Clinical trial results:
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

Summary

EudraCT number	2024-000442-10
Trial protocol	Outside EU/EEA
Global end of trial date	10 June 2024

Results information

Result version number	v1 (current)
This version publication date	21 November 2024
First version publication date	21 November 2024

Trial information

Trial identification

Sponsor protocol code	A8081056

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02473497
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	66 Hudson Boulevard East, New York, United States, NY 10001
Public contact	PfizerClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	PfizerClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 July 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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 participants with tumours harbouring either a chromosomal translocation or activating mutation involving the anaplastic lymphoma kinase (ALK) or receptor tyrosine kinase (ROS) proto-oncogene 1, ROS1 gene or an activating genetic alteration involving the c-MET gene, who have a genetic aberration involving ALK, ROS1, or c-MET but who cannot swallow crizotinib capsules.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	14
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	5
Children (2-11 years)	9
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 15 participants were enrolled in the study. 14 participants received treatment while 1 participant did not receive study treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Crizotinib

Arm description:

Participants received crizotinib orally, at a dose of 280 milligrams per square metre (mg/m^2) twice daily (BID) as either an oral solution or as coated microspheres on Day 1 of each cycle (each cycle = 28 days).

Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	PF-02341066
Other name	Xalkori
Pharmaceutical forms	Oral solution, Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received crizotinib orally, at a dose of 280 mg/m^2 BID as an oral solution or as coated microspheres.

Number of subjects in period 1	Crizotinib
Started	14
Completed	0
Not completed	14
Unspecified	5
Objective progression or relapse	3
Adverse event (AE)	3
Refused continued treatment, other than AE	3

Baseline characteristics

Reporting groups	
Reporting group title	Crizotinib
Reporting group description:	
Participants received crizotinib orally, at a dose of 280 milligrams per square metre (mg/m^2) twice daily (BID) as either an oral solution or as coated microspheres on Day 1 of each cycle (each cycle = 28 days).	

Reporting group values	Crizotinib	Total	
Number of subjects	14	14	
Age Categorical Units: Participants			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	5	5	
Children (2-11 years)	9	9	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	3.96		
standard deviation	± 3.72	-	
Gender Categorical Units: Participants			
Female	7	7	
Male	7	7	
Ethnicity Units: Subjects			
Hispanic or Latino	4	4	
Not Hispanic or Latino	10	10	
Race Units: Subjects			
White	9	9	
Black	1	1	
Other	4	4	

End points

End points reporting groups

Reporting group title	Crizotinib

Reporting group description:

Participants received crizotinib orally, at a dose of 280 milligrams per square metre (mg/m^2) twice daily (BID) as either an oral solution or as coated microspheres on Day 1 of each cycle (each cycle = 28 days).

Primary: Number of Participants With Serious Adverse Events (SAEs) as Assessed by Common Terminology Criteria for Adverse Events (CTCAE) Version (v) 4.03

End point title	Number of Participants With Serious Adverse Events (SAEs) as Assessed by Common Terminology Criteria for Adverse Events (CTCAE) Version (v) 4.03[1]

End point description:

An AE was defined as any untoward medical occurrence in a clinical investigation participant administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. An SAE was defined as any untoward medical occurrence at any dose that resulted in any of the following outcomes: death; life-threatening; required inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; congenital anomaly/birth defect; progression of malignancy under study. SAEs were graded according to CTCAE v4.03 (grade 1= mild, grade 2= moderate, grade 3= severe, grade 4= life-threatening and grade 5= death related to AE). Safety analysis set included all participants who received at least one dose of

End point type	Primary

End point timeframe:

From Day 1 of dosing up to 28 Days after end of treatment (EOT) [maximum up to approximately 36 months]

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint

End point values	Crizotinib			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Participants	5			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Grade 3-5 Adverse Events (AEs) as Assessed by CTCAE v4.03

End point title	Number of Participants With Grade 3-5 Adverse Events (AEs) as Assessed by CTCAE v4.03[2]

End point description:

An AE was defined as any untoward medical occurrence in a clinical investigation participant administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. AEs were graded according to CTCAE v4.03 (grade 1= mild, grade 2= moderate, grade 3= severe, grade 4= life-threatening and grade 5= death related to AE). Safety analysis set included all participants who received at least one dose of crizotinib.

