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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

XALKORI

Crizotinib

Procedure no: EMEA/H/C/002489/P46/026

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	02 Dec 2024	02 Dec 2024	☐
☐	CHMP Rapporteur Assessment Report	06 Jan 2025	06 Jan 2025	☐
☐	CHMP members comments	20 Jan 2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	23 Jan 2025	n/a	☐
☒	CHMP adoption of conclusions:	30 Jan 2025	30 Jan 2025	☒

Declarations

☒ The assessor confirms that this assessment does **not** include non-public information, including commercially confidential information (e.g. ASMF, information shared by other competent authorities or organisations, reference to on-going assessments or development plans etc), irrespective from which entity was received*.

**If the entity from which non-public information originates has consented to its further disclosure, the box should be ticked and there* would *be no need to add details below.*

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

Table of contents

1. Introduction

On November 11th 2024, the MAH submitted a completed paediatric study A8081056 for Crizotinib, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has been also provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study A8081056, an open label expanded access protocol for the treatment of up to approximately 40 adult or pediatric (defined as age <18 years) patients with tumors harboring either a chromosomal translocation or activating mutation involving the ALK or ROS1 gene or an activating genetic alteration involving the cMET gene who cannot swallow the crizotinib capsule but may be able to derive benefit from treatment with an alternative oral formulation of crizotinib is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

The alternative oral formulations were an oral solution and coated microsphere formulation, both of which demonstrated bioequivalence to the formulated capsule.

Crizotinib oral solution containing crizotinib (25 mg/mL), or coated microspheres were encapsulated to 3 dose strengths (20 mg, 40 mg, and 120 mg of crizotinib). The microspheres were dosed by opening the capsules then emptying the contents onto a dosing spoon and were administered with water. The capsules were not to be swallowed whole and were only to be taken as directed in the dosing instructions.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

Study A8081056: Crizotinib (Xalkori) Expanded Access Protocol for the Treatment of Adult or Pediatric Patients with solid or hematologic malignancies that harbor a crizotinib-sensitive molecular alteration but who are unable to swallow crizotinib capsules

2.3.2. Clinical study

Study A8081056, is an open label expanded access protocol for the treatment of up to approximately 40 adult or pediatric (defined as age <18 years) patients with tumors harboring either a chromosomal translocation or activating mutation involving the ALK or ROS1 gene or an activating genetic alteration involving the cMET gene who cannot swallow the crizotinib capsule but may be able to derive benefit from treatment with an alternative oral formulation of crizotinib (coated microspheres).

Description

Crizotinib is indicated in the U.S. for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. Commercially available dosage forms are 250 mg and 200 mg capsules. This expanded access protocol (EAP) is designed to provide access to an alternative oral formulation of crizotinib for those patients who are unable to swallow capsules.

Methods

Treatments

For adult patients, crizotinib 250 mg BID will be administered orally at approximately the same time each day on a continuous daily dosing schedule, ie, without break in dosing. For pediatric patients, crizotinib 280 mg/m2 BID will be administered orally at approximately the same time each day on a continuous daily dosing schedule, ie, without break in dosing.

Objective(s)

The objective of the study was to use expanded access to evaluate the safety of an alternative oral formulation (the oral liquid formulation or coated microsphere formulation) of crizotinib with tumours harbouring either a chromosomal translocation or activating mutation involving the ALK or ROS1 gene or an activating genetic alteration involving the c-MET gene, who had a genetic aberration involving ALK, ROS1, or c-MET but who could not swallow crizotinib capsules.

Outcomes/endpoints

Study objectives and endpoints are provided in Table 1 below:

Table 1 Study Objectives and Endpoints

Type	Objective	Endpoints
Safety	To use expanded access to evaluate the safety of an alternative oral formulation (the oral liquid formulation or coated microsphere formulation) of crizotinib in up to approximately 40 patients with tumors harboring either a chromosomal translocation or activating mutation involving the ALK or ROS1 gene or an activating genetic alteration involving the c-MET gene, who had a genetic aberration involving ALK, ROS1, or c-MET but who could not swallow crizotinib capsules.	All SAEs and Grade 3-5 adverse events as assessed by CTCAE v4.03.

