

Finally, dosing interruptions were frequent (68% and 75% of pooled ALCL patients and IMT patients respectively). The majority of treatment interruptions was < 1 week for ALCL pool whereas no such generalisation can be made for IMT pool.

The AEs which led to discontinuation, dose reduction and treatment interruption in study ADVL0912 were not presented due to the absence of a specific field in the CRF. However, those reasons are to be collected in the ongoing study CRISP proposed as PAM provided a favourable outcome of the CHMP which will allow further characterization of the safety profile.

Post marketing experience

Due to limited available data in paediatrics, a summary of all available safety data of post-marketing use of crizotinib in paediatric population as well as safety data issued from compassionate use in ALCL and IMT paediatric patients was requested and did not alter the described safety profile of crizotinib.

2.5.2 Conclusions on clinical safety

Xalkori showed a safety profile mainly related to gastrointestinal, hepatic, haematological and renal toxicity. These AE are known AR in adult population but occurred at a higher frequencies in paediatric patients than in the adult population. Similar severities to the adult population were observed except for neutropenia grade 3/4 which was observed at a notable higher frequency in paediatric patients. Additional monitoring and management of these AE are provided in the SmPC of Xalkori with adaptation for paediatric population when required.

In addition, as Visual disorders may be more challenging to assess in the paediatric population a specific monitoring and additional management are now recommended.

Concerns about bone toxicities and bone growth in the paediatric population will be addressed in part in ongoing study CRZ-NBALCL. In addition, "bone toxicities and impaired bone growth" has been added as important potential risk in the RMP.

Overall, the evaluation of additional requested data and the implementation of monitoring and management of key toxicities allowed to resolve number of uncertainties on the safety profile of Xalkori.

2.5.3 PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.5.4 Direct Healthcare Professional Communication

A Direct Healthcare Professional Communication (DHPC) is considered necessary in order to communicate on the risk of ocular toxicity (including risk of severe visual loss) and need for monitoring in paediatric patients with anaplastic lymphoma kinase (ALK) and positive anaplastic large cell lymphoma (ALCL) or with ALK positive inflammatory myofibroblastic tumour (IMT). The MAH should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent upon receipt of the Commission Decision with the revised SmPC with the changes highlighted to Paediatric oncologists, paediatric haemato-oncologists, ophthalmologists and hospital pharmacists. Additional recipients to be further defined at national level, incl. professional societies and national associations, depending on the national healthcare system and in agreement with the respective national competent authority.

2.6 Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 8.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 8.2 with the following content:

Safety concerns

Table 84 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 • Bone toxicity and Impaired Bone Growth in the Paediatric Population
Missing information	• Patients undergoing long-term treatment

CYP = Cytochrome P; 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.

Pharmacovigilance plan

Table 85 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)				
CRISP Study ITCC 053 Innovative Therapy for	A phase 1B of crizotinib either in combination or as single agent in paediatric patients with	To evaluate the risk factors, manifestations, and outcomes of ocular	Study Completion: February 2026	Final Analysis: 28 February 2027

Children with Cancer (Category: 3)	ALK, ROS1 or MET positive malignancies.	toxicities (including SVL/PSTE) associated with crizotinib in paediatric and young adult patients		
CRZ-NBALCL Study (Protocol WI218627) (Category: 3)	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)	To evaluate the AEs of ocular toxicity and bone toxicity and impaired bone growth associated with crizotinib in paediatric and young adult patients	Study Completion: June 2023	Final Analysis: 30 September 2024

Risk minimisation measures

Table 86 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: None
Bradycardia	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.5. 4.8	Routine pharmacovigilance activities beyond adverse

Table 86 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	PL sections 2, 4 Additional risk minimisation measures: Educational materials	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 Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None

Table 86 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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 DHCP (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
Bone Toxicity and Impaired Bone Growth in the Paediatric Population	Routine risk minimisation measures: SmPC section 5.3 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: CRZ-NBALCL study
Missing Information		
Patients undergoing long-term treatment	None	None

EU = European Union; ILD = Interstitisal 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.

2.7 Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new warning with regard to visual disorders and a warning on severe gastrointestinal toxicities in children has been added to the product information. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and accepted by the CHMP.

2.7.1 User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1 Therapeutic Context

3.1.1 Disease or condition

The MAH is seeking an extension of the original indication for crizotinib to include treatment of paediatric patients (age ≥ 6 to < 18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and with unresectable, recurrent, or refractory ALK-positive inflammatory myofibroblastic tumour (IMT).

