4 July 2024
EMA/351984/2024 Rev1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on a group of extensions of marketing authorisation and an extension of indication variation

XALKORI

International non-proprietary name: Crizotinib

EMEA/H/C/002489/X/0080/G

Note

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

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Table of contents

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
CFU: Colony Forming Units
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
HPLC: High performance liquid chromatography
HSCT: hematopoietic stem cell transplantation
ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS: Inductively coupled plasma mass spectrometry
IMT: inflammatory myofibroblastic tumor
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
Ph. Eur.: European Pharmacopoeia
PR: partial response
RD: relative dose
RE: Response Evaluable
RECIST: Response Evaluation Criteria in Solid Tumors
RH: Relative Humidity
RP2D: Recommended Phase 2 dose
SA: Safety Analysis
SAP: Statistical Analysis Plan
SCT: stem cell transplantation
SD: standard deviation
SmPC: Summary of Product Characteristics
TSE: Transmissible Spongiform Encephalopathy
TTR: time to tumor response
USP: United States Pharmacopoeia
USP/NF: United States Pharmacopoeia/National Formulary

UV: Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

Pfizer Europe MA EEIG submitted on 25 May 2023 a group of variations consisting of extensions of the marketing authorisation and the following variation:

Variation(s) requested		Type
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	II

Extension application to introduce a new pharmaceutical form (granules in capsules for opening) associated with new strengths (20, 50 and 150 mg), grouped with a type II variation (C.I.6.a) to include the treatment of paediatric patients with relapsed or refractory, systemic ALK-positive ALCL or unresectable, recurrent, or refractory ALK-positive IMT to change the lower end of the age range from ≥6 years to ≥1 year for Xalkori following the assessment of II/0072 based on final results from study ADVL0912. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 9.1 of the RMP has also been submitted.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7(2) of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. 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.

The development of an oral age appropriate peadiatric formulation was agreed with the PDCO as part of PIP EMEA-001493-PIP03-18-M01. A compliance check was submitted to the PDCO prior to this submission, confirming outstanding measures in the PIP are completed.

Pursuant to Article 23(2) of Regulation (EC) No 1901/2006, as amended, Pfizer Europe MA EEIG submitted to the Paediatric Committee on 23 January 2023 a request for verification of compliance with the agreed paediatric investigation plan for the above-mentioned medicinal product. The procedure started on 27 February 2023.

Opinion

The Paediatric Committee, having reviewed the data submitted in accordance with Article 23 of Regulation (EC) No 1901/2006, is of the opinion, as set out in the appended compliance report, that the measures are in compliance with the agreed above mentioned paediatric investigation plan and that the agreed timelines have been respected accordingly.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. 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

CHMP Peer reviewer(s): N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Tiphaine Vaillant

The application was received by the EMA on	25 May 2023
The procedure started on	15 June 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 September 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	12 September 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	21 September 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	12 October 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	18 January 2024
The CHMP Rapporteur's Assessment Report on the responses to the List of Questions was circulated to all CHMP and PRAC members on	20 February 2024
The PRAC Rapporteur's Assessment Report on the responses to the List of Questions was circulated to all PRAC and CHMP members on	23 February 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 March 2024
The CHMP Rapporteur's Updated Assessment Report was circulated to all CHMP and PRAC members on	15 March 2024

The CHMP agreed on a list of outstanding issues to be sent to the MAH on	21 March 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	28 May 2024
The CHMP Rapporteur's Assessment Report on the responses to the List of Outstanding Issues was circulated to all CHMP and PRAC members on	14 June 2024
The PRAC Rapporteur's Assessment Report on the responses to the List of Outstanding Issues was circulated to all CHMP and PRAC members on	13 June 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to XALKORI on	27 June 2024
A revised opinion, to include a similarity assessment was adopted by the CHMP on	5 July 2024
The CHMP adopted a report on similarity of Xalkori with Adcetris, Poteligeo and Ledaga on (see Appendix on similarity)	5 July 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The new proposed therapeutic indications concerns the treatment of:

- paediatric patients (age **≥1** to <18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL), and

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

2.1.2. Anaplastic Large cell lymphoma (ALCL)

2.1.2.1. 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).

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).

2.1.2.2. Management

ALCL is a chemosensitive malignancy both in pediatric 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 pediatric 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 5years 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 pediatric 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 pediatric patients whose disease relapses during first-line treatment, 5-year OS is only 25% (Woessmann et al, 2011).

Current Therapies for Pediatric Patients with ALCL

There is no consensus on the treatment of relapsed or refractory pediatric 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 relapsedor 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 ALKgene 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 toHSCT, in the most recent version of the NCCN treatment guidelines for ALCL (NCCN 2018guidelines[a]).

2.1.3. Inflammatory myofibroblastic tumor (IMT)

2.1.3.1. Epidemiology

IMT is a class of tumor 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 6synonyms (plasma cell granuloma; inflammatory myofibrohystiocytic proliferation; omental mesenteric myxoid hamartoma; inflammatory pseudotumor; 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 detectedby immunohistochemistry(Cook et al, 2001) with fluorescence in situ hybridization or next-generation sequencing also being used (Casanova et al, 2020).

2.1.3.2. Management

Current Therapies for Pediatric 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 tumor 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).

2.2. 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 pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic ALCL that is ALK- positive. In October 2022, Xalkori received approval in Europe for an 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 (variation II-72).

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 pediatric 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 tumor 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 antitumor efficacy of crizotinib, including marked cytoreductive antitumor activity, in tumor models implanted in athymic mice that expressed activated NPM-ALK, and complete regression of the tumor was observed in the Karpas-299 model at a dose of 100 mg/kg QD.

This extension of the marketing authorisation for the additional pharmaceutical form granules in capsules for opening, associated with 3 new strengths (20, 50, 150 mg) is intended for the paediatric indications of ALCL and IMT as discussed above.

The recommended dosage for paediatric patients with BSA ≥1.34 m^2 is :

Table 1. Paediatric patients with body surface area (BSA) ≥1.34 m^2: Recommended crizotinib capsules* starting dosage

Body Surface Area (BSA)**	Dose (Twice Daily)	Total Daily Dose
1.34 – 1.51 m^2	400 mg (2×200 mg capsule)	800 mg
1.52 – 1.69 m^2	450 mg (1×200 mg capsule + 1×250 mg capsule)	900 mg
≥1.70 m^2	500 mg (2×250 mg capsule)	1000 mg

* Refers to the XALKORI 200 mg and 250 mg hard capsules.
** For paediatric patients with BSA <1.34 m^2, refer to Table 2.

For paediatric patients with BSA <1.34 m^2, the granules in capsules for opening formulation of XALKORI should be used. The recommended dosage for paediatric patients with BSA <1.34 m^2 is provided in Table 2.

The granules are encapsulated into 3 dosage strengths: 20 mg, 50 mg and 150 mg crizotinib. If needed, attain the desired dose by combining different strengths of crizotinib granules in capsules for opening. No more than 4 capsules will be required for a single dose (see Table 2).

Table 2. Paediatric patients with body surface area (BSA) of 0.38 m^2 to 1.33 m^2: Recommended crizotinib granules* starting dosage

Body Surface Area (BSA)**	Dose (Twice Daily)	Total Daily Dose
0.38 to 0.46 m^2	120 mg (1 × 20 mg + 2 × 50 mg)	240 mg
0.47 to 0.51 m^2	140 mg (2× 20 mg + 2 × 50 mg)	280 mg
0.52 to 0.61 m^2	150 mg (1 × 150 mg)	300 mg
0.62 to 0.80 m^2	200 mg (1 × 50 mg + 1 × 150 mg)	400 mg
0.81 to 0.97 m^2	250 mg (2 × 50 mg + 1 × 150 mg)	500 mg
0.98 to 1.16 m^2	300 mg (2 × 150 mg)	600 mg
1.17 to 1.33 m^2	350 mg (1 × 50 mg + 2 × 150 mg)	700 mg

* Refers to the 20 mg, 50 mg and 150 mg crizotinib granules in capsules for opening.
** The recommended dosage for patients with a BSA less than 0.38 m^2 has not been established. For paediatric patients with BSA ≥1.34 m^2, refer to Table 1.

2.3. Quality aspects

2.3.1. Introduction

This extension application introduces a new pharmaceutical form of Xalkori associated with new strengths.

The finished product is presented as granules in capsule for opening containing 20 mg, 50 mg or 150 mg of crizotinib as active substance.

Other ingredients are:

Granules content: stearyl alcohol, poloxamer, sucrose, talc (E553b), hypromellose (E464), macrogol (E1521), glyceryl monostearate (E471) and medium chain triglycerides.

(The granules are filled into a pre-printed gelatine capsule which is not ingested.)

Capsule shell: gelatin, titanium dioxide (E171) and brilliant blue (E133) or black iron oxide (E172).

Printing ink: shellac (E904), propylene glycol (E1520), potassium hydroxide (E525) and black iron oxide (E172).

The product is available in high density polyethylene (HDPE) bottles with a polypropylene child resistant (CR) closure and an aluminium foil/polyethylene heat induction seal as described in section 6.5 of the SmPC.

2.3.2. Active Substance

No new information on the active substance crizotinib has been provided with this line extension application except for analytical test results for 12 batches of crizotinib active substance used in the development of the new formulation. The new presentations use active substance of the same quality as used in the approved presentations (200 mg and 250 mg hard capsules) and the active substance is manufactured by the approved manufacturing sites. The approved specification of the active substance is suitable for the new presentations and no additional tests are required.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

Xalkori granules present as white to off- white granules which are filled into a capsule.

Crizotinib 20 mg granules are provided in opaque size #4 hard gelatin capsules which have a light blue cap printed with "Pfizer" in black ink and a white body printed with "CRZ 20" in black ink.

Crizotinib 50 mg granules are provided in opaque size #3 hard gelatin capsules which have a grey cap printed with "Pfizer" in black ink and a light grey body printed with "CRZ 50" in black ink.

Crizotinib 150 mg granules are provided in opaque size #0 hard gelatin capsules which have a light blue cap printed with "Pfizer" in black ink and a light blue body printed with "CRZ 150" in black ink.

