CLINICAL STUDY REPORT SYNOPSIS

SYNOPSIS

Study Title: 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

Regulatory Agency or Public Disclosure Identifier Number:

US IND Number: 73,544

EudraCT Number: 2010-022978-14

Study Phase: Phase 1

Name of Study Intervention: PF-02341066

Trade Name OR Device Identification: Crizotinib

Name of Sponsor/Company: Pfizer, Inc

CSR Version and Report Date: Final Abbreviated CSR version 1.0; 19 December 2023

Number of Study Center(s) and Investigator(s):

16 sites (3 in China, 1 in Italy, 3 in Japan, 2 in Republic of Korea, 1 in Russian Federation, 1 in Taiwan and 5 in the United States).

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

No new publications were reported since the interim CSR.

Study Period:

Study Initiation Date (First Subject First Visit [FSFV]): 22 March 2011

Study Completion Date (Last Subject Last Visit [LSLV]): 07 September 2023

Termination of further treatment on the study occurred due to the availability of commercial supply or a rollover study that will allow active subjects to continue receiving treatment.

CLINICAL STUDY REPORT SYNOPSIS

Rationale:

XALKORI® (PF-02341066, hereafter referred to as crizotinib) is a small-molecule inhibitor of the anaplastic lymphoma kinase (ALK), hepatocyte growth factor receptor (HGFR), ROS1, and recepteur d'origne nantais (RON) receptor tyrosine kinase (RTKs).

This final clinical study report (CSR) summarizes the safety data as of study completion (LPLV date 07 September 2023) in patients whose tumors were found to have a translocation, mutation, or amplification involving ALK other than non-small cell lung cancer (NSCLC). Final efficacy data, and safety data as of the cut off date 03 Sep 2019 was presented in the interim CSR dated 28 Feb 2020. Data for 5 pediatric patients enrolled in this study are included in this report (3 pediatric patients with relapsed or refractory systemic ALK-positive anaplastic large cell lymphoma (ALCL) and 2 with unresectable, recurrent, or refractory ALK-positive inflammatory myofibroblastic tumors [IMT]).

Objectives, Endpoints, and Statistical Methods:

Table S1. Study Objectives and Endpoints

Type	Objective	Endpoints	Reference
Primary			
Safety Section	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.	Type, incidence, severity, seriousness and relationship to study medications of AE and any laboratory abnormalities.	Final safety data are presented in this CSR
Efficacy	To screen for efficacy in this patient population.	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).	Final data were presented in interim CSR
Secondary			
Efficacy	To correlate ALK genetic events to efficacy outcome measures including PFS and OS	PFS, OS, DR, 6-month and 1-year survival probability	Final data were presented in interim CSR
PK	To determine PK in this patient population using population PK methods and explore correlations between PK, response and/or safety findings.	Plasma concentrations of crizotinib.	Final data were presented in interim CSR

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives and Endpoints

Type	Objective	Endpoints	Reference
Genotype	To correlate ALK genetic events to outcome measures.	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.	An exploratory evaluation of ALK molecular profiling in tumor tissue by central testing was not performed due to insufficient samples.

Abbreviations: AE=adverse event; ALCL=anaplastic large cell lymphoma; ALK=anaplastic lymphoma kinase; CSR=Clinical Study Report; NHL=non-Hodgkin lymphoma; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression free survival; PK=pharmacokinetic(s); RECIST=Response Evaluation Criteria in Solid Tumors;

Methodology:

This was an open-label, multi-center, single-arm exploratory trial of an oral agent, crizotinib, in patients with advanced malignancy harboring a translocation, inversion, mutation or amplification event involving the *ALK* gene locus.

Patients with ALCL, IMT, and other advanced malignancies (excluding NSCLC) for which no standard therapy is available were eligible if they were positive during local ALK testing. The patients with positive local ALK testing are defined as patients with ALK-positive ALCL (ALCL group), ALK-positive IMT (IMT group) or other ALK-positive malignancies other than NSCLC (Other Tumors group) in this document.

This CSR presents the final safety analysis as of the study completion (LSLV date 07 September 2023) 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.

Number of Participants (planned and analyzed):

A total of 44 participants enrolled in the study; 17 with ALCL, 9 with IMT, and 18 with other tumors. Among the 44, 5 were pediatric participants; 3 with ALCL and 2 in the IMT group.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were participants with advanced malignancy harboring a translocation, inversion, mutation or amplification event involving the ALK gene locus.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

The manufacturing lot numbers for the study intervention(s) dispensed in this study are provided in Table S2.