3.1.2 Available therapies and unmet medical need

Anaplastic Large Cell Lymphoma (ALCL)

ALCL is a chemosensitive malignancy both in paediatric and adult patients. The majority (84-90%) of ALCL in children has been reported to be ALK-positive (Burkhardt et al, 2005; Le Deley et al, 2008; Mussolin et al, 2010); whereas, studies have shown only ~50% of adult ALCL contain the ALK fusion gene (Gascoyne et al, 1999; Mussolin et al, 2010). Treatment regimens are based on short-pulse chemotherapy and high-dose MTX, cyclophosphamide, vincristine, doxorubicin, vinblastine, and corticosteroids. There is no consensus on the treatment of relapsed or refractory paediatric ALCL. Unlike other lymphomas, ALCL is usually still chemosensitive at relapse. 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 HSCT after a second CR is frequently used for treatment of relapsed ALCL. Patients with subsequent relapses can also obtain prolonged remission following the administration of single-agent vinblastine. Crizotinib could be a new treatment option for paediatric patients with ALK-positive relapsed or refractory ALCL.

Inflammatory myofibroblastic tumour (IMT)

IMT is a class of tumour that presents a characteristic histological picture comprising a spindle cell proliferation with a chronic inflammatory infiltrate of plasma cells, lymphocytes, and histiocytes (Souid et al, 1993). Approximately 50%-70% of IMTs are positive for ALK expression (Mossé et al, 2009). Surgical resection is the mainstay of treatment, but a complete surgical resection may not always be possible. Local recurrences have been reported with tumour invasion and fatal outcomes and there are no approved therapies for patients with unresectable, recurrent, or refractory IMT and no standard therapy for aggressive unresectable tumours. IMTs may respond initially to systemic corticosteroids, non-steroidal anti-inflammatory drugs or chemotherapeutics including vincristine, methotrexate, etoposide, cisplatin, cyclophosphamide, vinorelbine, doxorubicin, and dacarbazine. Crizotinib could be a new treatment option for paediatric patients with ALK-positive IMT, a subgroup that currently lacks any approved therapies.

3.1.3 Main clinical studies

Efficacy data are mainly based on these 2 non-comparative studies. Study ADVL0912 was a phase I/II trial with a dose-escalation part and a dose expansion part. Efficacy population of study ADVL0912 includes 22 paediatric patients with ALK-positive ALCL and 14 paediatric patients with ALK-positive IMT. Study A8081013 is an ongoing phase Ib trial in which 3 paediatric patients with ALK-positive ALCL and 2 paediatric patients with ALK-positive IMT were included.

3.2 Favourable effects

The ORR for the 22 enrolled ALCL patients was 86.4% (95% CI: 66.7, 95.3) for both dose level groups (6 patients received 165 mg/m² BID with an ORR of 83.3% and 16 patients received 280 mg/m² BID and achieved an ORR of 87.5%). The ORR for the 14 patients in the IMT group was 85.7% (95%CI: 60.1, 96.0) across all dose levels; 1 patient enrolled at the 100 mg/m2 BID dose level and did not have an objective response, 1 patient enrolled at 165 mg/m² BID and had an objective response, and 12 patients enrolled at 280 mg/m² BID and had an ORR of 91.7%.

CRs were quite outstanding across study groups and observed in 77.3% (17/22) of patients in the ALCL group across both dose levels, and in 83.3% (5/6) and 75.0% (12/16) of patients at the 165 mg/m² BID and 280 mg/m² BID dose levels, respectively. In the IMT group, CRs were observed in 35.7% (5/14) of paediatric patients across dose levels.

ORR and CR results remained stable across all age groups, despite the absence of patients under the age of 3, also including ALCL patients between 18 and 21. These results are very encouraging. It is to be noted that 100% of the 4 patients between 18 and 21 years-old treated with crizotinib for ALCL achieved CR.

The median DR was of 3.6 months (range: 0.0 to 15.0 months) for the responders across both dose levels in the ALCL group; 5 patients with objective tumour response at the 165 mg/m² twice daily dose level had a median DR of 6.9 months and 14 patients with objective tumour response at the 280 mg/m² twice daily dose level had a median DR of 2 months. The DR is quite underestimated here because of the 10 patients who proceeded to HSCT after completing objective response (2 at the 165 mg/m² dose level and 8 at the 280 mg/m²dose level, censored at time of HSCT). A longer median DR (9.2 months) is noted for ALCL patients who did not receive an HSCT.

DR for patients with IMT were more durable, with a median DR of 14.8 months (range: 2.8 to 48.9 months) for the 12 responders. Eight of the 11 enrolled patients in the 280 mg/m² BID completed the study without any event.