The three strengths are sufficiently distinguished by the size, colour and printing of the capsule.

For administration, the capsule is opened and instructions on this are provided in the SmPC. The granules are administered orally, while the capsule shell is not ingested.

The qualitative and quantitative composition of the finished product was included in the submission dossier. 1234

The aim of formulation development was to develop a flexible solid oral dosage form in lower strengths suitable for paediatric patients aged 1 year and older. The new presentations both extend the dose range below the dose range attainable with the approved Xalkori hard capsules (200 mg and 250 mg) and offer a dosing option for younger paediatric patients who are unable to swallow the approved capsule formulation.

The quality target product profile (QTPP) was defined and information on the identified critical quality attributes was provided.The pharmaceutical development of the finished product has been adequately performed and described. The selected formulation, packaging and manufacturing process are justified.

A discussion on the physicochemical characteristics of active substance has been presented. Crizotinib is classified as a BCS 4 compound (low solubility/low permeability) according to the Biopharmaceutics Classification System. As regards the particle size of the active substance, it has been demonstrated that the approved specification limits for particle size of crizotinib are suitable.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except for the colourants contained in the capsule shell which comply with EU food legislation. There are no novel excipients used in the finished product formulation.

The development of the formulation has been described in sufficient detail. Different formulations were used in clinical studies. The first dosage form developed which allowed flexibility of dosing needed for the paediatric population was an oral solution (used for study A8081019). Formulation development of the oral solution of crizotinib focused on excipients needed for taste masking to improve palatability. However, even after optimisation of the palatability, clinical experience with the oral solution was challenging due to the poor taste of the active substance. This led to the initiation of the development of the granule formulation with the aim to maintain dose flexibility but to achieve improved palatability. The applicant made reference to similar products for which the acceptability of this dosage form (granules) for paediatric patients was already demonstrated and which are already approved in the EU for paediatric patients (for example, Alkindi).

To achieve taste masking, two types of immediate release coatings for the granules were initially investigated: a) a pH dependent barrier coating (i.e. reverse enteric coating) and b) a pH independent

coating (studied in A8081041). Then, a further non-pH independent coating material was also investigated. This coating material was considered to achieve the right balance between palatability and PK performance under fasted and fed conditions as well as under co-dosed conditions with a proton pump inhibitor and was therefore selected as the coating material for the proposed commercial formulation. A coating level was selected based on prior clinical experience with the previous prototype pH independent coating.

The particle size target for the uncoated granules was selected. The justifications provided for the selected particle size are acceptable.

To investigate the method of administration of the granules *in vitro* compatibility studies were conducted where the granules were mixed with mashed bananas, carrot puree or plain yogurt. The following tests were performed: a) assay/dosing instruction verification, b) in-use stability (at ambient conditions in soft foods) and c) dissolution (at ambient conditions in soft foods). For carrot puree or mashed banana, the dissolution profiles of crizotinib with food were similar to the dissolution profiles without food. For plain yogurt, the dissolution profile of crizotinib was similar to the profile without food at specified timepoints. The dissolution profiles of crizotinib with food were also similar to the profiles without food at specified timepoints. However, The applicant maintained that the option of sprinkling the granules onto soft food is not applicable and the SmPC includes the statement "the granules should not be sprinkled on food before administration".

For the pivotal bioequivalence study (A8081074), the granules were dosed directly to the mouth of the patient followed by administration of water. Xalkori granules in capsule for opening of 50 mg strength and 150 mg strength were found to be bioequivalent. The same formulation as proposed for marketing was used. For the 20 mg strength a waiver of strength was requested on the basis that the presentations are manufactured by the same manufacturing process, the qualitative composition of the different strengths is the same, the composition of the strengths are quantitatively proportional, and similarity of *in vitro* dissolution was demonstrated at pH 1.2, 4.5 and 6.8 between 150 mg granules, 50 mg granules and 20 mg granules. The waiver of strength for the 20 mg strength is acceptable.

The development of the dissolution method is sufficiently described. The discriminatory power of the dissolution method was investigated. Following questions from the CHMP, the method for routine quality control testing of granules for marketing has been further refined and this improved the discriminatory power. Complete dissolution could be achieved by reducing the agitation. The dissolution method is acceptable and the discriminatory power confirmed.

As an alternate dissolution method has been used to release clinical batches and during stability studies, comparative dissolution profiles using the proposed dissolution method for routine testing and the dissolution method used during clinical studies were presented for representative batches of all three strengths. Results demonstrated the comparability of the two methods for all strengths.

The development of the manufacturing process is adequately described. The manufacturing process was developed at the manufacturing site proposed for commercial manufacturing of the finished product. Changes made to the manufacturing process during development are sufficiently described. Process risk assessments were used to identify potential high-risk process variables and determined which studies were necessary to achieve product and process understanding to develop a control strategy. The information provided is satisfactory.

Holding times are proposed for the following intermediates: uncoated granules, coated granules and capsules. The maximum hold time for the bulk capsules has been changed during the procedure and reduced in response to questions raised by the CHMP. The proposed holding times are considered acceptable.

It was confirmed that the start of shelf-life for production batches is in compliance with the EMA "Note for Guidance on Start of Shelf-Life for the Finished Dosage Form" (EMEA/CVMP/453/01). Hold times are in place to support unplanned or unforeseeable events.

The primary packaging is high density polyethylene (HDPE) bottles with a polypropylene child resistant (CR) closure and an aluminium foil/polyethylene heat induction seal. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.3.3.2. Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site. A detailed description of the manufacturing process was included in the product dossier.

Process validation data was required and this was raised as a Major Objection (MO) during the procedure. In response, a validation report was provided covering process validation of three batches of coated granules, with each batch then further divided into three batches of granules in capsule for opening for each of the proposed strengths (20 mg, 50 mg and 150 mg). It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.3.3.3. Product specification

The finished product release specification shown in **Error! Reference source not found.** include appropriate tests for this kind of dosage form: appearance (visual), identity (HPLC, UV), assay (HPLC), degradation products (HPLC), dissolution (In house), content uniformity (HPLC) and microbial limits (Ph. Eur.).

The release specification of the finished product is acceptable and covers all the relevant points for the dosage form. The specification limit for degradation products is below the identification and qualification thresholds according to the ICH guidelines.

Additional tests were conducted during development of the finished product. The absence of those tests in the proposed finished product specification has been appropriately justified.

In response to a Major Objection (MO) raised during the procedure, the specification limits for dissolution were tightened for all three strengths. As part of the MO related to dissolution raised by the CHMP, the applicant was also asked to further clarify the physiologically based pharmacokinetic (PBPK) modelling used to justify dissolution specification limits. The quality-related questions raised on the development and validation of the PBPK model were satisfactorily addressed. The MO was considered resolved.

During the procedure, a question was also raised by the CHMP on the control of particle size of the granules. Particle size is controlled in the sieving step (see above) without implementation of in-process control to control the particle size and this is not considered sufficient. The CHMP recommended to add a particle size analysis method to the specification of the finished product for release testing (REC 001).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches of each strength using an ICP-MS method which was verified to be linear, with

sufficient accuracy and limit of quantification was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

Regarding the control of nitrosamines, it was confirmed in the context of this line extension that ICH Q3A/B limits are applicable due to the S9 indication of the product. No nitrosamines have been detected above the identification threshold in any batches of active substance or finished product. Based on the information provided, it is accepted that no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for several batches including three production-scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

2.3.3.4. Stability of the product

Stability data from three production scale batches of each strength of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. The batches were manufactured at the site proposed for commercial manufacturing, however primary packaging was conducted at a different site to the one proposed for marketing. Confirmation was provided that the primary stability batches were packaged in the commercial container closure system. Samples were tested for appearance, assay, degradation products, dissolution, water content, water activity and microbial limits. The stability indicating nature of the HPLC method used for impurities testing was confirmed through forced degradation studies. No significant trends were observed under long-term conditions and under accelerated conditions except for an increase in water activity and water content. All results remained within specification limits.

In addition, one batch per strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The study confirmed that the finished product is photostable.

Stress tests were conducted on each strength, and samples were exposed to a thermal stress cycle (4 days at -20 °C, 3 days at 40 °C / 75% RH, 3 days at -20 °C and 4 days at 40 °C / 75% RH) as well as to thermal and humidity stress (50 °C / 75% RH, 3 days). Relevant parameters (appearance, assay, degradation products and dissolution) remained essentially unchanged through the thermal stress cycle. Following thermal and humidity stress, caking was observed for the 20 mg strength as expected due to the low melting point of the excipients. Only the lowest strength was impacted

In addition, an in-use stability study where bottles were opened was also conducted on one batch of each strength. Results showed that there is no need for a specific storage precaution.

Based on available stability data, the proposed shelf-life of 2 years without any special precautions for storage as stated in the SmPC (section 6.3 and 6.4) is acceptable.

2.3.3.5. Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure two major objections were raised in relation to the need to provide process validation data and in relation to the dissolution test method. On both questions, satisfactory responses were received to resolve the major objections.

At the time of the CHMP opinion, there was one minor unresolved quality issue which has no impact on the Benefit/Risk ratio of the product which pertains to the need to implement a particle size test method for release testing. This point is put forward and agreed as recommendation for future quality development.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

REC 001. A particle size analysis method for release testing will be added to Section 3.2.P.5.2 Analytical Procedures, the validation of this test method will be added to Section 3.2.P.5.3 Validation of Analytical Procedure, and the release specification will be added to Section 3.2.P.5.1 Specifications.

2.4. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.4.1. Ecotoxicity/environmental risk assessment

The extension application for the medicinal product Xalkori for paediatric patients age >1 to <18 years, is not expected to result in an increase in the environmental exposure, as the previous ERA (July 2021) submitted in the variation application under procedure EMEA/H/C/002489/II/0072 for paediatric patients was based on paediatric patients < 18 years of age. Consequently, an update of the environmental risk assessment is not required.