Study participants

Main eligibility criteria:

1- Histologically or cytologically proven diagnosis of a primary or metastatic malignancy that is positive for a chromosomal translocation or activating mutation involving the ALK or ROS1 gene or an activating genetic alteration involving the cMET gene, as determined by local clinical testing that is appropriately validated in accordance with applicable regulatory guidelines and/or practice standards (patients with tumours harbouring other genetic alterations that may potentially benefit from treatment with crizotinib eg NTRK3 ETV6 fusion gene may be considered on a case by case basis subject to approval by the sponsor),

2- Inability to swallow crizotinib capsules, adult patients of whom must either have a feeding tube in place or have completed clinical evaluation of dysphagia without any reversible causes identified,

3- At least 12 months of age (patients <12 months of age will be evaluated on a case by case basis and discussed with the sponsor)

Main ineligibility criteria:

1- Currently receiving crizotinib, another ALK inhibitor, or an investigational product,

2- Adult patients who have been previously treated with crizotinib

Statistical Methods

Safety Analysis:

Grade 3-5 AEs and all SAEs were recorded on the CRF from the time the patient had taken at least 1 dose of crizotinib through 28 calendar days after the last administration of crizotinib.

Results

Recruitment

Study A8081056 was conducted at 5 sites in USA.

The study start date was December 21, 2016 (First Patient First Visit).

The study end date was June 10, 2024 (Last Subject Last Visit).

The final study report date is October 03, 2024

Patient Disposition

A total of 15 participants were enrolled at 5 centres in the US. The disposition of study participants in the table below:

Table 2 Disposition Events Summary - Full Analysis Set (Protocol A8081056)

Number (%) of Participants	CRIZOTINIB (N=15) n (%)
Enrolled	
Not Treated	1 (6.7)
Treated	14 (93.3)
Disposition phase: Treatment	
Discontinued	14 (93.3)
Reason for discontinuation	
Adverse Event	3 (20.0)
Objective Progression or Relapse	3 (20.0)
Participant Refused Continued Treatment for Reason Other Than Adverse Event	3 (20.0)
Withdrew Consent	0
Other	5 (33.3)
Ongoing	0
Disposition phase: Study	
Discontinued	15 (100.0)
Reason for discontinuation	
Adverse Event	3 (20.0)
Objective Progression or Relapse	3 (20.0)
Participant Refused Continued Treatment for Reason Other Than Adverse Event	3 (20.0)
Withdrew Consent	1 (6.7)
Other	5 (33.3)
Ongoing	0

Disposition Phase: Treatment - Discontinuation only includes participants in Safety Analysis Set.

Baseline data

Of the 14 treated participants, the median (range) age was 3.2 (0.1-10.9) years old, the gender distribution was balanced, and 9 (64.3%) were White. The most common primary diagnoses were inflammatory myofibroblastic tumor (42.9%) and neuroblastoma (21.4%).

Table 3 Demographic Characteristics - Safety Analysis Set (Protocol A8081056)

	CRIZOTINIB (N=14)
Age (Years)	
n[a]	14
Mean (SD)	4.0 (3.7)
Median (Range: min, max)	3.2 (0.1, 10.9)
Gender, n (%)	
Male	7 (50.0)
Female	7 (50.0)
Race, n (%)	
White	9 (64.3)
Black	1 (7.1)
Asian	0
Other	4 (28.6)
Ethnicity, n (%)	
Hispanic or Latino	4 (28.6)
Not Hispanic or Latino	10 (71.4)

[a] n is the number of participants with non-missing age.

Table 4 Primary Diagnoses - Safety Analysis Set (Protocol A8081056)

Number (%) of Participants	CRIZOTINIB (N=14) n (%)
Primary Diagnosis Term	
Fibrous histiocytoma	2 (14.3%)
Glioblastoma multiforme	1 (7.1%)
Glioma	1 (7.1%)
Inflammatory myofibroblastic tumour	6 (42.9%)
Medullary thyroid cancer	1 (7.1%)
Neuroblastoma	3 (21.4%)

MedDRA v27.0 coding dictionary applied.

Efficacy results

Not Applicable.

Safety results

Updated safety data are provided in Table 5 below.