Very rapid responses were observed in the ALCL group with a median time to response (TTR) of 0.9 months (0.8 to 2.1 months) across both dose levels. Median TTR was comparable between the 165 mg/m² BID and the 280 mg/m² BID dose level groups (0.9 months and 1 month, respectively). For IMT group, the responses were also quite rapid and comparable to those observed in ALCL group, with a median TTR of 1 month (0.8 to 4.6 months) across the two dose levels.

In both dose levels, crizotinib presents similar efficacy results. Data at 280 mg/m² BID are more robust considering the larger number of enrolled patients (most patients with ALCL (16 of 22) and most patients with IMT (12 of 14) were treated at 280 mg/m² BID). Moreover, due to the paediatric-inadequate dosage form, dose adjustments below 200 mg are not possible and the 280 mg/m² BID dose is allowing more flexible dose reduction recommendations.

A8081013 study, is an ongoing supportive study aiming to assess the efficacy, safety, and PK of crizotinib in patients with ALK+ tumours (other than NSCLC). Five paediatric patients were enrolled at data cut-off date. Efficacy data from this supportive study do not allow to draw robust conclusions for efficacy given the limitations in study design (even though it includes OS and PFS as secondary endpoints) and the limited number of paediatric patients enrolled at the time being. The results are however in line with those reported in the pivotal study and are quite supportive.

As part of the justification of the positive B/R balance for crizotinib in the two claimed indications among paediatric patients, the MAH provided an exhaustive overview of published data from different crizotinib non-sponsored studies, drawing a parallel with the ADVL0912 pivotal study results.

For ALCL patients, the MAH elaborates on the results from the French AcSé program. Since Crizotinib has shown significant clinical activity in relapsed/refractory ALK+ ALCL in small cohorts of patients and in order to avoid a generalized off-label use and allow for an equal and nationwide access to crizotinib, the French National Cancer Institute (INCa, state organization) launched the AcSé program in patients aged 1 year and older with advanced ALK+ ALCL. Median age was 21 years and the median number of prior chemotherapy lines was 2 including brentuximab in 66% of patients. Among the 15 evaluable patients, 10 achieved an OR (67%, CI95% [42%-85%]) (9CR, 1PR) and 5 experienced a disease progression. The response rate was similar in paediatric patients (67%, CI95% [24%, 94%]) and in adults (6/9, 67%, CI95% [31%, 91%]) and with a median follow-up of 12 months, the median PFS was 11.6 months (CI95% [1.41, NA]). A compassionate use program where Crizotinib was administered as monotherapy to 11 ALK+ lymphoma patients who were resistant/refractory to cytotoxic therapy also pointed out very encouraging results as the ORR was of 90.9%; (95%CI = 58.7% to 99.8%).

Efficacy results obtained within the small cohorts of patients treated for IMT report comparable ORR even though the 2018's results presented by the MAH for the EORTC 90101 CREATE study are not up to date since the final analysis as of data cut-off on 28th January 2021 describe an ORR reaching 66.7% (95% CI 34.9-90.1%) in ALK+ IMT patients and a 3-year OS rates of 83.3% (95% CI 48.2-95.6).

All these supplementary studies results are in line with the ADVL0912 pivotal study findings and are considered supportive.

3.3 Uncertainties and limitations about favourable effects

Given the rarity of ALCL and IMT in general and in particular in the paediatric setting, the number of patients that could be enrolled in each of the groups is small and the results would be sensitive to shifts in the data. Efficacy data were assessed as secondary endpoints in the pivotal study and indicate that crizotinib has a clinically meaningful benefit as a single agent in paediatric patients within the two claimed indications. It should be noted that limitations regarding the analysis of data from the pivotal study are related to the fact that the study was not sponsored by the MAH.

The MAH was asked to justify that available data support the full scope of the proposed indication by providing a more comprehensive description of the enrolled patients regarding prior therapies, treatment line and transplantation status. No details regarding exact treatment lines nature/settings were provided given the fact that the pivotal study was not powered to collect the requested information.

Post-transplant efficacy and safety data, 100-day mortality and GvHD rates are not available since the pivotal study was completed 10 years ago when standards and clinical practices were much different and no guidance was planned for proceeding to HSCT within the protocols. No such data were thus collected, which also applies for patients for whom crizotinib was used as a bridge to HSCT. The SmPC has been amended in order to highlight this data gaps.