2.4.2. Discussion on non-clinical aspects

Crizotinib is already used in existing marketed products and no significant increase in environmental exposure is anticipated with this extension of indication given the rarity of the condition in the age range 1-6 years old. The ERA submitted as part of the II/072 (paediatric patients >6 years old) still applies.

Therefore crizotinib is not expected to pose additional risk to the environment on the anticipated use in the indications under evaluation in this procedure.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

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.

Table 5. Summary of Clinical Pharmacology Studies Supporting the Development and Submission of the Granules in Capsules for Opening for Pediatric Patients

Protocol Number CSR Location	Protocol Title	Single Center Location	Study Dates (Start/End dates) and Status	Study Treatment	Study Population/ Number of Participants
Comparative Bioavailability and Bioequivalence Studies					
1069 Module 5.3.1.2	A Phase 1, Open Label, Crossover Study to Evaluate Palatability and Relative	US	12 June 2019/ 17 October 2019/ Completed	*Crizotinib cMS1*[a] (Treatments A and G in fasted state and Treatment E in fed state) Route: oral; Dose regimen: 250 mg *Crizotinib cMS2*[a]	Healthy adult participants Randomized: 25 Treated/Compl

Table 5. Summary of Clinical Pharmacology Studies Supporting the Development and Submission of the Granules in Capsules for Opening for Pediatric Patients

Protocol Number CSR Location	Protocol Title	Single Center Location	Study Dates (Start/End dates) and Status	Study Treatment	Study Population/ Number of Participants
	Bioavailability of Two Pediatric Microsphere Formulations of Crizotinib in Healthy Participants			(Treatments B and H in fasted state and Treatment F in fed state) Route: oral; Dose regimen: 250 mg *Crizotinib FC*[b] (Treatment C in fasted state) Route: oral; Dose regimen: 250 mg *Crizotinib OS* (Treatment D in fasted state) Route: oral; Dose regimen: 250 mg *Esomeprazole* (taken with cMS1 [Treatment G] and cMS2 [Treatment H] in fasted state) Route: oral; Dose regimen: 40 mg	eted: 25/23[c] *Treatment A: 23/22* *Treatment B: 25/23* *Treatment C: 23/23* *Treatment D: 22/22* *Treatment E: 11/11* *Treatment F: 11/11* *Treatment G: 11/11* *Treatment H: 11/11*
1074 (Module 5.3.1.2)	A Phase 1, Open-label, Crossover Study to Establish Bioequivalence of an Encapsulated Microsphere Formulations (eMS) to the Formulated Capsule (FC) of Crizotinib in Healthy Adult Participants	US	16 April 2021/ 15 December 2021/ Completed	*Crizotinib FC*[b] Route: oral; Dose regimen: 250 mg *Crizotinib eMS*[a] *unencapsulated* Route: oral [sprinkled]; Dose regimen: 250 mg *Crizotinib eMS*[a] *capsulated* Route: oral [whole]; Dose regimen: 250 mg All were administered following an overnight fast of at least 10 hours.	Healthy adult participants Randomized: 25 Treated/Completed: 25/23[d] *FC: 24/24* *eMS unencapsulated: 25/25* *eMS capsulated: 12/12*

Table 5. Summary of Clinical Pharmacology Studies Supporting the Development and Submission of the Granules in Capsules for Opening for Pediatric Patients

Protocol Number CSR Location	Protocol Title	Single Center Location	Study Dates (Start/End dates) and Status	Study Treatment	Study Population/ Number of Participants

a. In Study 1069, 2 cMS formulations were used (cMS1 and cMS2). The cMS1 and the eMS are the same coated granule formulation; the difference between the 2 formulations is that the cMS1 was supplied as bulk granules for Study 1069, while for Study 1074, the eMS was supplied as the proposed commercial image, ie, the coated granules encapsulated in hard gelatin capsules.

b. The FC formulation was used in Studies 1069 and 1074. Clinical use of crizotinib 250 mg capsules is compositionally the same as the commercial product (XALKORI), including the same capsule shell and printing.

c. 3 participants discontinued from the study. Two participants permanently discontinued the study following Treatment B (cMS2), 1 due to a treatment-related AE (Transaminases increased) and 1 was removed for behavioral issues per investigator's decision, who was replaced; 1 participant who was permanently discontinued the study following Treatment A (cMS1) due to AEs (Nausea, Depressed mood, Diarrhoea, and Decreased appetite [all were treatment-related except for Depressed mood].

d. There were 2 (8.0%) participants who permanently discontinued from the study following the administration of crizotinib 250 mg eMS unencapsulated and did not proceed to receive their next scheduled study intervention; one due to an AE (transaminases increased) and the other due to other reason (work schedule conflicted with the subsequent study period.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Two clinical biopharmaceutic studies are provided to support the use of the granules in capsules for opening formulation (Studies A8081069 and A8081074; hereafter referred to as 1069 and 1074, respectively).

Simulation using a previously developed PK model was provided. The simulation demonstrated that exposures (after exposition to the proposed doses) are consistent between BSA brackets. Additionally, even with lower doses simulated, the median Css trough are largely over the efficacious concentration of 111ng/mL, and the plots show that roughly 95% of the population is expected to have plasma concentrations of crizotinib above Ceff. A PBPK model was provided.

Study A8081069:

A Phase 1, Open Label, Crossover Study to Evaluate Palatability and Relative Bioavailability of Two Pediatric Microsphere Formulations of Crizotinib in Healthy Participants

This study was intended to select the more appropriate microsphere formulation between 2 candidates (cMS1 and cMS2) for commercialization based on both PK and palatability. In addition, a preliminary

assessment of the effect of a PPI (esomeprazole) and food on plasma PK of crizotinib following administration of cMS1 and cMS2 was also to be conducted to assist in the formulation selection. Esomeprazole is a commonly used over-the-counter PPI which is able to reduce gastric acid. Delayed release esomeprazole was to be used in this study for assessment of potential effect of PPI on PK of the microsphere formulations (cMS1 and cMS2).

Crizotinib was not expected to provide any clinical benefit to healthy participants. This study was designed primarily to generate PK and palatability data for further cMS development. Single oral dose of crizotinib 250 mg has been safely administered to approximately 160 healthy participants in 11 clinical studies.

Table 6 Study Objectives and Endpoints

Type	Objective	Endpoint
Primary		
Pharmacokinetics	To estimate the relative bioavailability of 2 new crizotinib formulations (cMS1 and cMS2) to the commercially available crizotinib FC at a single 250 mg dose administered under fasted conditions in adult healthy participants.	• Plasma AUC_{inf}, AUC_{last} and C_{max} for crizotinib.
Taste	To evaluate the palatability of crizotinib cMS1 and cMS2 formulations of 250 mg dose in comparison with the crizotinib OS of 250 mg dose in adult healthy participants.	• Taste questionnaire results.
Secondary		
Safety	To assess the safety and tolerability of crizotinib 250 mg single doses in 4 different formulations (cMS1, cMS2, FC and OS) when given fasted, with HF meal or with the PPI, esomeprazole, in adult healthy participants.	• Safety laboratory tests, ECGs, vital signs and AEs.
Pharmacokinetics	To explore the effect of food on the PK of cMS1 and cMS2.	• Plasma AUC_{inf}, AUC_{last} and C_{max} for crizotinib.
	To explore the effect of esomeprazole on the PK of cMS1 and cMS2.	• Other PK parameters: plasma T_{max}, $t_{½}$, CL/F, V_z/F for crizotinib.

Study A8081074:

A Phase 1, Open-Label, Crossover Study to Establish Bioequivalence of an Encapsulated Microsphere Formulation (eMS) to the Formulated Capsule (FC) of Crizotinib in Healthy Adult Participants

In order to overcome the poor taste/palatability associated with the oral solution formulation of crizotinib for pediatric patients, a new formulation, also called eMS, with improved palatability compared with the oral solution and acceptable PK characteristics was developed. The primary objective of this study was to establish the BE of the eMS formulation to the current commercial formulation, ie, FC, in adult healthy participants to support the commercialization of this new formulation.

Table 7 STUDY OBJECTIVES AND ENDPOINTS

Type	Objectives	Endpoints
Primary		
PK Section 5.2	• To establish the BE of a crizotinib eMS given unencapsulated (ie, opening the capsules and emptying the contents to the participants' mouths) to crizotinib FC at 250 mg single dose administered under fasted conditions in adult healthy participants.	• Plasma AUC_{inf} and C_{max}, AUC_{last} for crizotinib after administration of eMS and FC formulations.
Other		
PK Section 5.2	• To determine the relative bioavailability of the eMS administered as an intact capsule (encapsulated) relative to crizotinib FC.	• Plasma AUC_{inf}, AUC_{last} and C_{max} for crizotinib after encapsulated eMS, administered as an intact capsule, and FC administrations. • Other PK parameters: T_{max}, $t_{½}$, CL/F, V_z/F for crizotinib after each crizotinib treatment.
Safety Section 5.1	• To assess the safety and tolerability of crizotinib 250 mg as a single dose of eMS (unencapsulated or encapsulated) and FC.	• AEs and other safety measures (vital signs, ECGs, and safety laboratory tests) following each crizotinib treatment.

This study was an open-label, randomized, 3-period, 4-sequence study in adult healthy participants.

Approximately 28 participants were planned to be randomized to 4 treatment sequences with 7 participants in each sequence. According to the sequence in which they were randomized, all participants were planned to receive 2 single doses of crizotinib 250 mg as Treatment A and Treatment B in Periods 1 and 2. Additionally, half the total study participants were also planned to receive Treatment C in Period 3 and the other half were planned to complete the study after Period 2.

Table 8 Study Design

Treatment Sequence	Period 1		Period 2		Period 3	
1 (n=7)	A	At least 14 days washout	B	At least 14 days washout	C	28-35 days of follow up
2 (n=7)	B		A		C	
3 (n=7)	A		B		NA	
4 (n=7)	B		A		NA	

Treatment A (Reference for BE assessment): A single dose of crizotinib 250 mg of the FC formulation was planned to be administered on the morning of Day 1 after an overnight fast of at least 10 hours.

