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Committee for Medicinal Products for Human Use (CHMP)

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/P46/025

Note

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

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LIST OF ABBREVIATIONS

AE	adverse event
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
AST	aspartate aminotransferase
BID	twice daily
COG	Children's Oncology Group
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	predose plasma concentration
DBP	diastolic blood pressure
DR	duration of response
EC	European Commission
ECG	electrocardiogram
EFS	event-free survival
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
HSCT	hematopoietic stem cell transplantation
IHC	immunohistochemistry
IMT	inflammatory myofibroblastic tumour
LSLV	last subject last visit
MAH	Marketing-authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MP	molecular profiling
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NPM	nucleophosmin
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	Progressive disease
PDCO	Paediatric Committee
PFS	progression-free survival
PIP	Paediatric Investigational Plan
PK	Pharmacokinetics
PR	partial response
PT	preferred term
QD	once daily
QTcF	QTc corrected using Fridericia's formula
RE	Response Evaluable
RECIST	Response Evaluation Criteria in Solid Tumors
SA	Safety Analysis
SAE	serious adverse event
SAP	Statistical Analysis Plan
US	United States
WHO	World Health Organization

Introduction

On 27 August 2020, in accordance with EMA, the MAH submitted A8081013 provisional CSR under Article 46 of Regulation (EC) No1901/2006, as it will support the extension of the indication in paediatric patients with relapsed or refractory ALK-positive systemic ALCL and with ALK-IMT.

A PIP has been agreed for crizotinib with the PDCO in 2019 in the conditions of treatment of ALCL and treatment of IMT.

The PDCO agreed in PIP EMEA-001493-PIP03-18 that the completion of the measure for Study A8081013 is May 2020, the MAH is submitting the present interim CSR under Article 46 within 6 months of the referred date and not within 6 months of the LSLV as it has not yet occurred.

The MAH would like to clarify that the LSLV for Study A8081013 (currently reported as December 2020 in clinicaltrials.gov) is an estimate that is subject to re-evaluation and may be updated later in 2020. It is difficult to determine the LSLV date for this study because as per study protocol, patients are allowed to continue treatment with crizotinib as long as there is evidence of clinical benefit in the judgement of the Investigator.

A short critical expert overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that Study A8081013 / Phase 1b Open Label Study of the Safety and Clinical Activity of Crizotinib (PF-02341066) in Tumors With Genetic Events Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus) is part of a clinical development program. The extension consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted by June 2021. A line listing of all the concerned studies is annexed.

1.2. Information on the pharmaceutical formulation used in the study

Crizotinib was provided as capsules containing 200 mg or 250 mg of study medication and was packaged in HDPE bottles.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted an interim report for:

•Phase 1b Open-Label Study of the Safety and Clinical Activity of Crizotinib (PF-02341066) in Tumors with Genetic Events Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus (study number A8081013).

1.3.2. Clinical study

Study A8081013: a Phase 1b Open Label Study of the Safety and Clinical Activity of Crizotinib (PF-02341066) in Tumors with Genetic Events Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus).

Description

This study is a non-randomised, open-label, multicentre, single-arm exploratory study evaluating the antitumor activity, safety, and PK of crizotinib.

Initially, patients (≥ 16 years) with a histologic or cytologic proven diagnosis of ALCL or other advanced malignancy other than NSCLC, *e.g.,* IMT, for which no standard therapy was available and who were positive for harbouring a translocation, inversion, mutation or amplification event involving the ALK gene locus were enrolled into the study.

Initial reports of clinically meaningful results with crizotinib in patients with relapsed ALCL in the COG-Sponsored Study ADVL0912 were published in 2011 (Gambacorti-Passerini et al, 2011). Because of the clinical activity of crizotinib observed in Study ADVL0912, the age range in Study A8081013 was decreased to 15 years of age to allow additional paediatric patients with ALK-positive ALCL or IMT outside the US to enroll into this study.

Methods

Objective(s)

Primary objectives was to:

- Assess the safety of oral single agent crizotinib administered to patients with advanced ALK-positive ALCL or other advanced malignancy other than NSCLC known to have an ALK genetic event and Screen for efficacy in this patient population.