No Pfizer-sponsored studies in adults and in paediatric patients are planned or ongoing with crizotinib monotherapy in the claimed indications. The MAH proposed to implement PAMs requested by the FDA to further assess the PK and efficacy of crizotinib at the lower dose of 165 mg/m^2 BID. The MAH confirmed that there was no possibility to amend the study protocols in order to plan the whole package of efficacy analyses for the 280 mg/m^2 BID dose with a longer FU period for patients undergoing HSCT ensuring collection of data regarding 100-day mortality and acute/chronic GvHD rates for ALCL patients and surgery statues for the IMT population. However, the MAH has provided some reassurance by confirming that patients could however still be enrolled at the 280 mg/m² BID, as Study ITCC 053 has been designed to recruit up to 30 patients (including those with IMT) in the stratum 3. Patients with ALK+ rr ALCL can be enrolled in stratum 3 once stratum 1b (at 165 mg/m² BID) is completed. As requested during the previous round, these additional ongoing studies were added in the RMP and the results planned with reasonable timelines.

Two different formulations were used within the submitted studies including the oral solution which is not available on the market. An efficacy analysis by formulation was also provided but no clear conclusions regarding formulation-effect could be drawn for efficacy parameters compared to the previously assessed pooled data considering the very limited number of patients especially for the oral solution group (6 each in the ALCL and the IMT group). The MAH though confirmed that a paediatric microsphere encapsulated formulation is under development with 3 strengths: 20 mg, 50 mg, and 150 mg and a type 2 variation is planned for Q2 2023 in order to seek the line extension.

The data provided on abrupt relapses in ALCL and IMT patients are limited at this time and definitely need more characterization since the mechanism is yet unknown. Minimum inhibition duration and thus treatment duration to avoid such early relapses after treatment discontinuation also need to be better characterized. It is highly recommended that the MAH closely monitors documented abrupt relapses cases in the PSURs.

As a response to the request to plan a post authorisation study, the MAH will implement PAMs requested by the FDA to further assess the PK and efficacy of crizotinib at 165 mg/m^2 BID and secondly at 280 mg/m^2 BID in paediatric patients (see RMP).

3.4 Unfavourable effects

At the data cut-off dates for both ADVL0912 and A8081013 studies, the safety population includes 25 paediatric patients with ALK-positive ALCL and 16 paediatric patients with ALK-positive IMT. Safety data of 69 additional patients with other tumours were provided as supportive data.

TEAE were observed in 100% of the safety population with grade 3 or 4 adverse events reported in 95.5% of ALCL patients and 78.5 % of IMT patients at the intended dose (280 mg/m^2 BID).

The most frequently reported TEAE pertained to SOC Blood and lymphatic system disorders (Neutropenia, 90.2% and leukopenia, 78.0%), hepatobiliary disorders (elevated transaminases, 85.4%) and gastrointestinal disorders (Vomiting, 95.1%; Nausea, 82.9% and Diarrhoea, 85.4%).

In addition, other adverse events that occurred frequently were vision disorder (61%), Constipation (34.1%), and blood creatinine increased (41.5%), bradycardia (17.1%) and oedema (29.3%).

The most frequently reported all-causality Grade 3 or 4 AE in all paediatric patients was neutropenia (ALCL pool: 19 [76.0%] patients; IMT pool: 9 [56.3%] patients). Moreover, all grade 3/4 AEs from paediatric population were observed with the same severity (as grade 3/4 AE) in the adults population and are listed in the SmPC of Xalkori.

However, frequencies of most frequent AEs differed notably compared to adult population such as neutropenia which was observed at a significant higher frequency in paediatric patients compared to adult population (90.2 % vs 21%) as well as grade 3/4 neutropenia (63.8% vs 12.3%). It is endorsed that the proposed SmPC recommends a specific monitoring for paediatric population. However, a dose modification recommendation from a grade 3 neutropenia instead a grade 4 might be warranted.

In addition, gastro-intestinal toxicity was also observed at a higher frequency in the paediatric population compared to the adult population: nausea (82.9% vs 56.6%), diarrhoea (85.4% vs 54.0%) and vomiting (95.1 vs 50.8%). Recommendations to manage gastrointestinal toxicities with anti-emetic/anti-diarrhea agents specifically for paediatric population have been added in section 4.4 of the proposed SmPC considering the higher risk of dehydration in children.

Furthermore, elevated transaminases were also observed at a higher frequency in the paediatric population compared to the adult population (85.4% and 32.1 % respectively). Dose modifications as well as the recommendations for monitoring in the SmPC appears sufficient since very frequent.