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/Potency	Dosage Form
Crizotinib 200mg IR Size 1 White/Pink Capsule	9806533000	10-085282	200 mg	BULK COMMERCIAL IMAGE
Crizotinib 250mg IR Size 0 Pink/Pink Capsule	9806683000	10-085280	250 mg	BULK COMMERCIAL IMAGE
Crizotinib 250mg IR Size 0 Pink/Pink Capsule	35695.1	11-007546	250 mg	BULK COMMERCIAL IMAGE
Crizotinib 200mg IR Size 1 White/Pink Capsule	9807733001	11-005559	200 mg	BULK COMMERCIAL IMAGE
Crizotinib 250mg IR Size 0 Pink/Pink Capsule	9806683001	10-085281	250 mg	BULK COMMERCIAL IMAGE
Crizotinib 200mg IR Size 1 White/Pink Capsule	9806533001	11-001160	200 mg	BULK COMMERCIAL IMAGE
Crizotinib 250mg IR Size 0 Pink/Pink Capsule	9806633000	10-085075	250 mg	BULK COMMERCIAL IMAGE
Crizotinib 200mg IR Size 1 White/Pink Capsule	9806533002	11-001161	200 mg	BULK COMMERCIAL IMAGE
Crizotinib 200mg IR Size 1 White/Pink Capsule	9811333000	11-010445	200 mg	BULK COMMERCIAL IMAGE
Crizotinib 250mg Bottle 50ct (capsule)	9978443000 9807933002	12-000135	250 mg	BULK COMMERCIAL IMAGE
Crizotinib 250mg Bottle 50ct (capsule)	9978443005 9807933003	12-002354	250 mg	BULK COMMERCIAL IMAGE
Crizotinib 200mg IR Size 1 White/Pink Capsule	9811333002	12-003856	200 mg	BULK COMMERCIAL IMAGE
Crizotinib 200mg Bottle 50ct (capsule)	9979353001 9807703009	13-107272	200 mg	BULK COMMERCIAL IMAGE
Crizotinib 250mg Bottle 50ct (capsule)	9978443008 9807933006	12-004503	250 mg	BULK COMMERCIAL IMAGE
Crizotinib 250mg Bottle 50ct (capsule)	H60448/H38373	13-111061	250 mg	BULK COMMERCIAL IMAGE
Crizotinib 250mg Bottle 50ct (capsule)	J28149/J21124	14-002483	250 mg	BULK COMMERCIAL IMAGE

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/Potency	Dosage Form
Crizotinib 200mg Bottle 50ct (capsule)	L34421/L22232	15-001442	200 mg	BULK COMMERCIAL IMAGE
Crizotinib 250mg Bottle 50ct (capsule)	L34422/L23011	15-001443	250 mg	BULK COMMERCIAL IMAGE
Crizotinib 200mg IR Size 1 White/Pink Capsule	M09277	15-005906	200 mg	BULK COMMERCIAL IMAGE
Crizotinib 250mg IR Size 0 Pink/Pink Capsule	T79535	17-004069	250 mg	BULK COMMERCIAL IMAGE
Crizotinib 200mg IR Size 1 White/Pink Capsule	T79515	17-004068	200 mg	BULK COMMERCIAL IMAGE
Crizotinib 250mg IR Size 0 Pink/Pink Capsule	DN9999	20-001640	250 mg	BULK COMMERCIAL IMAGE
Crizotinib 200mg IR Size 1 White/Pink Capsule	DN9997	20-001639	200 mg	BULK COMMERCIAL IMAGE
Crizotinib 250mg Bottle 50ct (capsule)	L47855/L23011	15-001673	250 mg	BULK COMMERCIAL IMAGE
Crizotinib 200mg IR Size 1 White/Pink Capsule	N44237	16-002145	200 mg	BULK COMMERCIAL IMAGE

Abbreviations: IR=immediate release;

Duration of Study Intervention:

Patients could have continued treatment with crizotinib on this study as long as there was evidence of clinical benefit in the judgment of the Investigator.