Secondary objectives were to:

- Correlate ALK genetic events (translocation, mutation/amplification) to efficacy outcome measures including PFS and OS,

- Determine pharmacokinetics (PK) in this patient population using population PK (POPPK) methods and explore correlations between PK, response and/or safety findings,

- Correlate ALK genetic events (translocation, mutation/amplification) to outcome measures.

CHMP comment

The lack of a comparator in this single arm study (SAT) makes it difficult to draw any clear conclusion about crizotinib benefit as compared to other therapeutic options. However, these objectives of this SAT are considered appropriate to assess the antitumor activity and the safe use of crizotinib in the (paediatric) population investigated.

Study design

This study is an ongoing open-label, non-randomised, multi-center, single-arm exploratory study of an oral agent, crizotinib, in patients with advanced malignancy harbouring a translocation, inversion mutation or amplification event involving the ALK gene locus.

Study population /Sample size

Main eligibility criteria:

1- Age ≥ 15 years

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

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

4- Positive for ALK amplification events

5- Positive for ALK activating point mutations

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

7- ECOG performance status 0-3

Main ineligibility criteria:

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

2- Concurrent treatment on another therapeutic clinical trial

3- Prior therapy specifically directed against ALK

Sample size

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

Treatments

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

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

Outcomes/endpoints

Efficacy:

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

Secondary endpoints were:

- PFS, OS, DR

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

- Plasma concentrations of crizotinib,

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

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

Safety:

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

Statistical Methods

Safety Analysis:

Frequencies of patients experiencing at least one adverse event (AE) will be displayed by body system and preferred term according to MedDRA terminology.

Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Severity of the AEs will be graded according to the NCI CTCAE Version 4.0.

The number and percentage of patients who experienced any serious AE (SAE), treatment related AE, and treatment related SAE will also be summarized. AE data will be presented across cycles and by cycle, as appropriate. The denominator for each cycle is defined as those patients available at the start of the cycle who received at least 1 dose of crizotinib for that cycle. Emphasis in the analyses will be placed on AEs classified as treatment emergent.

Additional summaries of AEs and other safety data will be presented in tabular and/or graphical format and summarized descriptively, as appropriate.

Efficacy Analysis:

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

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

Primary Efficacy Analysis:

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

Secondary Efficacy Analysis:

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

CHMP comment

As a reminder, crizotinib is currently authorised for the treatment of adult with NSCLC (ALK-positive or ROS1-positive). The present study proposed to include paediatric patients with ALK-positive ALCL or ALK-positive IMT in the authorized population. No change was proposed to the indication statement. Therefore, the assessment of efficacy data from Study A8081013 primarily focuses to ensure that no concerns jeopardize the use of crizotinib for paediatric patients from 15 years of age.

Results

Recruitment/ Number analysed

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

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

The data cutoff date was 03 September 2019.

The study report date is 28 February 2020.

Publications Based on the Study:

1. Gambacorti-Passerini C, Messa C, Pogliani EM. Crizotinib in anaplastic large-cell lymphoma. N Engl J Med 2011; 364(8):775-6.

2. Gambacorti-Passerini C, Farina F, Stasia A et al. Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. J Natl Cancer Inst. 2014; 106(2):djt378.

3. Gambacorti-Passerini C, Orlov S, Zhang L, et al. Safety and efficacy of crizotinib in ALK-positive lymphomas: a phase 1b open-label study. Blood 2017; 130: 4128.

4. Gambacorti-Passerini C, Orlov S, Zhang L, et al. Long-term effects of crizotinib in ALK-positive tumors (excluding NSCLC): A phase 1b open-label study. Am J Hematol 2018; 93(5):607-614.

5. Horibe K, Braiteh F, Huang HQ, et al. Safety and clinical activity of crizotinib in patients with ALK-rearranged hematologic malignancies. Blood (2013) 122 (21): 4342.

Overall Population

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

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

Paediatric Population

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

Baseline data

Table 1: Baseline Demographic Characteristics, Paediatric Subjects

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

CHMP comment:

Given the inclusion criteria, the paediatric population is represented by adolescents. Paediatric patients represent ~ 11.4% (5/44) of the population enrolled in this study. Characteristics of this patients were the following: Median age 16 years (range 15-17 years); 40% female, 60% male; 100% were Asian and the weight > 40kg.

Efficacy results

Antitumour activity data are provided in Table below.