Table 5 Safety Results for Paediatric Patients with Solid or Hematologic Malignancies (Study A8081056 – LPLV Date: 10 June 2024)

Exposure	The 14 participants were treated with crizotinib for a median (range) duration of 25.21 (0.29-150.86) weeks; 2 received crizotinib coated microsphere for a median (range) duration of 77.5 (4.14-150.86) weeks and 12 received crizotinib solution for a median (range) duration of 25.21 (0.29-85.57) weeks.
Adverse Events	
Grade 3 or 4 All-Causality AEs	A total of 10 out of 14 treated participants (71.4%) reported a Grade 3 or 4 all-causality AE . The most frequently reported (≥20%) Grade 3 all-causality AE was NEUTROPENIA (28.6%). Grade 4 all-causality AEs reported were NEUTROPENIA (21.4%), Diarrhoea (7.1%), and Pain (7.1%).
Grade 3 or 4 Treatment-related AEs	A total of 9 out of 14 participants (64.3%) reported a Grade 3 or 4 treatment-related AE. The most frequently reported (≥20%) Grade 3 treatment-related AE was NEUTROPENIA (28.6%). Grade 4 treatment-related AEs reported were NEUTROPENIA (14.3%) and Diarrhoea (7.1%).
Deaths (Grade 5 AEs)	A total of 1 Grade 5 AE due to the disease under study (Disease progression) was reported during the study which was not considered to be treatment-related.
Serious Adverse Events	
All-Causality SAEs	There was 1 all-causality SAE reported in more than 1 participant (Pneumonia; reported in 2 participants).
Treatment-related SAEs	2 participants experienced treatment-related SAEs: 1 participant experienced Diarrhoea, and the other participant experienced NEUTROPENIA and Vomiting.
Dose Modifications and Discontinuations Associated With Adverse Events	
Permanent Discontinuation of Crizotinib due to AEs	A total of 3 participants (21.4%) permanently discontinued crizotinib and discontinued from the study associated with AEs: NEUTROPENIA in 2 participants, considered to be treatment-related; Dehydration in 1 participant, considered not to be treatment-related.
Dose Reductions Associated with AEs	A total of 4 participants (28.6%) experienced AEs leading to dose reduction of crizotinib; all these AEs were NEUTROPENIA and considered to be treatment-related.
Temporary Discontinuation of Crizotinib Associated with AEs	A total of 7 participants (50%) experienced at least 1 all-causality AE leading to a dosing interruption of crizotinib; 6 participants had at least 1 treatment-related AE leading to a dosing interruption. The most frequent all-causality AE leading to a dosing interruption was NEUTROPENIA, which was reported in 5 participants; no other AEs leading to a dosing interruption occurred in more than 1 participant.

Treatment Emergent Adverse Events

Table 6 Treatment-Emergent Adverse Events (All Causality) - Safety Analysis Set (Protocol A8081056)

Number (%) of Participants	CRIZOTINIB n (%)
Participants evaluable for adverse events	14
Number of adverse events	36
Participants with adverse events	11 (78.6)
Participants with serious adverse events	5 (35.7)
Participants with Maximum Grade 3 or 4 adverse events	10 (71.4)
Participants with Maximum Grade 5 adverse events	1 (7.1)
Participants discontinued from study due to adverse events[a]	3 (21.4)
Participants with dose reduced due to adverse events	4 (28.6)
Participants with temporary discontinuation due to adverse events	7 (50.0)

An infinite lag time is applied for this study.
Per protocol, Grade 3-5 Adverse Events and all Serious Adverse Events were to be recorded. Unsolicited Grade 1-2 Adverse Events have also been recorded and are presented in tables.
Except for the Number of Adverse Events Participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study.
MedDRA v27.0 coding dictionary applied.

Table 7 Summary of Treatment-Emergent Adverse Events by MedDRA Preferred or Cluster Term and Maximum CTCAE Grade in Descending Frequency Order (All Causality) - Safety Analysis Set (Protocol A8081056)