Treatment B (Test for BE assessment): A single dose of crizotinib 250 mg of the eMS formulation was planned to be administered unencapsulated, ie, opening the capsules and emptying the contents to the participants' mouths, on the morning of Day 1 after an overnight fast of at least 10 hours.
Treatment C: A single dose of crizotinib 250 mg of the eMS formulation was planned to be administered as intact capsules (encapsulated) on the morning of Day 1 after an overnight fast of at least 10 hours.

Demographic data were quite balanced in the 3 treatment groups.

Absorption

A biowaiver is provided for the 20 mg strength. In pediatric patients (study ADVL0912), crizotinib exposure increased approximately proportionally to dose over the clinical dose range i.e., 165 mg/m2 to 280 mg/m2 BID at steady state.

Main study for the BE portion is Study A8081074. This study shows that once unencapsulated (as designed for commercialisation), the eMS granules can be considered as bioequivalent with the commercialised formulation at the dose of 250 mg. Unencapsulated granules can also be considered bioequivalent with the encapsulated granules at the dose of 250 mg.

Study A8081019 showed BE of the OLF form with the CSF, but does not relate to comparison of OLF and the new intended-for-commercialisation formulation.

Regarding food effect, it was shown in Study A8081069 that exposure after a high fat meal was decreased between 0.7 fold (AUCs) and 0.75 fold of original value (Cmax).

Distribution

NA

Elimination

NA

Dose proportionality and time dependencies

In pediatric patients (study ADVL0912), crizotinib exposure increased approximately proportionally to dose over the clinical dose range i.e., 165 mg/m2 to 280 mg/m2 BID at steady state.

Special populations

Modelling and simulation used BWT as significant covariate.

Simulation was based on paediatric population. The population PK modelling showed that in predicted profiles, the median Css trough are largely over the efficacious concentration of 111ng/mL, and the plots show that roughly 95% of the population is expected to have plasma concentrations of crizotinib above Ceff

The crizotinib granules in capsules for opening are being developed as a flexible solid oral dosage form for pediatric patients. They have been designed to be age appropriate and easy to swallow as the granules are emptied from capsules for administration. Dosing flexibility is achieved by combining the contents of capsules, as needed, to obtain the required target dose. The granules in capsules for opening drug product is composed of taste masked, coated, microspheres encapsulated into a hard gelatin capsule of 20 mg, 50 mg, and 150 mg strengths.

The 20 mg, 50 mg, and 150 mg granules in capsules for opening contents are intended to be emptied directly to the patient’s mouth or emptied to a consumer supplied dry oral dosing aid (eg, spoon, medicine cup) and then to the patient’s mouth, followed by sufficient water.

Pharmacokinetic interaction studies

It was shown in Study A8081069 that exposure of crizotinib when PPI is taken was decreased between 0.88 fold (AUCs) and 0.77 fold (Cmax) of original value.

2.5.2.2. Pharmacodynamics

N/A

2.5.3. Discussion on clinical pharmacology

A PBPK model for crizotinib was developed to predict the bioequivalence of newly formulated pediatric granules in capsule form compared to the reference commercial formulation (formulated capsule (FC)). This model was then utilized to establish in vitro dissolution acceptance criteria for the pediatric granules in capsule form. The secondary objective of this research was to employ the model to predict the performance of the granules in capsule form under various conditions. The validated model was used to predict the performance of granules in capsule form at lower doses and assess the impact of food intake and proton pump inhibitor (PPI) on absorption. Additionally, the model was employed to forecast comparable performance between granules in capsule form and granules without capsules.

Several clinical studies were utilized to develop and validate the PBPK model. Model verification involved comparing the predicted and observed geometric mean ratios of pharmacokinetic (PK) parameters. The model's validation included demonstrating observed bioequivalence after a single dose between FC and PIC (tablet or granule formulations). Overall, the results indicated that the model possesses predictive capabilities to simulate the single-dose pharmacokinetics of oral formulations in healthy participants under both fed and fasted conditions using in vitro dissolution data. Furthermore, the model confirmed the results of study A8081074, suggesting that the granule formulation in capsules would be bioequivalent to the granule formulation without capsules when administered under fasted conditions. However, the model exhibited a limitation in predicting the PPI effect with the commercialized formulation (FC) since the ratios of the predicted and observed (P/O) data without PPI for AUCinf value of crizotinib were slightly above 1.2-fold (P/O: 1.22, i.e., over prediction). This was also observed with the proposed formulation, i.e., granules without capsules, where the P/O of AUCinf value for crizotinib with PPI was 1.39, impacting the T/R Ratio in the bioequivalence studies with and without PPI (Study A8081035 and A8081069). Additionally, an overprediction was noted with the tablet formulation, where the P/O AUCinf and Cmax were 1.29 and 1.31, respectively. The same overprediction was observed for the granules without capsule formulation under fed conditions, with a P/O AUCinf and Cmax of 1.34 and 1.22, respectively (Study A8081069).

The applicant used this PBPK model to confirm the in vitro dissolution specifications for granules in the capsule formulation. (See also Quality section).

The Applicant gave details on the decreases in Crizotinib exposure after food or PPI, so it is agreed that the effect is clinically irrelevant for adults. PBPK did not take into account additional acidity in paediatric population initially, but this was implemented in the next round. The MAH also provided additional literature and discussion concerning the food effect and PPI effects on BE in the paediatric

population; this is well documented and changes in exposure due to physiological changes due to age in paediatric population, or due to PPI, are not expected.

PK of crizotinib is dose linear at the therapeutic dose ranges, and therefore the biowaiver for the 20 mg strength new formulation can be accepted. Crizotinib oral granules in capsules for opening administered with a high-fat/high-calorie meal reduced crizotinib AUC_{inf} and C_{max} by approximately 15% and 23%, respectively, compared to the same formulation administered under fasted conditions. Crizotinib granules in capsules for opening can be administered with or without food (see SmPC section 4.2 and 5.2)

The MAH utilized the PBPK model, which had been previously developed and validated using a comprehensive set of in vitro and in vivo data. This model was employed to compare the oral solution (OLF) and granules formulations through the application of the virtual bioequivalence (VBE) approach. The virtual bioequivalence assessment included consideration of observed intrasubject coefficient of variation (ICV) values, which were determined to be 17.80% for AUCinf and 17.69% for Cmax. The predetermined sample size for bioequivalence assessments, involving healthy adult subjects (Sim-Healthy Volunteers), was set at N=24 per trial. After conducting 1000 trial simulations, the estimated geometric mean ratio (GMR) for AUCinf and Cmax between the OLF and granules formulations were found to be 98.33 and 89.94, respectively. The probability of achieving bioequivalence was calculated to be 99.9% for AUCinf and 90.3% for Cmax.

Administration of a single 250 mg crizotinib dose of oral granules in capsules for opening following treatment with esomeprazole 40 mg once daily for 5 days resulted in an approximately 19% decrease in crizotinib AUC_{inf} and 23% decrease in C_{max}. The extent of the change in total exposure was not considered clinically meaningful. The relevant warning is stated under section 4.5 in the SmPC.

Based on these results, it is suggested that the Crizotinib granules formulation could be deemed bioequivalent to the oral solution in adults. Due to all the previous discussions regarding PBPK modelling including physiological differences in paediatric populations such as gastric acidity, transit time, and intestinal absorption, literature documentation, and the food effect study presented for the granulated formulation, BE can therefore be concluded to in paediatric patients. In the SmPC section 5.2 it is stated that following oral single-dose administration in the fasted state, the crizotinib granules in capsules for opening are bioequivalent to crizotinib capsules.

2.5.4. Conclusions on clinical pharmacology

The new formulation with the three strengths of 20, 50 and 150 mg can be considered acceptable from a bioequivalence point of view. Extrapolation can be accepted for the paediatric population.

Relevant information has been included in the SmPC sections 4.2 and 5.2.

2.5.5. Clinical efficacy

A clinical overview has been provided to support the registration of the new proposed formulation: granules in capsules for opening for pediatric patients. New dose administration recommendations are proposed for the granules in capsules for opening along with an update of the existing pediatric indications for the treatment of pediatric patients with relapsed or refractory, systemic ALK-positive ALCL or unresectable, recurrent, or refractory ALK-positive IMT, and to change the lower end of the age range from ≥6 years to ≥1 year.

Two clinical biopharmaceutic studies are provided to support the use of the granules in capsules for opening formulation (Studies A8081069 and A8081074; hereafter referred to as 1069 and 1074, respectively).- as discussed above. This is a biopharmaceutic focused submission and no efficacy results are included.

Reference is made to applicable information provided in prior regulatory submissions (variation EMEA/H/C/002489/II/0072).

Summary of main efficacy results

There are no new crizotinib efficacy data presented in this application, and therefore an updated Summary of Clinical Efficacy was not included within the current submission. The MAH claims that since the granules in capsules for opening were demonstrated to be bioequivalent to the formulated capsules, there is no anticipated change in the clinical benefit of crizotinib with use of the granules in capsules for opening.

2.5.5.1. Dose response study(ies)

New dose administration recommendations are proposed for the granules in capsules for opening along with an update of the existing pediatric indications for the treatment of pediatric patients with relapsed or refractory, systemic ALK-positive ALCL or unresectable, recurrent, or refractory ALK-positive IMT, and to change the lower end of the age range from >=6 years to ≥1 year.

The recommended dosage for paediatric patients with BSA <1.34 m^2 is provided below.

The granules are encapsulated into 3 dosage strengths: 20 mg, 50 mg and 150 mg crizotinib. If needed, attain the desired dose by combining different strengths of crizotinib granules in capsules for opening. No more than 4 capsules will be required for a single dose.