Treatment-related AE were reported in 100% of the ALCL and IMT pool population. The most frequent treatment related AE pertained to SOC gastrointestinal disorders (Diarrhoea, 75.6%; Vomiting, 92.7%; Nausea, 82.9%) hepatobiliary disorders (ELEVATED TRANSAMINASES, 82.9%) and blood and lymphatic

system disorders (NEUTROPENIA, 90.2%), LEUKOPENIA (70.7%). The most frequently reported Grade 3 or 4 treatment-related AE across all 4 pools was NEUTROPENIA (56.1%).

Except for NEUTROPENIA which was reported twice, each treatment related SAE was reported only once (hypoalbuminemia, blood creatinine increase, kidney enlargement, cyanopsia, infective myositis, skin infection, tumour lysis syndrome, bradycardia, CPK increase, nausea, diarrhea and vomiting).

Dosing interruption (70.7%) were more frequent than dose reductions (19.5%). The majority of treatment interruption was < 1 week for ALCL pool whereas no such generalisation can be made for IMT pool.

3.5 Uncertainties and limitations about unfavourable effects

Safety data in the targeted population are limited and do not allow for a comprehensive safety assessment. This could be acceptable considering the rarity of both disease. Although provided data shows a safety profile with similar type of adverse events, differences in frequencies can already be observed. It is not clear if the higher exposure of crizotinib observed in children compared to an adult population may impact the safety profile, however, preliminary studies suggest an impact on neutropenia and vision disorders.

Concerns remain about the lack of comprehensiveness of safety data regarding the reporting of laboratory values of study ADVL0912. Moreover, bone toxicities and bone growth are a particular cause of concern. Besides pharmacovigilance reports, a non-clinical signal has been identified and evidenced a decrease in bone formation in immature rats. A comprehensive review of all available clinical data was provided but due to confounding factors and the limited number of patients treated with crizotinib a potential effect on bone could not be ruled out. On this matter, bone toxicity and impaired bone growth are monitored in ongoing study CRZ-NBALCL (see RMP). Blood testosterone and Tanner are currently monitored in the ongoing CRISP study which will allow further characterisation of the impact of crizotinib on puberty (see RMP).

A DHCP is to be circulated to communicate the safety issue of vision disorders (including risk of severe visual loss) and need for monitoring in paediatric patients with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) or, recurrent, or refractory anaplastic lymphoma kinase (ALK)-positive unresectable inflammatory myofibroblastic tumour (IMT), at the same time with commission decision for the new indications.

3.6 Effects Table

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
			ALCL	IMT		Studies ADVL0912 and A8081013
ORR	CR, CRu or PR. Best response determined from the	Percentage (95% CI)	86.4% (66.7, 95.3)	85.7% (60.1, 96.0)	High and stable rates of ORR achieved across treatment	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	sequence of objective statutes				groups	
CR	Disappearance of all evidence of disease from all sites (target and non-target lesions)	Percentage	77.3%	35.7%	High and stable rates of ORR achieved across treatment groups	
DR		Median time in months	3.6 (0-15)	14.8 (2.8 - 48.9)	Patients were censored at transplantation for ALCL group (**52.6%** of patients). This duration is considered sustained to offer opportunity of HSCT. Objective responses were durable in general.	
TTR		Median time in months	0.9 (0.8 - 2.1)	1.0 (0.8 - 4.6)	Rapid and durable responses were obtained across treatment groups.	
Unfavourable Effects						
			ALCL	IMT		Studies ADVL0912 and A8081013
TEAE any grade, all-cause	Incidence	%	100.0	100.0		
TEAE treatment-related	Incidence	%	100.0	100.0		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
TEAE Grade ≥ 3	Incidence	%	96.0	81.3		
TEAE treatment related Grade ≥ 3	Incidence	%	68.0	62.5		
Serious TEAE (SAE)	Incidence	%	36.0	12.5		
TEAE leading to dose reduction	Incidence	%	16.0	25.0		
TEAE leading to dose interruption	Incidence	%	68.0	75.0		
TEAE treatment-related leading to permanent discontinuation	Incidence	%	4.0	25.0		
TEAE treatment-related leading to death	Incidence	%	0	0	1 patient in the other tumour group had a grade 5 event due to both disease progression and protocol treatment	
Neutropenia	Incidence	%	92.0	87.5		
Transaminases increase	Incidence	%	96.0	68.8		
Diarrhe	Incidence	%	100.0	62.5		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
a						
Vomiting	Incidence	%	100.0	87.5		
Vision disorders	Incidence	%	72.0	43.8		
Blood creatinine increase	Incidence	%	32.0	56.3		
QT prolongation	Incidence	%	8.0	6.3		
Bradycardia	Incidence	%	20.0	12.5		

3.7 Benefit-risk assessment and discussion

3.7.1 Importance of favourable and unfavourable effects

Crizotinib is intended to constitute a new targeted therapy for R/R ALK-positive ALCL and R/R or unresectable IMT.