Number of Participants Evaluable for AEs	CRIZOTINIB (N=14)						
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Missing or Unknown	Total
Number (%) of Participants: by Cluster / Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	0	0	7 (50.0)	3 (21.4)	1 (7.1)	0	11 (78.6)
NEUTROPENIA [17]	0	0	4 (28.6)	3 (21.4)	0	0	7 (50.0)
ELEVATED TRANSAMINASES [14]	2 (14.3)	0	2 (14.3)	0	0	0	4 (28.6)
Dehydration	0	0	2 (14.3)	0	0	0	2 (14.3)
Hypokalaemia	0	0	2 (14.3)	0	0	0	2 (14.3)
Pneumonia	0	0	2 (14.3)	0	0	0	2 (14.3)
Alkalosis hypochloraemic	0	0	1 (7.1)	0	0	0	1 (7.1)
BLOOD CREATININE INCREASED [27]	0	0	1 (7.1)	0	0	0	1 (7.1)
Blood alkaline phosphatase increased	1 (7.1)	0	0	0	0	0	1 (7.1)
Bronchiolitis	0	0	1 (7.1)	0	0	0	1 (7.1)
Cellulitis	0	0	1 (7.1)	0	0	0	1 (7.1)
Clostridium difficile infection	0	1 (7.1)	0	0	0	0	1 (7.1)
Diarrhoea	0	0	0	1 (7.1)	0	0	1 (7.1)
Disease progression	0	0	0	0	1 (7.1)	0	1 (7.1)
Hydrocephalus	0	0	1 (7.1)	0	0	0	1 (7.1)
Hypernatraemia	0	0	1 (7.1)	0	0	0	1 (7.1)
Hypocalcaemia	0	0	1 (7.1)	0	0	0	1 (7.1)
Hyponatraemia	0	0	1 (7.1)	0	0	0	1 (7.1)
Pain	0	0	0	1 (7.1)	0	0	1 (7.1)
SARS-CoV-2 test positive	1 (7.1)	0	0	0	0	0	1 (7.1)
Vomiting	0	0	1 (7.1)	0	0	0	1 (7.1)
Weight increased	0	0	1 (7.1)	0	0	0	1 (7.1)
Wound complication	1 (7.1)	0	0	0	0	0	1 (7.1)

Per protocol, Grade 3-5 Adverse Events and all Serious Adverse Events were to be recorded. Unsolicited Grade 1-2 Adverse Events have also been recorded and are presented in tables.
MedDRA v27.0 coding dictionary applied

Serious Adverse Events

Table 8 Summary of Serious Adverse Events by MedDRA Preferred Term and Clustered Term and Maximum CTCAE Grade in Descending Frequency Order (All Causality) - Safety Analysis Set (Protocol A8081056)

Number of Participants Evaluable for AEs	CRIZOTINIB (N=14)						
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Missing or Unknown	Total
Number (%) of Participants: by Clustered / Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	0	0	5 (35.7)	0	1 (7.1)	0	6 (42.9)
Pneumonia	0	0	2 (14.3)	0	0	0	2 (14.3)
Alkalosis hypochloraemic	0	0	1 (7.1)	0	0	0	1 (7.1)
BLOOD CREATININE INCREASED [27]	0	0	1 (7.1)	0	0	0	1 (7.1)
Bacteraemia	0	0	1 (7.1)	0	0	0	1 (7.1)
Bronchiolitis	0	0	1 (7.1)	0	0	0	1 (7.1)
Cellulitis	0	0	1 (7.1)	0	0	0	1 (7.1)
Dehydration	0	0	1 (7.1)	0	0	0	1 (7.1)
Diarrhoea	0	0	0	1 (7.1)	0	0	1 (7.1)
Disease progression	0	0	0	0	1 (7.1)	0	1 (7.1)
Hydrocephalus	0	0	1 (7.1)	0	0	0	1 (7.1)
Hypernatraemia	0	0	1 (7.1)	0	0	0	1 (7.1)
NEUTROPENIA [17]	0	0	1 (7.1)	0	0	0	1 (7.1)
Pain	0	0	0	1 (7.1)	0	0	1 (7.1)
Vomiting	0	0	1 (7.1)	0	0	0	1 (7.1)
Wound complication	1 (7.1)	0	0	0	0	0	1 (7.1)

Per protocol, Grade 3-5 Adverse Events and all Serious Adverse Events were to be recorded. Unsolicited Grade 1-2 Adverse Events have also been recorded and are presented in tables.
MedDRA v26.1 coding dictionary applied

2.3.3. Discussion on clinical aspects

No new safety signals were identified from the safety profile of the 14 paediatric patients treated with the alternative oral formulation of crizotinib (coated microspheres) as part of the open label expanded access protocol (Study A8081056). The most frequent grade 3 and 4 treatment-related AE were neutropenia and diarrhoea which is consistent with the known safety profile of crizotinib hard capsule. There was one death in the paediatric population reported during the study due to disease progression.

Although the number of patients exposed is small and the median of treatment limited, the alternative oral crizotinib formulations could be considered as tolerated in the treated population with no new safety signals identified.

Benefit-risk balance remains unchanged.

3. Rapporteur’s CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.