Table 9. Paediatric patients with body surface area (BSA) of 0.38 m^2 to 1.33 m^2: Recommended crizotinib granules* starting dosage

Body Surface Area (BSA)**	**Dose (Twice Daily)**	**Total Daily Dose**
0.38 to 0.46 m^2	120 mg (1 × 20 mg + 2 × 50 mg)	240 mg
0.47 to 0.51 m^2	140 mg (2× 20 mg + 2 × 50 mg)	280 mg
0.52 to 0.61 m^2	150 mg (1 × 150 mg)	300 mg
0.62 to 0.80 m^2	200 mg (1 × 50 mg + 1 × 150 mg)	400 mg
0.81 to 0.97 m^2	250 mg (2 × 50 mg + 1 × 150 mg)	500 mg
0.98 to 1.16 m^2	300 mg (2 × 150 mg)	600 mg
1.17 to 1.33 m^2	350 mg (1 × 50 mg + 2 × 150 mg)	700 mg

* Refers to the 20 mg, 50 mg and 150 mg crizotinib granules in capsules for opening.
** The recommended dosage for patients with a BSA less than 0.38 m^2 has not been established. For paediatric patients with BSA ≥1.34 m^2, see below

Table 10 **Paediatric patients with body surface area (BSA) ≥1.34 m^2: Recommended crizotinib capsules* starting dosage**

Body Surface Area (BSA)**	**Dose (Twice Daily)**	**Total Daily Dose**

Body Surface Area (BSA)**	Dose (Twice Daily)	Total Daily Dose
1.34 – 1.51 m^2	400 mg (2×200 mg capsule)	800 mg
1.52 – 1.69 m^2	450 mg (1×200 mg capsule + 1×250 mg capsule)	900 mg
≥1.70 m^2	500 mg (2×250 mg capsule)	1000 mg

* Refers to the XALKORI 200 mg and 250 mg hard capsules.
** For paediatric patients with BSA <1.34 m^2, refer to Table 2.

Additional analyses

The Applicant has conducted an extrapolation concept and plan from paediatric patients 6 years and older to patients less than 6 years old. The concept and plan is discussed according to the E11 extrapolation of paediatric data guidance. According to this, there are no meaningful differences between the 6-<18-year-old and the 1-<6-year-old populations with respect to disease characteristics, physiology, AE profile, or pharmacokinetics of crizotinib. Thus, there is confidence that there would be no clinically meaningful differences in objective response and safety of crizotinib between these 2 age groups. It has been demonstrated that the granules in capsules formulation is bioequivalent with both the oral solution used in Study ADVL0912 study population, and with the hard capsule formulation on which approval in the 6-<18-year-old population was granted.

2.5.6. Discussion on clinical efficacy

With regards to efficacy and safety, no new data was submitted to support the claimed extension of indication in the treatment of paediatric patients (age ≥ 1 to < 18 years) with recurrent or refractory ALK-positive unresectable inflammatory myofibroblastic tumour (IMT) and relapsed or refractory systemic ALK-positive anaplastic large cell lymphoma (ALCL) for the granules formulation.

Relevant efficacy and safety data that that are discussed across this report are derived from procedures EMA/H/C/002489/P46/025 and EMEA/H/C/002489/II/0072 in which the extension of indication for Xalkori was approved to include treatment of paediatric patients (age ≥ 6 to < 18 years) with recurrent or refractory ALK-positive unresectable IMT and relapsed or refractory systemic ALK-positive ALCL based on the results from clinical studies ADVL0912 and A8081013. Of note, at the time of the assessment of the previous extension of indication, two different formulations were used within the studies ADVL0912 and A8081013:

- an oral solution which is not available on the market;

- the already marketed capsules.

At the time of the II/0072 variation assessment, the extreme rarity of ALCL and IMT was highlighted and the limited amount of data presented was thus considered sufficient to draw conclusions on the B/R in the sought indication, also with regards to the outstanding clinically meaningful results.

For reference, the ORR for the 22 enrolled ALCL patients was of 86.4% (95% CI: 66.7, 95.3) for both (165 and 280 mg/m²BID) dose levels groups. The ORR for the 14 patients in the IMT group was 85.7% (95%CI: 60.1, 96.0) across both dose levels. Overall, only 4 patients under 6 were enrolled in the IMT group in the 280 mg/m²BID dose level group and 4 in the ALCL group in the 165 mg/m²BID dose level group.

At that time, the MAH completed the data with an exhaustive overview of published data. For ALCL patients, the MAH elaborated on the results from the French AcSé basket program as supportive data, which raised similar response rate in pediatric 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%). With regards to the ongoing supportive study A8081013, five paediatric patients were enrolled at data cut-off date. Efficacy results were as well consistent with those reported in the pivotal study.

Altogether, the efficacy results were considered significant and in line with the ADVL0912 pivotal study findings supporting an extension of indication in paediatric patients (age ≥6 to <18 years) with relapsed or refractory systemic ALK-positive ALCL and recurrent or refractory ALK-positive unresectable IMT.

The MAH provided an extended extrapolation plan to help establish the B/R balance of Xalkori granules within the sought indication (in paediatric patients aged ≥1) and a thorough discussion on PK extrapolation, dispelling doubts on exposition rates, responses in younger patients. Clinical data regarding clinical features, pathogenesis and prognostic factors. However, clinical differences should be taken into account when assessing efficacy and safety extrapolation since no comparison between age groups is available; The MAH conducted a literature search on the comparisons between adults and paediatric physiologic parameters such as gastric acidity, transit time, and components of intestinal fluids. Due to the limited physiological absorption data for paediatric oncology patients aged 1-6 years of age, the search was broadened to include data from healthy adult and paediatric participants. Overall, the physiology and components of the organ systems involved in the oral absorption of medications are similar between paediatric participants one year of age and older and adults (see also Clinical Pharmacology). The applicant supported with literature data that there is no significant difference in gastric pH, total GI, and transit time values between paediatric subjects under and over 6 years old, and that both passive and active transport are mature by 4 months of age; the efforts made by the MAH are acknowledged as well as the reassuring PK data providing bioequivalence proof between OS, capsules and granules.

Published data describing the antitumor activity of crizotinib in patients aged 1–<6 years with ALK-positive ALCL or ALK-positive IMT came from studies or cases series conducted in wider paediatric populations. In most publications (data not shown), it was not possible to align antitumor responses with individual patients, and patient ages are mainly specified as a median value or a range, which limited the purpose. Nonetheless, published data from clinical trials were supportive of antitumor activity in younger patients following crizotinib treatment, based on the age ranges of the study populations. These published studies showed an efficacy benefit for patients with ALK-positive ALCL and ALK-positive IMT that was consistent with the efficacy outcomes from Study ADVL0912.

2.5.7. Conclusions on the clinical efficacy

No new information was submitted to support a positive B/R in the claimed extension of indication in treatment of paediatric patients (age ⩾ 1 to < 18 years) with recurrent or refractory ALK-positive unresectable inflammatory myofibroblastic tumour (IMT) and relapsed or refractory systemic ALK-positive anaplastic large cell lymphoma (ALCL).

Further, the post authorisation studies to contextualize efficacy in the paediatric population as agreed in the context of II/72, also apply in these extensions of indications (see RMP):

- A pooled efficacy analysis of crizotinib at 165 mg/m2 BID in paediatric patients from Studies ADVL0912, CRZ-NBALCL and CRISP (ITCC-053) is scheduled to be provided to the EMA by 31 August 2027. (agreed within procedure II/072).

2.5.8. Clinical safety

2.5.8.1. Patient exposure

The characterization of the safety profile of the crizotinib granules in capsules for opening has been limited to single dose administrations in healthy participants in Studies 1069 and 1074.

The MAH states that no new safety issues were identified when the granules in capsules for opening were administered as whole capsules. Thus, since the granules in capsules for opening were demonstrated to be bioequivalent to the approved XALKORI 200 mg and 250 mg capsules, there is no anticipated change in the established crizotinib safety profile with use of the granules in capsules for opening.

2.5.8.2. Adverse events

Table 11 PF-02341066 Protocol A8081069 Treatment-Emergent Adverse Events - All-Causality and Treatment-Related

Number of Participants	Crizotinib cMS1 250 mg All-Causality (n)/Treatment-Related (n)	Crizotinib cMS2 250 mg All-Causality (n)/Treatment-Related (n)	Crizotinib FC 250 mg All-Causality (n)/Treatment-Related (n)	Crizotinib OS 250 mg All-Causality (n)/Treatment-Related (n)	Crizotinib cMS1 250 mg + HF meal All-Causality (n)/Treatment-Related (n)	Crizotinib cMS2 250 mg + HF meal All-Causality (n)/Treatment-Related (n)	Crizotinib cMS1 250 mg + Esomeprazole All-Causality (n)/Treatment-Related (n)	Crizotinib cMS2 250 mg + Esomeprazole All-Causality (n)/Treatment-Related (n)
Participants evaluable for adverse events	23	25	23	22	11	11	11	11
Number of adverse events	27 /21	20 /17	20 /18	15 /13	6 /4	5 /5	8 /5	3 /2
Participants with adverse events	12/11	9/9	11/9	6/6	4/3	4/4	4/2	1/1
Participants with serious adverse events	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0
Participants with severe adverse events	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0
Participants discontinued from study due to adverse events	1/1	1/1	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0

Table 12 PF-02341066 Protocol A8081069 Number of Participants with Treatment Emergent Adverse Events by SOC and PT: All-Causality and Treatment-Related