Given the rarity of ALCL and IMT and thus the low number of patients enrolled, and the non-comparative design of the study, it is hard to draw clear conclusions from a statistical point of view, however, results based on the secondary endpoints are considered clinically meaningful and quite outstanding. The ORR for the 22 enrolled ALCL patients was 86.4% (95% CI: 66.7, 95.3) for both dose level groups. The ORR for the 14 patients in the IMT group was 85.7% (95%CI: 60.1, 96.0) across all dose levels. CRs were also high across study groups and remained stable across all age groups, despite the absence of patients under the age of 3, also including ALCL patients between 18 and 21.

The MAH also provided an exhaustive overview of published data from different crizotinib non-sponsored studies, drawing a parallel with the ADVL0912 pivotal study results. For ALCL patients, the results from the French AcSé basket program were presented. Since crizotinib has shown significant clinical activity in relapsed/refractory ALK+ ALCL in small cohorts of patients and in order to avoid a generalized off-label use and allow for an equal and nationwide access to crizotinib, the French National Cancer Institute (INCa, state organization) launched the AcSé program in patients aged 1 year and older with advanced ALK+ ALCL. Median age was 21 years and the median number of prior chemotherapy lines was 2 including brentuximab in 66% of patients. Among the 15 evaluable patients, 10 achieved an OR (67%, CI95% [42%-85%]) (9CR, 1PR) and 5 experienced a disease progression. The response rate was similar in paediatric patients (67%, CI95% [24%, 94%]) and in adults (6/9, 67%, CI95% [31%, 91%]) and with a median follow-up of 12 months, the median PFS was 11.6 months (CI95% [1.41, NA]). A compassionate use program where crizotinib was administered as monotherapy to 11 ALK+ lymphoma patients who were resistant/refractory to cytotoxic therapy also pointed out very encouraging results as the ORR was of 90.9%; (95%CI = 58.7% to 99.8%). Efficacy results obtained within the small cohorts of patients treated for IMT report comparable ORR even though the 2018 results presented by the MAH for the EORTC 90101 CREATE study are not up to date

since the final analysis as of data cut-off on 28th January 2021 describe an ORR reaching 66.7% (95% CI 34.9-90.1%) in ALK+ IMT patients and a 3-year OS rates of 83.3% (95% CI 48.2-95.6). Altogether, these results are in line with the ADVL0912 pivotal study findings and are considered highly supportive. With regards to the ongoing supportive study A8081013, five paediatric patients were enrolled at data cut-off date. Efficacy results are as well consistent with those reported in the pivotal study.

Efforts made by the MAH in order to collect and analyse the audit findings following CHMP request are acknowledged and valued. It should be noted that the findings are more qualifying to "deficiencies" than protocol deviations that can be collected in a more standardized trial. In one hand and since the search for such information was done retrospectively, the MAH states that it has been done "to the extent possible", which can lead to some bias in the analysis. On the other hand, when assessing the list of major deviations with a potential impact on efficacy, which was the major concern, none of the deviations appears to question study results.

Since no Pfizer-sponsored studies in adults and in paediatric patients are planned or ongoing with crizotinib monotherapy in the claimed indications and in order to address the identified data, the MAH proposed to implement PAMs requested by the FDA to further assess the PK and efficacy of crizotinib at 165 mg/m^2 BID and secondly at 280 mg/m^2 BID in paediatric patients. ALK+ IMT Patients can thus be enrolled at the 280 mg/m² BID, as Study ITCC 053 plans to recruit at least 15 paediatric patients with ALK, ROS1 or MET mutations in the stratum 3. Patients with ALK+ rr ALCL can be enrolled in stratum 3 once stratum 1b (at 165 mg/m² BID) is completed. As requested in the previous round, these additional ongoing studies are added in the RMP and the results planned with reasonable timelines.

With respect to DR which was quite underestimated in the ALCL group because of 10 patients who proceeded to HSCT (censored at time of HSCT), a longer median DR was observed for ALCL patients who did not receive a HSCT and IMT patients, and very rapid responses were observed in the ALCL group with a median TTR of ~1 month (280 mg/m^2 BID) for both indications. However, it should be noted that a complementary analysis presenting DR results with censoring rules according to the EMA guideline was requested but unresolved since EMA censoring methods couldn’t be implemented for the pivotal study ADVL0912 with no complementary sensitivity nor supportive applicable analyses.