Summary of Results:

Demographic and Other Baseline Characteristics:

No demographics or baseline characteristics changes were reported since data cutoff date for the interim CSR (03 September 2019). Briefly, 56.8% of participants were males, and median age was 32.0 years. Among the 5 pediatric treated participants, 60.0% were males, and the median age was 16.0 years.

- For all participants, the median age of the overall ALCL, IMT, and Other Tumor groups was 25.0, 32.0 and 49.0 years, respectively.

CLINICAL STUDY REPORT SYNOPSIS

- In the ALCL and IMT pediatric groups, the median age was 15.0 and 16.5 years, respectively.

Exposure:

- For all participants, the median duration of treatment for the ALCL group was 402.30 weeks, for the IMT group was 480.00 weeks, and for the Other Tumors group was 7.10 weeks.

  - For the pediatric population, the median duration of treatment was similar between the ALCL group (514.90 weeks) and the IMT group (506.95 weeks).

Efficacy Results:

The final efficacy data were presented in the interim CSR, see Table S1.

Safety Results:

The safety results presented in this CSR support that the safety profile of long-term treatment with crizotinib is manageable. The safety profile in the pediatric population was generally consistent with that of the overall population.

All-Causality AEs and Treatment-Related AEs

- For all participants, the most frequently reported all-causality AEs (>40% of participants) in decreasing frequency were VISION DISORDER (22 participants; 50.0%), ELEVATED TRANSAMINASES (21 participants; 47.7%), diarrhea (20 participants; 45.5%), nausea (19 participants; 43.2%), and vomiting (19 participants; 43.2%).

  - For pediatric participants, the most frequently reported all-causality AEs (≥4 participants) in decreasing frequency were nausea (5 participants; 100%), diarrhea (4 participants; 80%), LEUKOPENIA (4 participants; 80%), UPPER RESPIRATORY INFECTION (4 participants; 80%), and vomiting (4 participants; 80%).

- For all participants, the most frequently reported treatment-related AEs (>40% of participants) in decreasing frequency were VISION DISORDER (21 participants; 47.7%), diarrhea (20 participants; 45.5%), and ELEVATED TRANSAMINASES (19 participants; 43.2%).

  - For pediatric participants, the most frequently reported treatment-related AEs (≥4 participants) in decreasing frequency were nausea (5 participants; 100%), diarrhea (4 participants; 80%), LEUKOPENIA (4 participants; 80%), and vomiting (4 participants; 80%).

All-Causality SAEs and Treatment-Related SAEs

There were no new SAEs reported since the interim CSR.

CLINICAL STUDY REPORT SYNOPSIS

- For all participants, the most frequently reported all-causality SAEs (>4% of participants) in decreasing frequency were blood creatine phosphokinase increased (4 participants; 9.1%), disease progression (3 participants; 6.8%), and respiratory failure (2 participants; 4.5%).

- For all participants, the reported treatment-related SAEs (>2% of participants) in decreasing frequency were blood creatine phosphokinase increased (4 participants; 9.1%) CARDIAC FAILURE (1 participant; 2.3%), cerebral infarction (1 participant; 2.3%), deep vein thrombosis (1 participant; 2.3%), diarrhea(1 participant; 2.3%), INTERSTITIAL LUNG DISEASE (1 participant; 2.3%), myocardial ischemia (1 participant; 2.3%), nausea (1 participant; 2.3%), and vomiting (1 participant; 2.3%).

- For pediatric participants, the reported all-causality SAEs (all in 1 participant; 20%) were blood creatine phosphokinase increased, diarrhea, nausea, and vomiting, all of which were considered to be treatment-related SAEs.

Deaths

- There were no new deaths since the data cut off for the interim CSR. For participants in the ALCL group all deaths within 28 days of last dose of crizotinib were due to disease under study. For participants in the IMT and Other Tumors groups, most deaths were due to disease under study. For participants in the Other Tumor group there were 2 deaths due to study drug toxicity (cerebral infraction and interstitial pneumonia).

    - In the pediatric population, no deaths occurred.

Conclusions:

Efficacy

The final efficacy data were presented in interim CSR.

Safety

The safety results presented in this CSR support that the long-term safety profile of crizotinib is manageable. Safety results as of study completion (LPLV date 07 September 2023) were similar to the results reported in the interim CSR.

The safety profile of crizotinib described in this study was generally consistent with the known safety profile of crizotinib; no new safety signals or long-term emerging AEs were identified. No new safety signals were identified from the safety profile of the 5 pediatric patients.