Number of Participants evaluable for AEs by system organ class and MedDRA (v22.1) Preferred Term	Crizotinib cMS1 250 mg All-Causality (n)/Treatment-Related (n) (N=23)	Crizotinib cMS2 250 mg All-Causality (n)/Treatment-Related (n) (N=25)	Crizotinib FC 250 mg All-Causality (n)/Treatment-Related (n) (N=23)	Crizotinib OS 250 mg All-Causality (n)/Treatment-Related (n) (N=22)	Crizotinib cMS1 250 mg + HF meal All-Causality (n)/Treatment-Related (n) (N=11)	Crizotinib cMS2 250 mg + HF meal All-Causality (n)/Treatment-Related (n) (N=11)	Crizotinib cMS1 250 mg + Esomeprazole All-Causality (n)/Treatment-Related (n) (N=11)	Crizotinib cMS2 250 mg + Esomeprazole All-Causality (n)/Treatment-Related (n) (N=11)
With Any Adverse Event	12/11	9/9	11/9	6/6	4/3	4/4	4/2	1/1
EYE DISORDERS	1/0	0 /0	0 /0	1/0	0 /0	0 /0	1/0	0 /0
Erythema of eyelid	0 /0	0 /0	0 /0	1/0	0 /0	0 /0	0 /0	0 /0
Ocular hyperaemia	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0	1/0	0 /0
Vision blurred	1/0	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0
GASTROINTESTINAL DISORDERS	10/10	8/8	7/7	6/6	3/3	3/3	2/2	1/1
Abdominal distension	1/1	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0
Abdominal pain	3/3	3/3	4/4	2/2	1/1	0 /0	1/1	0 /0
Abdominal pain upper	0 /0	1/1	0 /0	0 /0	0 /0	0 /0	1/1	0 /0
Constipation	1/1	0 /0	1/1	2/2	0 /0	1/1	0 /0	1/1
Diarrhoea	7/7	6/6	5/5	3/3	2/2	2/2	1/1	0 /0
Eructation	0 /0	0 /0	1/1	0 /0	0 /0	0 /0	0 /0	0 /0
Flatulence	0 /0	1/1	0 /0	1/1	0 /0	0 /0	0 /0	0 /0
Nausea	2/2	2/2	1/1	2/2	1/1	0 /0	1/1	0 /0
Vomiting	1/1	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1/0	1/0	1/0	0 /0	1/0	0 /0	0 /0	0 /0

Number of Participants evaluable for AEs by system organ class and MedDRA (v22.1) Preferred Term	Crizotinib cMS1 250 mg All-Causality (n)/Treatment-Related (n) (N=23)	Crizotinib cMS2 250 mg All-Causality (n)/Treatment-Related (n) (N=25)	Crizotinib FC 250 mg All-Causality (n)/Treatment-Related (n) (N=23)	Crizotinib OS 250 mg All-Causality (n)/Treatment-Related (n) (N=22)	Crizotinib cMS1 250 mg + HF meal All-Causality (n)/Treatment-Related (n) (N=11)	Crizotinib cMS2 250 mg + HF meal All-Causality (n)/Treatment-Related (n) (N=11)	Crizotinib cMS1 250 mg + Esomeprazole All-Causality (n)/Treatment-Related (n) (N=11)	Crizotinib cMS2 250 mg + Esomeprazole All-Causality (n)/Treatment-Related (n) (N=11)
Skin abrasion	1/0	1/0	1/0	0 /0	1/0	0 /0	0 /0	0 /0
INVESTIGATIONS	1/1	0 /0	0 /0	1/1	0 /0	0 /0	0 /0	0 /0
Transaminases increased	1/1	0 /0	0 /0	1/1	0 /0	0 /0	0 /0	0 /0
METABOLISM AND NUTRITION DISORDERS	0 /0	1/1	1/1	1/1	0 /0	0 /0	0 /0	0 /0
Decreased appetite	0 /0	1/1	1/1	1/1	0 /0	0 /0	0 /0	0 /0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0	1/0	0 /0
Back pain	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0	1/0	0 /0
NERVOUS SYSTEM DISORDERS	6/5	2/2	6/5	1/1	1/0	2/2	1/0	1/1
Dizziness	3/3	2/2	2/2	0 /0	0 /0	0 /0	0 /0	0 /0
Dysgeusia	0 /0	1/1	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0
Headache	2/0	1/0	1/0	1/0	1/0	0 /0	1/0	1/0
Lethargy	2/2	0 /0	3/3	1/1	0 /0	2/2	0 /0	1/1
PSYCHIATRIC DISORDERS	0 /0	1/0	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0
Depressed mood	0 /0	1/0	0 /0	0 /0	0 /0	0 /0	0 /0	0 /0
RENAL AND URINARY DISORDERS	1/0	0 /0	0 /0	0 /0	0 /0	0 /0	1/1	0 /0

Evaluation of Each Laboratory Parameter

The most common laboratory abnormalities were increased percentage of monocytes (monocytes/leukocytes >1.2 × ULN) which was reported in 7 out of 8 treatments and increased urate (>1.2 × ULN) which was reported in 4 treatments. None of these were considered as an AE by the investigator.

Three participants had ALT elevation during the study met preset criterion (>3 × ULN), 2 following Treatment A (cMS1 fasted) and 1 following Treatment D (OS fasted).

There were no participants meeting the categorical summarization criteria of vital signs data in this study.

Across all ECG parameters for all treatments, only 2 QTcB values (1 participant following Treatment G [cMS1+esomeprazole] and a second participant following Treatment H [cMS2+esomeprazole]) met the preset criteria (30 ≤ increase from baseline <60 msec), while no QTcF abnormalities were identified. The findings were not considered clinically meaningful by the investigator.

Summary of Adverse Events in study A8081074

All-causality AEs were reported in 58.3% (14/24) participants following crizotinib 250 mg FC, 44.0% (11/25) participants following crizotinib 250 mg eMS unencapsulated and 33.3% (4/12) participants following crizotinib 250 mg eMS encapsulated.

Treatment-related AEs were reported in 41.7% (10/24) participants following crizotinib 250 mg FC, 40.0% (10/25) participants following crizotinib 250 mg eMS unencapsulated, and 25.0% (3/12) participants following crizotinib 250 mg eMS encapsulated.

No SAEs or severe AEs were reported in this study. All AEs were mild in severity.

One participant discontinued from the study due to a treatment-related AE (transaminases increased; following the administration of crizotinib 250 mg eMS unencapsulated in Period 1.

Table 13 Treatment-Emergent Adverse Events (All Causalities) - Safety Analysis Set (Protocol A8081074)

Number (%) of Participants	Crizotinib 250mg FC n (%)	Crizotinib 250mg eMS Unencapsulated n (%)	Crizotinib 250mg eMS Encapsulated n (%)
Participants evaluable for adverse events	24	25	12
Number of adverse events	20	17	6
Participants with adverse events	14 (58.3)	11 (44.0)	4 (33.3)
Participants with serious adverse events	0	0	0
Participants with severe adverse events	0	0	0
Participants discontinued from study due to adverse events[a]	0	1 (4.0)	0

Table 14 Treatment-Emergent Adverse Events (Treatment Related) - Safety Analysis Set (Protocol A8081074)

Number (%) of Participants	Crizotinib 250mg FC n (%)	Crizotinib 250mg eMS Unencapsulated n (%)	Crizotinib 250mg eMS Encapsulated n (%)
Participants evaluable for adverse events	24	25	12
Number of adverse events	13	11	4
Participants with adverse events	10 (41.7)	10 (40.0)	3 (25.0)
Participants with serious adverse events	0	0	0
Participants with severe adverse events	0	0	0
Participants discontinued from study due to adverse events[a]	0	1 (4.0)	0

Table 15 Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities) - Safety Analysis Set (Protocol A8081074)

Number of Participants Evaluable for AEs Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	Crizotinib 250mg FC (N=24) n (%)	Crizotinib 250mg eMS Unencapsulated (N=25) n (%)	Crizotinib 250mg eMS Encapsulated (N=12) n (%)
With Any Adverse Event	14 (58.3)	11 (44.0)	4 (33.3)
EAR AND LABYRINTH DISORDERS	0	0	1 (8.3)
Ear pain	0	0	1 (8.3)
EYE DISORDERS	0	1 (4.0)	0
Photophobia	0	1 (4.0)	0
GASTROINTESTINAL DISORDERS	11 (45.8)	10 (40.0)	3 (25.0)
Abdominal discomfort	3 (12.5)	1 (4.0)	0
Abdominal distension	0	1 (4.0)	0
Abdominal pain	0	1 (4.0)	0
Abdominal pain upper	0	0	1 (8.3)
Constipation	0	1 (4.0)	0
Diarrhoea	5 (20.8)	3 (12.0)	1 (8.3)
Nausea	7 (29.2)	5 (20.0)	2 (16.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (4.2)	1 (4.0)	0
Fatigue	0	1 (4.0)	0
Vessel puncture site pain	1 (4.2)	0	0
INVESTIGATIONS	0	1 (4.0)	0
Transaminases increased	0	1 (4.0)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (4.2)	0	0
Back pain	1 (4.2)	0	0
NERVOUS SYSTEM DISORDERS	3 (12.5)	0	1 (8.3)
Headache	2 (8.3)	0	1 (8.3)
Somnolence	1 (4.2)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	2 (8.0)	0
Pruritus	0	2 (8.0)	0

Table 11. Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Treatment Related) - Safety Analysis Set (Protocol A8081074)

Number of Participants Evaluable for AEs Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	Crizotinib 250mg FC (N=24) n (%)	Crizotinib 250mg eMS Unencapsulated (N=25) n (%)	Crizotinib 250mg eMS Encapsulated (N=12) n (%)
With Any Adverse Event	10 (41.7)	10 (40.0)	3 (25.0)
GASTROINTESTINAL DISORDERS	10 (41.7)	9 (36.0)	3 (25.0)
Abdominal discomfort	2 (8.3)	0	0
Abdominal distension	0	1 (4.0)	0
Abdominal pain	0	1 (4.0)	0
Abdominal pain upper	0	0	1 (8.3)
Diarrhoea	4 (16.7)	3 (12.0)	1 (8.3)
Nausea	7 (29.2)	5 (20.0)	2 (16.7)
INVESTIGATIONS	0	1 (4.0)	0
Transaminases increased	0	1 (4.0)	0

2.5.8.3. Serious adverse event/deaths/other significant events

No deaths, SAEs, or severe AEs occurred in in Study 1069.

No deaths, SAEs or severe AEs were reported in Study 1074.