The MAH discussed in depth the 5 literature references provided describing two abrupt relapses cases from which one patient was switched to ceritinib with rapid clinical improvement and a durable CR. The other patient resumed crizotinib and remained in CR. There was an additional case of a patient progressing while receiving crizotinib, the MAH broadly discussed this case which was not an abrupt but a relapse one. The data provided regarding abrupt relapses in ALCL and IMT patients are limited at this time and definitely need more characterization since the mechanism is not known yet. Minimum inhibition duration and thus treatment duration to avoid such early relapses after treatment discontinuation also need to be better characterized. It is highly recommended that the MAH closely monitors documented abrupt relapses cases in the PSURs.

Lastly, two different formulations were used within the submitted studies including the oral solution which is not available on the market. The MAH agreed that the commercially available capsules are highly unsuitable for the 1-6 years old population, in which swallowing issues are very likely to occur. An efficacy analysis by formulation was also provided but no clear conclusions regarding formulation-effect could be drawn for efficacy parameters compared to the previously assessed pooled data considering the very limited number of patients especially for the oral solution group (6 each in the ALCL and the IMT group). It should be noted that a paediatric microsphere encapsulated formulation is under development with 3 strengths: 20 mg, 50 mg, and 150 mg and a variation is planned for Q2 2023 in order to seek the line extension.

Crizotinib showed a safety profile mainly related to gastrointestinal, hepatic, haematological and renal toxicity. These AE were observed in adult population at lower frequencies. Similar severities were observed except for neutropenia grade 3/4 observed at a notable higher frequency in paediatric patients. Additional monitoring and management of these AE are provided in the SmPC of Xalkori with adaptation for paediatric population when required, however amendments of dose modification recommendations may be needed.

Visual disorders were observed in the paediatric population similarly to adult population; following a request, the MAH added specific monitoring and additional management recommendations in the SmPC.

Concerns about bone toxicities and impaired bone growth in the paediatric population will be addressed in ongoing study CRZ-NBALCL. In addition, the safety concern "bone toxicities and impaired bone growth" has been added in the RMP as important potential risk in the RMP

Furthermore, blood testosterone decrease which is a known adverse reaction of Xalkori in adult was not observed in paediatric population during the clinical trials submitted for this application. However, blood testosterone as well as Tanner stage are currently monitored in the ongoing study CRISP proposed as PAM provided favourable outcome of the CHMP which will allow further characterisation of the impact of crizotinib on puberty.

Overall, Xalkori toxicity appears clinically manageable provided additional measures. Although the safety database remains limited, the evaluation of the additional requested data and the implementation of monitoring and management of key toxicities have resolved number of uncertainties on the safety profile of Xalkori.

3.7.2 Balance of benefits and risks

The MAH is seeking an extension of the original indication for crizotinib to include treatment of paediatric patients (age ≥ 6 to < 18 years) with R/R ALK- ALCL and with unresectable, R/R ALK-positive IMT.

The conclusions of the CHMP are based on the results of a single non-comparative pivotal study and one supportive study. Data obtained from historical comparator studies were also submitted to assist with the interpretation of efficacy data from the single-arm studies.

Around 20 patients require a relapse-therapy each year in Europe. Given the rarity of ALCL and IMT and thus the low number of patients enrolled, and the non-comparative design of the study, it is hard to draw conclusions from a statistical point of view. Moreover, efficacy analysis were only considered as secondary endpoints in the pivotal study. This being said, the reported efficacy results are very encouraging and quite outstanding. The ORR for the 22 enrolled ALCL patients was 86.4% (95% CI: 66.7, 95.3) for both dose levels groups. The ORR for the 14 patients in the IMT group was 85.7% (95%CI: 60.1, 96.0) across all dose levels. CRs were also high across study groups and remained stable across all age groups, despite the absence of patients under the age of 3, also including ALCL patients between 18 and 21. With regards to the ongoing supportive study A8081013, five paediatric patients were enrolled at data cut-off date. Efficacy results are as well consistent with those reported in the pivotal study.

With respect to DR which was quite underestimated in the ALCL group because of 10 patients who proceeded to HSCT, a longer median DR was observed for ALCL patients who did not receive a HSCT and IMT patients, and very rapid responses were observed in the ALCL group with a median TTR of ~1 month (280 mg/m^2 BID) for both indications. It should be noted that a complementary analysis presenting DR results with censoring rules according to the EMA guideline was not possible since EMA censoring methods couldn't be implemented for the pivotal study ADVL0912 with no complementary sensitivity nor supportive applicable analyses.