Table 2: Antitumour Activity Results for Paediatric Patients with ALK-Positive ALCL or ALK-Positive IMT (Data Cutoff Date: 03.09.19)

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

Pharmacokinetic Results

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

Biomarker Results

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

Safety results

There were no deaths in the paediatric population during the study. The safety profile of crizotinib was generally consistent with the known safety profile of crizotinib, even with long-term treatment; no new safety signals or long-term emerging AEs were identified.

1.3.3. Discussion on clinical aspects

The purpose of the A8081013 study, an ongoing MAH-sponsored study of an authorised medicinal product, was to assess the efficacy, safety, and PK of crizotinib in patients whose tumours were found to have a translocation, mutation, or amplification involving the ALK gene locus, in tumour types other than NSCLC.

A PIP has been agreed for crizotinib with the PDCO in 2019 in the conditions of treatment of ALCL and treatment of IMT.

Relapsed or refractory systemic ALCL and unresectable, recurrent, or refractory IMT are both rare, serious, and life-threatening diseases, and an unmet medical need remains for improved therapies for paediatric patients.

Crizotinib is currently authorised for the treatment of adult with NSCLC (ALK-positive or ROS1-positive). The present study proposed to include paediatric patients with ALK-positive ALCL or ALK-positive IMT in the authorized population. No change was proposed to the indication statement. Therefore, the assessment of efficacy data from Study A8081013 primarily focuses to ensure that no concerns jeopardize the use of crizotinib for paediatric patients from 15 years of age.

This study enrolled a total of 5 paediatric patients (3 with relapsed or refractory systemic ALK-positive ALCL and 2 with unresectable, recurrent, or refractory ALK-positive IMT) as of the data cutoff date of 03 September 2019. Paediatric patients represent ~ 11.4% (5/44) of the population enrolled in this study. Given the inclusion criteria, the paediatric population is represented by adolescents.

The study does not allow to draw robust conclusions for efficacy, due to limitations in study design and the limited number of paediatric patients. However, in the population targeted by this study and in particular adolescents with ALK-positive ALCL or ALK-positive IMT, antitumor activity was observed with crizotinib.

No new or unexpected safety signals were observed from the study and the safety results are consistent with prior studies and the established safety profile for crizotinib. Considering that the PIP for crizotinib is not yet completed, no changes in the SmPC were proposed by the MAH.

At this stage no changes in the SmPC are proposed by the CHMP.

2. Overall conclusion and recommendation

☒ Fulfilled:

The Art 46 study has been considered completed by PDCO through a partial compliance check and there are no required changes to the SmPC. Considering that the ongoing assessment of variation II/72 will provide more comprehensive data on safety and efficacy, the Art 46 is considered fulfilled.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Xalkori Active substance: crizotinib

Study title	Study number	Date of completion	Date of submission of final study report
A literature review summarising all available published paediatric safety and efficacy results from crizotinib in the intended indication of relapsed/refractory ALK-positive ALCL and relapsed/refractory or inoperable ALK-positive IMT	NA	23 July 2020	June 2021 (as part of a Type II variation to extend the crizotinib indication in the paediatric ALK-positive ALCL and IMT population (aged >6 years - <18 years of age)

Clinical studies

Product Name: Xalkori Active substance: crizotinib

Study title	Study number	Date of completion	Date of submission of final study report
A Phase 1/2 Study of PF-02341066, An Oral Small Molecule Inhibitor of Anaplastic lymphoma Kinase (ALK) and C-Met, in Children With Relapsed/Refractory Solid Tumors and Anaplastic Large Cell Lymphoma	ADVL0912	19 January 2018	June 2021 (as part of a Type II variation to extend the crizotinib indication in the paediatric ALK-positive ALCL and IMT population (aged >6 years - <18 years of age)
Phase 1b Open-Label Study of the Safety and Clinical Activity of Crizotinib (PF-02341066) in Tumors With Genetic Events Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus	A8081013	LSLV not occurred	August 2020 (Article 46)
A Phase 1, Open Label, Crossover Study to Evaluate Palatability and Relative Bioavailability of Two Paediatric Microsphere Formulations of Crizotinib in Healthy Participants	A8081069	17 October 2019	[Redacted]
Bioequivalence single dose cross over study with crizotinib in adults comparing the selected age appropriate formulation with the formulated capsule	Not Applicable	Ongoing	[Redacted]