2.5.8.4. Palatability test

Participants were asked to fill out a questionnaire after crizotinib administration (immediately after crizotinib dosing, 5, 10, and 20 minutes after crizotinib administration). The ultimate goal of the taste evaluation in this study was to assist in the selection of the optimal microsphere formulation (cMS1 or cMS2). The taste questionnaire was used to determine the microsphere formulation that offered improved palatability compared to the OS formulation. For bitterness, tongue/mouth burn, throat burn, mouth feel and overall liking, both Treatments A (cMS1) and B (cMS2) had numerically lower scores than Treatment D (OS) at the 4 postdose time points, which suggested that the cMS1 and cMS2 formulations had more favorable scores than the OS formulation. These analyses indicated improved palatability of cMS1 and cMS2 formulations in comparison to the OS formulation. Since the cMS1 formulation showed a better food effect that the cMS2, the choice of the cMS1 formulation is agreed**.**

Taste Sensory Attributes Evaluations

Participants were asked to fill out the Taste Questionnaire after crizotinib administration during Treatments A, B and D. The Taste Questionnaire was administered at 1 (immediately after crizotinib dosing), 5, 10, and 20 minutes after crizotinib administration.

The ultimate goal of the taste evaluation in this study was to assist in the selection of the optimal microsphere formulation (cMS1 or cMS2). The taste questionnaire was used to determine the microsphere formulation that offered improved palatability compared to the OS formulation. cMS1 was therefore preferred over cMS2, the food effect appearing less important with the cMS1 formulation.

2.5.8.5. Laboratory findings

Few laboratory abnormalities met specified criteria in this study. The only 2 laboratory test abnormalities considered clinically significant and reported as an AE were AST >3 × ULN and ALT >3 × ULN which occurred in 1 participant following the administration of crizotinib 250 mg eMS unencapsulated. The corresponding AE of transaminases increased resulted in the participant's study discontinuation.

One participant had a supine systolic blood pressure meeting the protocol pre-defined categorization criterion (change ≥30 mmHg decrease) following the administration of crizotinib 250 mg eMS unencapsulated.

There were no changes in vital signs considered clinically significant and reported as an AE by the investigator.

There were no ECG results meeting the protocol pre-defined categorization criteria for QTcF, PR interval or QRS complex. There were no changes in ECG measurements considered clinically significant and reported as an AE by the investigator.

2.5.8.6. Discontinuation due to adverse events

One participant discontinued from the study due to a treatment-related AE following the administration of crizotinib 250 mg eMS unencapsulated.

Instructions for dose reductions are as follows:

Table 16 Paediatric patients with body surface area (BSA) ≥1.34 m2: Recommended XALKORI capsules*dose reductions

Body Surface Area (BSA)**	**First Dose Reduction**		**Second Dose Reduction*****	
	Dose (Twice daily*)	**Total Daily Dose**	**Dose** (Twice daily*)	**Total Daily Dose**
1.34 – 1.69 m^2	250 mg	500 mg	200 mg	400 mg
≥1.70 m^2	400 mg	800 mg	250 mg	500 mg

Refers to the XALKORI 200 mg and 250 mg hard capsules.
** For paediatric patients with BSA <1.34 m^2, refer to Table 6.
*** Permanently discontinue in patients who are unable to tolerate crizotinib after 2 dose reductions.

2.5.8.7. Post marketing experience

As of November 2022, crizotinib was approved in more than 95 countries worldwide for the indication of ALK-positive advanced NSCLC and 75 countries worldwide for the indication of ROS1-positive advanced NSCLC, including the US, EU, Japan, and Switzerland. In the US, crizotinib received approval in January 2021 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 in July 2022 for the treatment of adult and paediatric patients 1 year of age and older with unresectable, recurrent, or refractory ALK-positive IMT.

2.5.9. Discussion on clinical safety

The characterization of the safety profile of the crizotinib granules in capsules for opening has been limited to single dose administrations in healthy participants in Studies 1069 and 1074.

Safety evaluations included monitoring of vital signs, 12-lead ECGs, physical examination findings, AEs, SAEs, and clinical laboratory tests.

For study 1069, a phase 1 study aiming to evaluate palatability and relative bioavailability of two paediatric microsphere formulations of crizotinib in healthy participants. A single dose of crizotinib was administered in 25 healthy adult participants. The observed safety profile was in line with what is known for Xalkori. The most frequently reported AEs were Diarrhoea, Abdominal pain, Nausea, and Lethargy. All AEs were mild in severity, except for 1 moderate AE of Transaminases increased. No deaths, SAEs, or severe AEs occurred in this study. Two participants discontinued from the study due to AEs (one was associated with a moderate Transaminases increased AE related to cMS1 (subject to line extension) administered under fasting conditions, resolved in 1 month and the other one was associated with mild AEs of Nausea, Depressed mood, Diarrhoea and Decreased appetite following cMS2 formulation administered under fasting conditions). Moreover, 3 participants had an ALT elevation during the study that met pre-set criterion (>3 × ULN), from which 2 occurred within the cMS1 fasted setting. No clinically significant abnormalities in vital signs or ECGs were observed in any participant.

Regarding the palatability test, for bitterness, tongue/mouth burn, throat burn, mouth feel and overall liking, both Treatments A (cMS1) and B (cMS2) had numerically lower scores than Treatment D (OS) at the 4 postdose time points, which suggested that the cMS1 and cMS2 formulations had more favorable scores than the OS formulation. These analyses indicated improved palatability of cMS1 and cMS2 formulations in comparison to the OS formulation. As discussed under Clinical Pharmacology, the cMS1 formulation was the chosen formulation**.**

Study 1074 is a Phase 1 study aiming to establish bioequivalence of an encapsulated microsphere formulation (eMS) to the formulated capsule (FC) of Crizotinib in healthy adult participants. Treatment-related AEs were reported in 41.7% (10/24) participants following crizotinib 250 mg FC, 40% (10/25) participants following crizotinib 250 mg eMS unencapsulated, and 25% (3/12) participants following crizotinib 250 mg eMS encapsulated. No deaths, SAEs or severe AEs were reported in this study and all AEs were mild in severity. Moreover, one participant discontinued from the study due to a treatment-related AE following the administration of crizotinib 250 mg eMS unencapsulated.

Following the administration of crizotinib 250 mg eMS unencapsulated, the most frequently reported treatment-related AEs (⩾10% participants) were nausea (20.0%) and diarrhoea (12.0%) vs only nausea (16.7%) for the crizotinib 250 mg eMS encapsulated formulation.

The only 2 laboratory test abnormalities considered clinically significant and reported as an AE were AST >3 × ULN and ALT >3 × ULN which occurred in 1 participant following the administration of crizotinib 250 mg eMS unencapsulated. No changes in vital signs or ECG measurements were considered clinically significant and reported as an AE by the investigator.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.5.10. Conclusions on the clinical safety

The MAH only provided new data from two healthy volunteers' trials assessing PK and Safety of the

granules formulation in adult patients. No new safety signals were identified within these studies. No safety data were provided within the sought indications, in the paediatric population. Since PK bioequivalence has been established between OS, capsules and granules, the absence of clinical data with the granules formulation is deemed acceptable.

Further, the post authorisation studies to contextualize safety in the paediatric population as agreed in the context of II/72, also apply in these extensions of indications (see RMP):

- The CRISP study (ITCC 053) CSR is scheduled to be provided to the EMA by 28 February 2027 as part of an ongoing additional pharmacovigilance activity to further evaluate ocular toxicities. It is expected the oral granule formulation will be made available to study participants in early 2025.
- The CSR for the CRZ-NBALCL study is scheduled to be provided to the EMA by 30 September 2024 as part of an ongoing additional pharmacovigilance activity to further evaluate ocular toxicity.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 17: Summary of safety concerns

Summary of safety concerns	
Important identified risks	- Hepatotoxicity - Pneumonitis/ILD - QTc Prolongation - Bradycardia - Renal Cyst - Gastrointestinal perforation - Cardiac failure
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 - Risk of medication Errors
Missing information	- Patients undergoing long-term treatment

2.6.2. Pharmacovigilance plan

Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Table 18. 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 Children with Cancer (Category: 3)	A phase 1B of crizotinib either in combination or as single agent in pediatric patients with ALK, ROS1 or MET positive malignancies.	Ocular toxicities associated with crizotinib in pediatric and young adult patients	Study Completion: February 2026	Final Analysis: 28 February 2027
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)	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

2.6.3. Risk minimisation measures

Additional risk minimisation measures

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

Educational materials – Patient Brochure

Objectives: The objective of the proposed additional measure is to provide an appropriate tool designed to enhance the awareness and knowledge of patients about the following safety concerns; Hepatotoxicity, Pneumonitis/ILD, QTc prolongation, Bradycardia, Renal cyst, Gastrointestinal perforation, Cardiac failure,

Reproductive toxicity (including pregnant and lactating women), and Severe vision loss/Potential sight threatening event; and to ensure the optimal use of crizotinib.

Rationale for the additional risk minimization activity:

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

Direct Healthcare Professional Communication (DHPC)

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

Rationale for the additional risk minimization activity:

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

Table 19. 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

Table 19. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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 PL sections 2, 4 Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Renal cyst	Routine risk minimisation measures: SmPC section 4.8 PL sections 4 Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Gastrointestinal Perforation (EU and Switzerland)	Routine risk minimisation measures: SmPC sections 4.4,4.8 PL sections 2, 4 Additional risk minimisation measures: Educational materials	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Cardiac failure	Routine risk minimisation measures: SmPC section 4.4	Routine pharmacovigilance

Table 19. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
(EU, Japan, Switzerland and other ex-US Countries[a])	PL section: 4 Additional risk minimisation measures~~:~~ Educational materials	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
Severe Vision Loss/Potential Sight Threatening Event	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.7, 4.8 PL sections 2, 4 Additional risk minimisation measures: Educational materials DHPC (specific to the paediatric population)	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: CRISP study ITCC 053, CRZ-NBALCL study
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 longterm treatment	None	None

EU = Eurepoean 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.

2.6.4. Conclusion

The CHMP considered that the risk management plan version 9.1 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

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

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The MAH hereby submitted a grouped Type II Variation and an extension application for a new formulation for XALKORI (granules in capsules for opening) for the treatment of paediatric patients with Anaplastic Large Cell Lymphoma (ALCL) and Inflammatory Myofibroblastic Tumour (IMT).

The granules in capsules for opening formulation are meant to permit the administration of crizotinib to paediatric patients where the hard capsules are not suitable and to those with a body service area (BSA) of 0.60-1.33 m2. The expansion of the lower age range of the paediatric indications from 6 years to 1 years old reflects those patients with a BSA in the lower range. The development of an oral age appropriate peadiatric formulation was agreed with the PDCO as part of PIP EMEA-001493-PIP03-18-M01. A compliance check was submitted to the PDCO prior to this submission, confirming outstanding measures in the PIP are completed.

3.1.1. Disease or condition

Anaplastic Large Cell Lymphoma (ALCL)

ALCL is a chemosensitive malignancy both in pediatric 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 pediatric 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 tumor (IMT)
IMT is a class of tumor 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 tumor 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.

3.1.2. Main clinical studies

This is a biopharmaceutic focused submission and no safety nor efficacy results have been included beyond the limited safety results from the biopharmaceutic studies described in this application.

The granules in capsules for opening were considered to be bioequivalent to the formulated capsules. The characterization of the safety profile of the crizotinib granules in capsules for opening has been limited to single dose administrations in healthy participants in the clinical pharmacology Studies 1069 and 1074.

3.2. Favourable effects

No new efficacy data were submitted within the current application to change the lower end of the age range of the paediatric indication from ≥6 years to ≥1 year. Reference is made to data derived from procedures EMA/H/C/002489/P46/025 and EMEA/H/C/002489/II/ 0072 in which the extension of indication for Xalkori was approved to include treatment of paediatric patients (age ≥ 6 to < 18 years) with recurrent or refractory ALK-positive unresectable IMT and relapsed or refractory systemic ALK-positive ALCL based on the results from clinical studies ADVL0912 and A8081013.

In II/0072, the ORR for the 22 enrolled ALCL patients was of 86.4% (95% CI: 66.7, 95.3) for both (165 and 280 mg/m²BID) dose levels groups. The ORR for the 14 patients in the IMT group was 85.7% (95%CI: 60.1, 96.0) across both 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. Overall, 4 patients under 6 were enrolled in the IMT group in the 280 mg/m²BID dose level group and 4 in the ALCL group in the 165 mg/m²BID dose level group. 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 with a median TTR of less than a month for both indications. The applicant supported extrapolation data with literature showing there is no significant difference in gastric pH, total GI, and transit time values between paediatric subjects under and over 6 years old, and that both passive and active transport are mature by 4 months of age.

3.3. Uncertainties and limitations about favourable effects

No efficacy and safety data have been submitted to support a B/R in the claimed extension of indication paediatric patients (age ≥ 1 to < 18 years) with recurrent or refractory ALK-positive unresectable IMT and relapsed or refractory systemic ALK-positive ALCL who will be administered the new granules formulation.

The data discussed in previous sections were derived from procedures EMA/H/C/002489/P46/025 and EMEA/H/C/002489/II/0072 in which the extension of indication for Xalkori was approved to include treatment of paediatric patients (age ≥ 6 to < 18 years) with recurrent or refractory anaplastic lymphoma kinase (ALK)-positive unresectable inflammatory myofibroblastic tumour (IMT) based on the results from Studies ADVL0912 and A8081013 where two formulations were administered to patients: hard capsules and a non- marketed oral solution, initially developed to respond to the need for a paediatric appropriate formulation. Moreover, only 4 patients in each indication was under 6, driving limited data in this young population. Available data in patients under 6 at time of the previous extension EMEA/H/C/002489/II/0072 concerned two dose regimen, while extension here is only claimed for the higher, 280 mg/m2, regimen: 280 mg/m²BID in 4 patients under 6 in the IMT group; 165 mg/m²BID in 4 patients under 6 in the ALCL group.

Further, the pooled efficacy analyses to contextualize efficacy in the paediatric population as agreed in the assessment of II/72, in paediatric patients from Studies ADVL0912, CRZ-NBALCL and CRISP (ITCC-053) will be provided post authorisation (see RMP).

3.4. Unfavourable effects

In 25 healthy adult participants in Study 1069 most frequently reported AEs were Diarrhoea, Abdominal pain, Nausea, and Lethargy. All AEs were mild in severity, except for 1 moderate AE of Transaminases increased. No deaths, SAEs, or severe AEs occurred in this study. Two participants discontinued from the study due to AEs (one was associated with a moderate Transaminases increased AE related to cMS1 (subject to line extension) administered under fasting conditions, resolved in 1 month and the other one was associated with mild AEs of Nausea, Depressed mood, Diarrhoea and Decreased appetite following cMS2 formulation administered under fasting conditions). Moreover, 3 participants had an ALT elevation during the study that met pre-set criterion (>3 × ULN), from which 2 occurred within the cMS1 fasted setting. No clinically significant abnormalities in vital signs or ECGs were neither observed in any participant.

In Study 1074 treatment-related AEs were reported in 41.7% (10/24) participants following crizotinib 250 mg FC, 40% (10/25) participants following crizotinib 250 mg eMS unencapsulated, and 25% (3/12)

participants following crizotinib 250 mg eMS encapsulated. No deaths, SAEs or severe AEs were reported in this study and all AEs were mild in severity.

Regarding the palatability test, for bitterness, tongue/mouth burn, throat burn, mouth feel and overall liking, both Treatments A (cMS1) and B (cMS2) had numerically lower scores than Treatment D (OS) at the 4 postdose time points, which suggested that the cMS1 and cMS2 formulations had more favorable scores than the OS formulation. These analyses indicated improved palatability of cMS1 and cMS2 formulations in comparison to the OS formulation.

Following the administration of crizotinib 250 mg eMS unencapsulated, the most frequently reported treatment-related AEs (⩾10% participants) were nausea (20.0%) and diarrhoea (12.0%) vs only nausea (16.7%) for the crizotinib 250 mg eMS encapsulated formulation.

The only 2 laboratory test abnormalities considered clinically significant and reported as an AE were AST >3 × ULN and ALT >3 × ULN which occurred in 1 participant following the administration of crizotinib 250 mg eMS unencapsulated.

3.5. Uncertainties and limitations about unfavourable effects

The MAH only provided new data from two healthy volunteers' studies assessing PK and Safety of the granules formulation where no new safety signals were identified in healthy volunteers.

No safety data were provided within the sought indications, in the paediatric population.

Further, the pooled efficacy analyses to contextualize safety in the paediatric population as agreed in II/72, in paediatric patients from Studies ADVL0912, CRZ-NBALCL and CRISP (ITCC-053) will be provided post authorisation (see RMP).

3.6. Effects Table

N/A

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Relevant efficacy and safety data that that are discussed across this report are derived from procedures EMA/H/C/002489/P46/025 and EMEA/H/C/002489/II/0072 in which the extension of indication for Xalkori was approved to include treatment of paediatric patients (age ≥ 6 to < 18 years) with recurrent or refractory ALK-positive unresectable IMT and relapsed or refractory systemic ALK-positive ALCL based on the results from clinical studies ADVL0912 and A8081013. Despite the extreme rarity of ALCL and IMT and the limited amount of data presented, the outstanding clinically meaningful results, supported by the findings of an exhaustive overview of published data and extrapolation analyses was considered sufficient to draw conclusions on the B/R in the sought indication.

Altogether, the efficacy results were considered significant and in line with the ADVL0912 pivotal study findings supporting an extension of indication in paediatric patients (age ≥6 to <18 years) with relapsed or refractory systemic ALK-positive ALCL and recurrent or refractory ALK-positive unresectable IMT.

The observed safety profile in healthy adults was in line with what is known for Xalkori. In addition, a palatability test showed improved palatability compared to the OS formulation. Since the cMS1 formulation showed a better food effect than the cMS2, the choice of the cMS1 formulation is fully endorsed.

The MAH provided an extended extrapolation plan to help establish the B/R balance of Xalkori granules within the sought indication. A thorough discussion using literature data, showing no significant differences in gastric pH, total gastrointestinal (GI) transit time, and values between paediatric subjects and adults. This was supported by a virtual bioequivalence (VBE) assessment comparing an oral solution and granule formulation of crizotinib in 5,000 virtual subjects aged 1-6 years using a PBPK model developed from paediatric data. This PBPK model accounts for the previously discussed physiological differences and the potential for greater variability in paediatric patients, using an intra-subject coefficient of variation (ICV) of 29%. The results showed a high probability of bioequivalence (BE) success (99.7%), indicating a low risk of clinically meaningful differences in bioavailability between the two formulations under paediatric conditions.

This data reassures the pharmacokinetic extrapolation, dispelling doubts about exposure rates, responses, and the safety profile of Xalkori granules in younger patients.

3.7.2. Balance of benefits and risks

The overall B/R of Xalkori (granules in capsules for opening) in the treatment of paediatric patients (age ≥ 1 to < 18 years) with relapsed or refractory, systemic ALK-positive ALCL is considered positive.

The overall B/R of Xalkori (granules in capsules for opening) in the treatment of paediatric patients (age ≥ 1 to < 18 years) with recurrent or refractory anaplastic lymphoma kinase (ALK)-positive unresectable inflammatory myofibroblastic tumour (IMT) is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of XALKORI is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Xalkori is not similar to Adcetris, Poteligeo and Ledaga within the meaning of Article 3 of Commission Regulation (EC) No 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Xalkori 20 mg, 50 mg, 150 mg, Granules in capsule for opening is

favourable in the following indications:

- The treatment of paediatric patients (age 1 to <18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK) positive anaplastic large cell lymphoma (ALCL)
- The treatment of paediatric patients (age 1 to <18 years) with recurrent or refractory anaplastic lymphoma kinase (ALK) positive unresectable inflammatory myofibroblastic tumour (IMT)

The CHMP therefore recommends the extensions of the marketing authorisation for Xalkori subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

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

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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 (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:
    - Breathing problems associated with pneumonitis/ILD
    - Light-headedness, fainting, chest discomfort or irregular heartbeat associated with bradycardia, QT prolongation and cardiac failure
    - Abnormalities in liver blood tests associated with hepatotoxicity
    - Visual changes, including guidance to assess visual symptoms in the paediatric population
    - Stomach disorders associated with gastrointestinal perforation
- The importance 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.