As part of establishing the positive B/R balance for crizotinib in the two claimed indications among paediatric patients, the MAH provided an exhaustive overview of published data from different crizotinib non-sponsored studies, drawing a parallel with the ADVL0912 pivotal study results. For ALCL patients, the MAH elaborates on the results from the French AcSé program. The AcSé program was launched in patients aged 1 year and older with advanced ALK+ ALCL. Median age was 21 years and the median number of prior chemotherapy lines was 2 including brentuximab in 66% of patients. Among the 15 evaluable patients, 10 achieved an OR (67%, CI95% [42%-85%]) (9CR, 1PR) and 5 experienced a disease progression. The response rate was similar in paediatric patients (67%, CI95% [24%, 94%]) and in adults (6/9, 67%, CI95% [31%, 91%]) and with a median follow-up of 12 months, the median PFS was 11.6 months (CI95% [1.41, NA]). A compassionate use program where crizotinib was administered as monotherapy to 11 ALK+ lymphoma patients who were resistant/refractory to cytotoxic therapy also pointed out very encouraging results as the ORR was of 90.9%; (95%CI = 58.7% to 99.8%). Efficacy results obtained within the small cohorts of patients treated for IMT also report comparable ORR even though the 2018's results presented by the MAH for the EORTC 90101 CREATE study are not up to date since the final analysis as of data cut-off on 28th January 2021 describe an ORR reaching 66.7% (95% CI 34.9-90.1%) in ALK+ IMT patients and a 3-year OS rates of 83.3% (95% CI 48.2-95.6). Altogether, these results are in line with the ADVL0912 pivotal study findings and are considered highly supportive.

Although the safety database remains limited, crizotinib toxicity appears clinically manageable considering recommendations of monitoring and management implemented for paediatric patients in the SmPC. The healthcare professionals are alerted to the risk of ocular toxicities via a DHPC.

3.7.3 Additional considerations on the benefit-risk balance

A divergent view was expressed by a CHMP member as follows:

We consider that the rationale for ALK targeting of these very rare ALK-positive tumours and the anti-tumour activity of crizotinib in the studied paediatric population is clear. However, in our view the data are of insufficient quality to serve as an adequate basis for B/R assessment. The concerns relate to amongst others the small sample size, the inadequate collection of baseline characteristics, and events during follow-up, e.g. response assessment following hematopoietic stem cell transplant, in this heterogeneous target populations. As a result the study populations are not well described and the duration of response cannot be estimated. The alternative approach, being extrapolation, cannot be applied in the absence of approved indications in the adult IMT and ALCL setting. With the notion that paediatric data need to be interpreted against the same standards as those obtained in adults and any deviation from such standards should only be considered when justified (as per e.g. the Guideline on small populations (CHMP/EWP/83561/2005)); in our view the benefit is not established based on the submitted data, rendering the B/R negative and this extension of indication non-approvable.

3.8 Conclusions

The overall B/R of Xalkori in the treatment of paediatric patients (age ≥ 6 to < 18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and with recurrent, or refractory ALK-positive unresectable inflammatory myofibroblastic tumour (IMT) is positive.

3. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by a majority of 30 out of 31 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication to include treatment of paediatric patients (age ≥ 6 to < 18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and with recurrent, or refractory ALK-positive unresectable inflammatory myofibroblastic tumour (IMT) for Xalkori based on the results from Studies ADVL0912 and A8081013; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The Annex II was updated to include key elements of the educational material as additional risk minimisation measures. Version 8.2 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

Additional risk minimisation measures

The MAH shall agree the content and format of the educational material with the National Competent Authority. The final wording used on the educational material should be in line with the approved product information.

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

The educational pack should contain the following:

1. Summary of Product Characteristics and Package Leaflet.
2. Patient brochure including a Patient Alert Card (text as agreed by the CHMP).
3. 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:
o Breathing problems associated with pneumonitis/ILD
o Light-headedness, fainting, chest discomfort or irregular heartbeat associated with bradycardia, QT prolongation and cardiac failure
o Abnormalities in liver blood tests associated with hepatotoxicity
o Visual changes, including guidance to assess visual symptoms in the paediatric population
o Stomach disorders associated with gastrointestinal perforation
- The importance to notify 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 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.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Xalkori is not similar to Adcetris, Ledaga and Poteligeo within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

4. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Xalkori-H-C-2489-II-0072'