End point type	Primary

End point timeframe:

From Day 1 of dosing up to 28 Days after EOT (maximum up to approximately 36 months)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint

End point values	Crizotinib			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Participants				
Participants with grade 3 or 4 AEs	10			
Participants with grade 5 AEs	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 of dosing up to 28 Days after EOT (maximum up to approximately 36 months)

Adverse event reporting additional description:

Same event may appear as both non-SAE and SAE but are distinct events. An event may be categorized as serious in 1 participant and non-serious in another, or a participant may have experienced both SAE and non-SAE. Safety analysis set included all participants who received at least one dose of crizotinib.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Crizotinib

Reporting group description:

Participants received crizotinib orally, at a dose of 280 mg/m^2 BID as either an oral solution or as coated microspheres on Day 1 of each cycle (each cycle = 28 days).

Serious adverse events	Crizotinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 14 (35.71%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Wound complication			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Hydrocephalus				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Disease progression				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	2 / 14 (14.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchiolitis				

subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Alkalosis hypochloraemic			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypernatraemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Crizotinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 14 (71.43%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	4		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	3		
Neutrophil count decreased			

subjects affected / exposed occurrences (all) SARS-CoV-2 test positive subjects affected / exposed occurrences (all) Weight increased subjects affected / exposed occurrences (all)	4 / 14 (28.57%) 8 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	 4 / 14 (28.57%) 26		
Infections and infestations Clostridium difficile infection subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1		
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all) Hypernatraemia subjects affected / exposed occurrences (all) Hypocalcaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1 1 / 14 (7.14%) 2 1 / 14 (7.14%) 1 2 / 14 (14.29%) 2 1 / 14 (7.14%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 July 2015	Clarifications and additions were made to the Schedule of Activities and eligibility criteria, based on an FDA request. Clarified that crizotinib will be administered as a single agent. Clarified that participants more than or equal to (>=)21 years of age will receive crizotinib 250 mg BID, whereas participants less than (<)21 years of age will receive crizotinib 280 mg/m^2 BID.
26 January 2017	Amended inclusion criterion #5 to allow paediatric participants with alanine aminotransaminase (ALT) and/or aspartate aminotransaminase (AST) levels less than or equal to (<=)10*the upper limit of normal and bilirubin levels <=2*the upper limit of normal to be eligible for the study. This change was made to allow access to crizotinib for those paediatric participants who are more heavily pre treated and thus, may be likely to have elevated liver function tests. Due to this change in inclusion criteria for preexisting elevations of AST and ALT, Hy's law criteria for paediatric participants was modified accordingly. The concomitant use of drugs that elevate gastric pH including protein pump inhibitors or histamine 2 antagonists were excluded from the study. The eligibility criteria was updated to allow participants who were already receiving crizotinib (e.g. on another clinical study) and required an oral formulation. Sections 7.1.1 and 8.5: clarified that laboratory data values won't be collected on the Case Report Form. SAEs and Grade >=3 AEs based on laboratory test abnormalities will be collected on the AE pages of the CRF. Removed screening requirement for triplicate ECGs to a single ECG measurement.
22 January 2019	Inclusion/exclusion criteria were modified to facilitate participants' access to crizotinib: inclusion criteria #8, #9, #10 and #11 were removed and new inclusion criterion 12 was added, to ensure recovery from prior treatment toxicities rather than a fixed time frame; exclusion criterion #3 was removed to allow inclusion of adult participants that received crizotinib before; exclusion criterion #8 was amended to exclude participants with any grade interstitial fibrosis or interstitial lung disease, not only those with grade 3-4. This change was implemented in the most recent update of the Investigator Brochure exclusion criterion #10: atazanavir was removed from the text because it is not present anymore in the FDA's updated list of strong CYP3A inhibitors. Exclusion criterion #14 was amended to shorten the washout period, per request by site with participant in critical conditions. Section 5.3 (investigational product supplies), 5.4 (administration) and 5.9 (concomitant treatments) were updated and dosing instructions added for microsphere formulation, for consistency with revised Investigational Product manual. Appendix 2 was updated with more detailed dosing information, for oral solutions and microspheres.
18 January 2022	Paediatric safety and anti-tumour activity data from Studies ADVL0912 and A8081013 were added (Section 1.1.3) to be consistent with the most recent update of the IB (September 2021). Prophylactic use of antiemetics for paediatric participants were added to Section 5.7.1 to be consistent with the wording in the United States Prescribing Information (USPI). To be consistent with the Dear Health Care Practitioner (DHCP) letter issued on 19 January 2021, ophthalmologic examinations were added to Table 1 (Schedule of Activities); dose modification criteria for visual events were updated in Table 2. The Protocol Administrative Change Letter (PACL) issued in April 2020 to address the impact of COVID-19 was indicated in Section 6 and included as Appendix 4.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported